16+

ISSN 1028-4427 (Print)
ISSN 2542-131X (Online)

Гений Ортопедии
Orthopaedic Genius

Том 30
№ 1
2024

Научно-теоретический и практический журнал
Основан в память академика Г.А. Илизарова

Курган

Учредитель и издатель журнала:

федеральное государственное бюджетное учреждение «Национальный медицинский исследовательский центр травматологии и ортопедии имени академика Г.А. Илизарова» Министерства здравоохранения Российской Федерации

Издание журнала осуществляется при поддержке Ассоциации по изучению и применению метода Илизарова России (A.S.A.M.I. Россия)

Журнал включен в перечень научных специализированных изданий ВАК, в которых могут публиковаться основные результаты диссертационных работ на соискание ученой степени кандидата наук, ученой степени доктора наук (3.1.8 – травматология и ортопедия)

Журнал включен в Реферативный журнал и Базы данных ВИНИТИ

Сведения о журнале ежегодно публикуются в международной справочной системе по периодическим и продолжающимся изданиям «Ulrich's Periodicals Directory»

Журнал включен в библиографические и реферативные базы данных РИНЦ и SCOPUS

Журнал включен в электронные информационные ресурсы базы данных EBSCO

Электронная версия журнала размещена на сайтах

http://ilizarov-journal.com
http://elibrary.ru
http://cyberleninka.ru

Адрес: 640014, Россия, г. Курган, ул. М. Ульяновой, 6
Телефоны: (3522) 43-06-94 – редакция
(3522) 23-42-60 – реклама
Интернет: http://ilizarov-journal.com/
Email: genius@ilizarov.ru

Оригинал-макет изготовлен ОИАиВР ФГБУ «НМИЦ ТО имени академика Г.А. Илизарова» Минздрава России

Журнал зарегистрирован Федеральной службой по надзору в сфере связи, информационных технологий и массовых коммуникаций ПИ № ФС77-68207 от 30 декабря 2016 года

Территория распространения: Российская Федерация, зарубежные страны

Язык: русский, английский

Издается 6 раз в год

Цена свободная

Dear friends,

We present to your attention the first issue of our journal this year. It has a new format with the sections “Clinical Studies”, “Theoretical and Experimental Research”, “Case Reports” and “Literature Review”.

The “Clinical Studies” section of this issue includes seven publications. The section opens with the work of a team of authors from St. Petersburg (Kalita et al.), in which the authors assessed the results of limb salvage surgical treatment of injuries to the distal phalanx of the fingers and substantiated the algorithm for treating injuries of the fingers using an original technique. Based on the results obtained, the authors conclude that the proposed method improves the outcomes of reconstructive surgical interventions in the treatment of the defects of the nail phalange tip in three-joint fingers.

Galkin et al. (Moscow) used large clinical data to study the effect of maintaining hip joint isometry on the outcome during surgical approach by changing the method of treating external rotators in reconstructive operations in the management of traumatic destruction of the posterior parts of the acetabulum. Having analyzed the results, the authors underline that maintaining isometry in the hip joint allows for significantly better clinical outcomes in the treatment of this complex category of injuries.

Long-term results and complications of surgical treatment of 130 patients with Achilles tendon ruptures are discussed by authors from Moscow (Magnitskaya et al.). Based on the data obtained, the authors conclude that open Achilles tendon repair techniques have a greater risk of infectious complications but a lower likelihood of recurrent ruptures. Previous injections of hormonal drugs into the area of the calcaneal tendon, the use of augmentation tapes or autografts in calcaneal tendon repair increase the likelihood of infectious complications.

The experience of the Belgrade Children's University Hospital in lengthening and correction of limb deformities in 12 patients with severe fibular hemimelia is presented in the work of Lazović et al. (Serbia, Kurgan). Based on the outcomes, the authors concluded that the strategy of early foot and ankle reconstruction in children with severe fibular hemimelia followed by tibial lengthening at the age of 4-6 years was effective and could be used in a variety of clinical situations. In type 3C fibular hemimelia, the use of external fixation to correct the deformity and simultaneously lengthen the tibia in the first stage is an alternative reasonable strategy.

The authors from Uzbekistan (Urinbaev et al.) studied the effectiveness of surgical treatment of pseudarthrosis of the lateral condyle of the humerus in children using combined methods of osteoplastic surgery with the Ilizarov apparatus. The paper presents the experience of surgical treatment of 57 children with fibular bone grafts and various methods of limb fixation. The authors note the high effectiveness of the treatment as good results were achieved in 79.6 % of cases. There was only one case of poor outcome.

Stupina et al. (Kurgan) analyzed the pathogenetic and clinical significance of palmar aponeurosis fungal infection in Dupuytren's contracture. The surgical material was examined at the light-optical level and with scanning electron microscopy. Fungal infection of the palmar aponeurosis was detected in 20 out of 41 patients; various types of tissue reaction to the introduction of fungi into the palmar aponeurosis and the blood vessels perforating it were found. The authors have statistically proven the relationship between fungal infection of the aponeurosis and an increase in the frequency of early relapses of contracture. To increase the duration of the relapse-free period and, potentially, the life expectancy of patients, consultations with infectious disease mycologists and correction of modifiable risk factors for candidiasis are necessary.

Authors from Moscow (Ivanov et al.) compared different methods for determining “bone age” using radiographs of the hand in patients with active growth plates and anteromedial instability of the knee

joint. The data obtained by the authors as a result of the study showed a difference between chronological and bone age. It allowed them to conclude that it is necessary to assess bone age by planning surgical treatment of patients with open growth plates, as well as of predicted and target growth.

The issue continues with a problematic article by Mukhametov et al. (Ufa, Smolensk, Chelyabinsk, Yekaterinburg), dedicated to theoretical research in the field of bone graft substitutes and the use of a large variety of synthetic materials, including metals, polymers and ceramics. A detailed analysis of clinical trials of synthetic biomaterials based on hydroxyapatite and tricalcium phosphate, listed in registries and various databases, was carried out in order to identify the potential for clinical use, as well as possible side effects of CPC as a substitute for bone grafts. The authors pointed that the combination of hydroxyapatite and tricalcium phosphate has many advantages. Their separate use or in combination does not have any serious side effects.

Two articles in this issue focus on experimental developments. Tretyakov et al. (Republic of Belarus) conducted a pathomorphological assessment of the effectiveness of intra-articular application of soluble platelet factors for treatment of experimental osteoarthritis in 120 rats. Preliminary modeling of osteoarthritis was carried out using an original method. The study showed that intra-articular administration of modified PORFT/PRP (platelet-rich plasma) led to a pronounced therapeutic effect, manifested by an improvement in the morphofunctional state of the hyaline cartilage on the 6th day, in comparison with plasma and serum.

Malishevsky et al. (Tyumen) conducted a comparative analysis of the biomechanical properties of various types of suture material for producing tendon stitching in an experiment. The results obtained allowed the authors to conclude that polytetrafluoroethylene and nickel-titanium threads showed the best biomechanical properties for tendon repair in linear strength, good elasticity and low plasticity of the suture material. There were no significant differences between polypropylene and braided polyamide threads.

The clinical case report presented in this issue concerns the problem of soft-tissue reconstruction of the palmar surface of both hands after thermal injury in a child aged two years and four months. The patient underwent surgery: excision of scars, skin grafting of both hands with a vascularized fasciocutaneous flap from the radial artery basin. Twelve years after surgical treatment, the patient had all types of restored grip in both hands. Both hand had acceptable aesthrtics.

Five review articles that conclude the issue are devoted to the analysis of the prospects for the use of implants made of zirconium ceramic materials in traumatology and orthopedics (Volokitina et al., Yekaterinburg), the use of mesenchymal stem cells and exosomes in the treatment of bone defects (Greben et al., Moscow), risk factors in formation of a failed distraction regenerate as a complication of distraction osteosynthesis, and its prevention and treatment (Novikov et al.; Kurgan, Tyumen), problems of using internal osteosynthesis for ankle fractures with distal syndesmosis rupture (Gafurov et al., Uzbekistan).

The issue closes with the work of the authors from Stavropol and St. Petersburg (N.N. Grigorieva and G.A. Airapetov), devoted to the mechanisms of development of pathology of the musculoskeletal system after COVID-19 infection. Having analyzed a large amount of literature, the authors conclude that COVID-19 infection has a negative impact on the musculoskeletal, endocrine and immune systems resulting in the risk of degenerative diseases of the musculoskeletal system and infectious complications in the early postoperative period in patients that undergo interventions due to orthopedic pathology.

Dear readers, we hope that you will gain new knowledge that would be useful in your daily work. We invite you to cooperate and submit your papers. We will be glad if you can share the results of your research and the use of innovative diagnostic and treatment methods with colleagues.

A.V. Burtsev, MD
Chief Editor of Genij Ortopedii

Original Articles

Case report

Literature review

Оригинальные статьи

Случай из практики

Обзор литературы

Original article
https://doi.org/10.18019/1028-4427-2024-30-1-7-17

Evaluation of the results of salvage surgical treatment of distal phalanx injuries and substantiation of the algorithm of finger salvage treatment

E.R. Kalita✉, I.V. Chmyrev, N.G. Gubochkin

Military Medical Academy named after S.M. Kirov, St. Petersburg, Russian Federation

Corresponding author: Ekaterina R. Kalita, kalita.ekaterina@yandex.ru

Abstract

Introduction The rates of hand injuries in the structure of total of injuries range from 30 to 50 % in recent decades. The improvement of approaches to the choice of optimal options for treatment of injuries of the distal phalanges of fingers that ensure the preservation of anatomical integrity and function of fingers remains relevant.

The purpose of the work was a comparative analysis of the clinical efficacy of various methods for surgical treatment of trauma to the distal phalanx of fingers.

Methods Forty-seven patients (18 men and 29 women, mean age 34.2 ± 13.3 years) with injuries to the distal phalanges of the fingers were examined and treated. The patients were divided into 2 groups. Group 1 (comparison) was 25 patients. Conventional approaches to the formation of finger stumps were used by shortening the bone part of the phalanx, forming two opposite flaps and applying several interrupted sutures; group 2 (main group) were 22 patients treated according to the surgical tactics developed by us. The proposed tactics of reconstructive plasty of the defects in the nail phalanges of three joint fingers involves the formation of a stump of the nail phalanx with a visual effect of elongation of the phalanx due to local or cross-plasty with dermo-fascial flaps. Comparison of treatment results in the groups of patients was performed 1, 3, 6, 12 months after reconstruction operations.

Results It was established that the use of the developed surgical treatment of the injury to the distal phalanx of the fingers results in less severity (compared to the use of standard methods) of pain on days 10-21 after surgery (by 44.8-54.3 %), lower levels of the Quick DASH indicators after 3-12 months, decrease in Vancouver scoring of skin scar severity changes after 6-12 months, higher patient satisfaction with the functional result of treatment. Based on the results obtained, a diagnostic and treatment algorithm for providing medical care to hand injuries has been proposed.

Discussion The results of the study indicate the effectiveness of the developed method of plastic surgery of fingertip defects of nail phalanges in the three joint fingers by moving the palmar-lateral and dorsal-lateral blood-supplied flaps from the fingers of the same name and neighboring fingers without shortening the bone stumps of the nail phalanges while achieving an esthetic result by visual lengthening of the fingertip phalanx. Based on the results obtained, a diagnostic and treatment algorithm for providing medical care to patients with finger injuries has been proposed.

Conclusion The proven method improves the results of reconstructive surgical interventions in the treatment of fingertip defects the of tnail phalanx in three joint fingers.

Keywords: finger injury, nail phalanx, end defect, skin flap plastic surgery, pain syndrome, skin scar

For citation: Kalita ER, Chmyrev IV, Gubochkin NG. Evaluation of the results of salvage surgical treatment of distal phalanx injuries and substantiation of the algorithm of finger salvage treatment. *Genij Ortopedii*. 2024;30(1):7-17. doi: 10.18019/1028-4427-2024-30-1-7-17

INTRODUCTION

The recent incidence of hand injuries in the total trauma ranges from 30 to 50 % [1-4]. Moreover, the rates of disability after hand injuries remain high [2, 5-7]. One of severe injuries is traumatic hand segment detachment and hand amputation in which the disability rates range 54-67 % [6, 8, 9].

A number of complications may develop after distal finger phalanx amputation, including long-term wound healing, hypersensitivity, sensation of pain, intolerance of cold, scar retraction, flexion contracture, chronic ulcers, infection and other disturbances [10-14]. The necessity of complex treatment that includes recovery of the desmo-myo-arthrogenic component is substantiated firstly by the importance of adequate repair of the dermogenic component since the normal function of the hand is possible only if skin is integral, especially its palmar (support) surface [3, 9, 15, 16]. However, the principles of choosing the tactics and methods of skin plasty surgery for distal finger phalanx injuries have been studies insufficiently while the data of the available literature have not been systematized and the general principles of management of such patients have not been well developed.

At present, a number of authors opine that the formation of the stump (including the one with some residual shortening) that is able to preserve some types of grasping and to optimize the terms of rehabilitation is the method of choice in traumatic destruction and amputation of finger phalanges [17-22].

Therefore, the improvement of approaches to the choice of optimal methods of skin plasty in patients with deep burns, extensive laceration wounds with bone exposure and post-burn deformities of the hand that would preserve anatomical integrity and functions of fingers has clinical relevance.

The **purpose** of the work was a comparative analysis of the clinical efficacy of various methods for surgical treatment of trauma to the distal phalanx of fingers.

MATERIALS AND METHODS

Forty-seven injured patients were examined and treated (18 males and 29 females) in the mean age 36.3 ± 14.2 year (range, 22 to 52 years) who were admitted to the clinic of thermal injuries of the Kirov Military Medical Academy with injuries of nail phalanges of fingers.

The patients were enrolled into two groups.

– Group 1 (comparison group) included 25 patients who were treated for trauma or thermal injury with standard methods of finger stump formation by shortening of the bony part of the phalanx, creation of the opposite flaps and applying several interrupted sutures.

– Group 2 (research) included 22 patients who were treated with the proposed surgical tactics comprising reconstruction plasty of soft-tissue structures of the nail phalanx that did not involve its bony component shortening.

Patients' groups matched in age and in morphological features of the distal injuries in three joint fingers.

Inclusion criteria were:

– вage from 18 to 50 years;

– post-traumatic fingertip defects of three joint fingers in acute, subacute and long-term periods after injuries.

Exclusion criteria were:

– decompensated somatic pathology;

– infection in the involved area;

– type 2 diabetes mellitus in sub- and decompenstion stage.

Patients with soft-tissue defect area less than 10 mm² were not included in the study as the wounds of such size may be covered through wound edge epithalization to restore the integrity of skin integuments.

Distribution of patients according to traumatic disease duration is given in Table 1. Twenty patients were injured several hours before admission and the rest 27 were injured: 9 patients not more than 24 hours prior to admission (19.1 %), 15 subjects up to 7 days (31.9 %), three individuals had trauma within 7 days to 1.5 months (6.4 %). There were significant differences in terms of fingertip trauma duration.

Table 1

Distribution of patients according to traumatic disease duration at admission

Injury term prior to admission for surgical treatment	Group 1 (comparison), *n* = 25		Group 2 (main research), *n* = 22	
	Abs. *n*	%	Abs. *n*	%
First hours post-injury	12	48.0	8	36.4
Up to 24 hours	5	20.0	4	18.2
From 1 to 7 days	7	28.0	8	36.4
From 7 days to 1.5 months	1	4.0	2	9.0

The clinical picture in the patients included in the study was determined by the factors of injury, thermal or mechanical. Burns as a trauma factor for finger partial soft-tissue loss was a factor in 11 cases (23.4 %), including 6 (27.3 %) in the research group and 5 (20.0 %) in the comparison group (Table 2).

Таблица 2

Распределение пациентов по повреждающим факторам травмы

Trauma factor	Group 1 (comparison), *n* = 25		Group 2 (main research), *n* = 22	
	Abs. *n*	%	Abs. *n*	%
Burns	5	20.0	6	27.3
Laceration	15	60.0	13	59.1
Crush wounds	5	20.0	3	13.6

Laceration and cut wounds were most frequent, in 28 patients (60.0 %), including 13 (59.1 %) in the main group and 15 cases (59.1 %) in the comparison group. Eight patients (17.0 %) referred with crush fractures of nail phalanges and soft-tissue crushing of varying severity including three cases (13.6 %) in the main research and five (20.0 %) in the comparison groups.

All patients underwent a radiographic study of the injured area.

High variability in the shape and size of injuries made planning of standard surgical interventions difficult. However, the approach proposed by us to surgical treatment of such patients was based on the principle of preservation of the nail phalanx bony part.

One more factor that affected the clinical stage of the study was varied vectors of phalanx detachment, and first of all, with matrix and nail plate base loss. There were three such patients in the whole sample (6.4 %); soft-tissue crushing was diagnosed in two cases of the main group (9.1 %) and in three patients of the comparison group (11.1 %). An oblique line of phalanx evulsion with preservation of a nail part (1-2 mm) and of nail matrix was seen in 9 cases of the main research group (40.9 %) and in 12 cases (54.5 %) of the comparison group.

Figure 1 shows an almost circular defect of the 5th finger and a preserved part of the nail phalanx and preserved nail plate. The fourth digit is intact.

The main objective in the use of the reconstruction plasty variant proposed for fingertip defects in the three-joint fingers that was proven by the treatment of the research group was a plasty of the nail phalanx defect with a visual effect of its lengthening. It is provided by local and cross plasty with faciocutaneous flaps. Tailoring of such flaps is defined by defect shape and sizes.

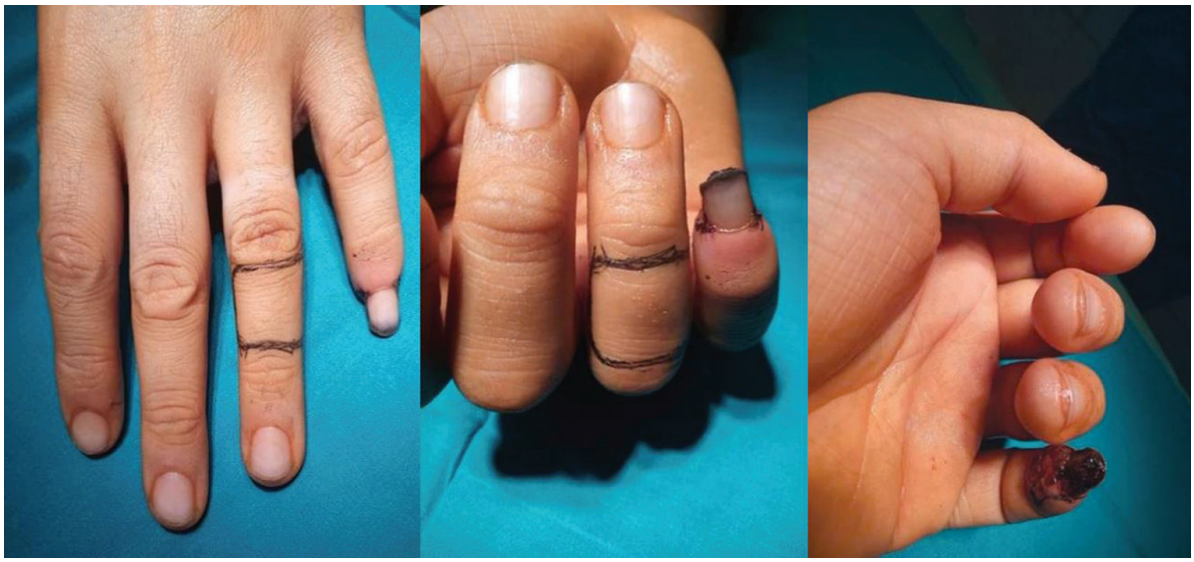

Fig. 1 Appearance of fingers 4 and 5 before surgery

The principle difference of such approach from the standard technique for finger stump formation is rejection to shorten the bony part of the nail phalanx, use of fasciocutaneous flap capable not only to cover the defect but also to visually lengthen the nail phalanx by a special tailoring of the flap shape.

The intervention was performed under combined anesthesia (conduction one with sedative support); skin, subcutaneous fat and superficial fascia were cut in the shape of rectangle, rhomb or racket-shaped. The complex of tissues in all three shapes was formed in such a way that enabled to include the transverse branch of the proper lateral palmar digital artery.

The blood-supplied fasciocutaneous flap formed was harvested with holders, turned towards the defect so that a small excess of tissues was available on the peripheral part of the transferred tissue complex to shape the fingertip. First two fixing stitches were done in the area of the nail matrix on its edges, the rest ones were

The plastic material was the skin of the elbow fold or of the axilla area in females and forearm skin in males. Such an approach hides the skin scar defect. The flap was harvested with electrical dermatom, the set thickness of the flap was 0.2-0.3 mm (thin flap). The donor site defect was sutured in a line and separation to 5-8 mm from the wound edges.

The size of the tissue complex depended on the defect size but did not exceed (36 ± 5) × (16 ± 3) mm for lateral flaps and (32 ± 3) × (15 ± 2) mm for rectangular and rhomb flaps.

Figure 2 shows the appearance after flap transfer from the 4th finger on the nail phalanx of the 5th digit. The donor site defect has not been closed yet.

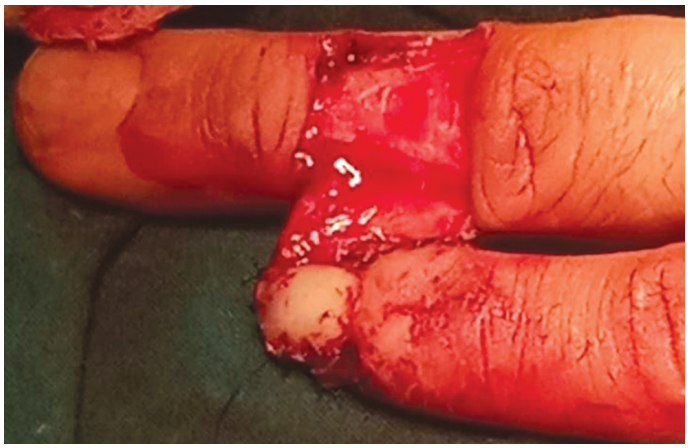

Fig. 2 The donor site defect before closure

The transferred tissue complex was fixed with independent interrupted sutures leaving long ends of stitches. Next, two layers of gauze napkins were applied. Several (5-7) premade small gauze balls were placed inside. The edges of the napkin were folded so as to form a compression dressing. It was fixed by pair-wise binding separate long stitches. The bandage tightly held the tissue complex and prevented it shift during 7-9 days, and then was removed.

Figure 3 shows stages of donor site defect closure with a split cutaneous flap (0.4 mm thick) harvested from the ipsilateral forearm. The integument tissues of the nail phalanx of the 5th finger were repaired. The support surface has a fasciocutaneos flap on the dorsal side of the 4th finger that is stable to loads.

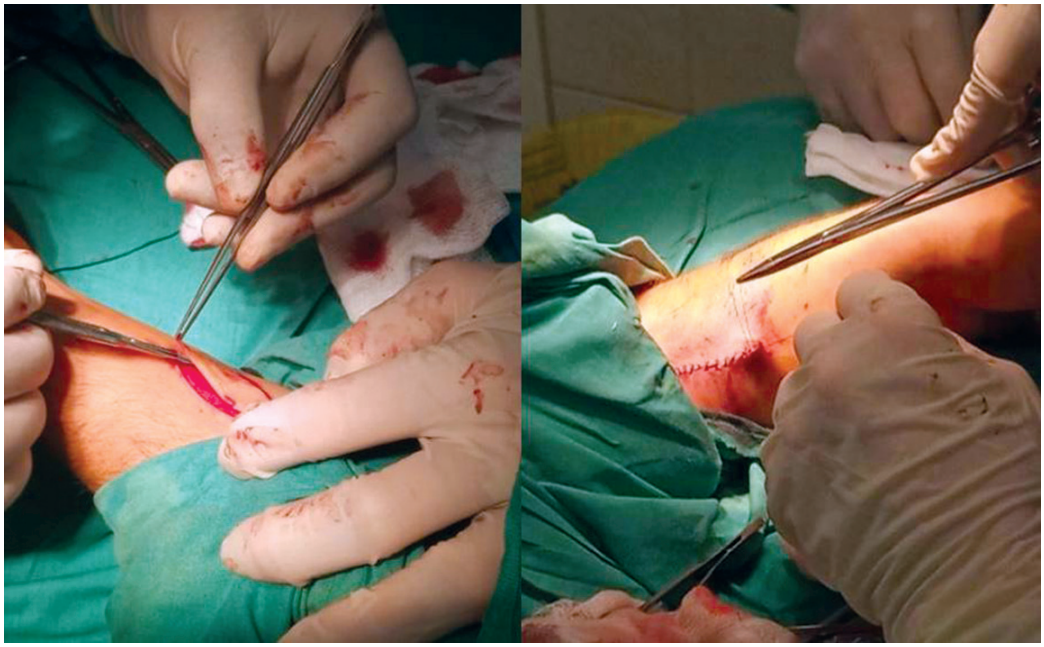

Fig. 3 Appearance of the donor site defect after surgery

An oblique U-shaped cut on the dorsal surface of the neighbor finger at the level of the middle phalanx was formed in such a way that it provided defect coverage and soft-tissue stock by turning the flap to the side of the recipient finger.

The recipient bed was prepared with a second cut; the edges of the fasciocutaneous defect were refreshed and if required 1-2 mm of the nail phalanx stump was resected. The rest of the nail phalanx was not resected.

Once stable blood flow in the fasciocutaneous flap had restored, its shaping continued until reasonable fingertip shape. If there were at least 1-2 mm of the nail plate, the distal part of the fasciocutaneous flap was stitched to it with 2-3 sutures of 4/0 thread.

The final stage of surgical intervention included applying anticeptic napkins, separation of adjoining fingers with cotton or gauze discs followed by plaster bandage for 18 to 21 days for fixation of the donor and recipient fingers for exclusion of occasional displacement. Once this term ended, the flap was cut to have final modeling which should be oriented by the shape of the nail phalanx of the neighboring finger (Fig. 4).

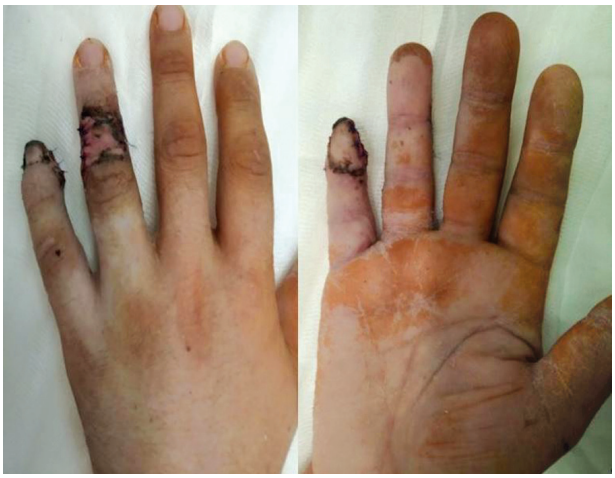

Fig. 4 Appearance of fingers 4 and 5 after the operation

Postoperative care of the patients followed general standards that foresee prophylactic administration of antibiotics and anticoagulants in the therapeutical doses for prevention of complications.

Medication therapy was performed to relieve pain; analgetics and vitamins were prescribed; local cooling bandages were used; the limb position was elevated to reduce swelling.

The specificity of the management was immobilization of the involved fingers and of the entire hand for a relatively long period (for 4-5 weeks). Immobilization was produced with a plaster cast or bandaging with currently used fixation materials (turbocast, cellacast, etc). The measures were directed to prophylaxis of blood flow disturbances in the transferred tissue complexes, creation of favourable conditions for qualitative survival of tissues on the wounded surface of the stump tip.

Once the wound healed, exercises to recover the range of motion were initiated, gradually increasing loading from finger flexion to holding 2-3 kg loads for three weeks. Long immobilization resulted in combined contractures of interphalangeal and metacarpal phalangeal joints but implemented the possibility of healing and remodeling of the tissue flaps without rough scars. The patients regularly trained to recover the range of motion in the finger joints that started straight upon completion of immobilization, continued with gradual increase in flexion range for one to two months.

As far as the patients of the study had different types of injuries, the treatment approaches also varied. In particular, one to three corrective operations were required to cover post-burn defects of finger integuments (elimination of flap fat, removal of excessive skin to shape the stumps) versus the trauma caused with cutting objects.

To analyze the results of treatment, the data of patients' examinations were compared in the early postoperative period and 3, 6 and 12 months after reconstruction interventions.

Postoperative pain severity was measured with a 10-point Visual Analogue Scale (VAS) on days 10 to 21. In the following terms, the functional state of the arm and hand was assessed in everyday life with DASH (Disability of the Arm, Shoulder and Hand) outcome measure.

Also, the presence and severity of skin scars in the area of surgical intervention were studied with modified Vancouver scar scoring scale (P1:scar type; P2:consistence; P3:colour; P4 scar sensitivity).

Statistical analysis of the study results was performed using Statsoft software packages STATISTICA 10 and Microsoft Excel 2016. Mean values with standard error of the mean were calculated, while qualitative parameters were presented as frequencies of occurrence of signs as a percentage of the total number of patients in the corresponding groups.

Intergroup comparisons on quantitative indicators were carried out using the nonparametric Mann – Whitney rank test in the case of a nonparametric distribution of indicator values and/or a significant difference in variances in the groups. To analyze differences in qualitative parameters, the chi-square test or Fisher's exact test was used. Differences were considered significant if p did not reach the threshold value of the statistical significance level of the null hypothesis (alpha) equal to 0.05.

RESULTS

Examination of the intervention area in the postoperative period showed that swelling and venous flow disturbance in the transferred flap tissues subsided within 7 to 9 days in the majority of patients. In most cases, flap survival was complete. Primary healing was achieved in all 22 patients of the main research group treated with the use of the method proposed by us. No complications were observed in the course of treatment. Sutures were removed on average after 12-14 days after the intervention. The bandage from the donor site was taken off after the same term. Flap excess dissection and final shaping of the soft-tissue complex was performed not earlier than 21 days after the operation that ensured the positive outcome of the treatment en general.

The analysis of pain in the early postoperative period showed that the VAS values did not differ in the groups on the first postoperative days but in the following days the pain value was significantly lower ($p < 0.05$) in the main group relative the corresponding values in the comparison group (Table 3).

Table 3

Dynamics of patients' subjective evaluation of pain severity in the involved and surgical intervention area in the early postoperative period (VAS points)

Post-surgery term	Group 1 (comparison), *n* = 25	Group 2 (main research), *n* = 22
1	8.4 ± 1.3	8.2 ± 0.8
7	6.5 ± 0.4	4.9 ± 0.6*
14	5.2 ± 0.3	3.3 ± 0.2*
21	3.9 ± 0.3	1.8 ± 0.4*

Note: * – significant differences (at p < 005) relative values in group 1 (comparison group) Mann – Whitney U-test

The evaluation of the Quick DASH indicators showed that its values before surgery and one months after surgery were similar but three months after and in the following terms after treatment the parameters of this scale in the main research group were significantly lower (p < 0.05) than in the comparison group (Fig. 5). Those data proved a higher functional result of the proposed by us treatment approach.

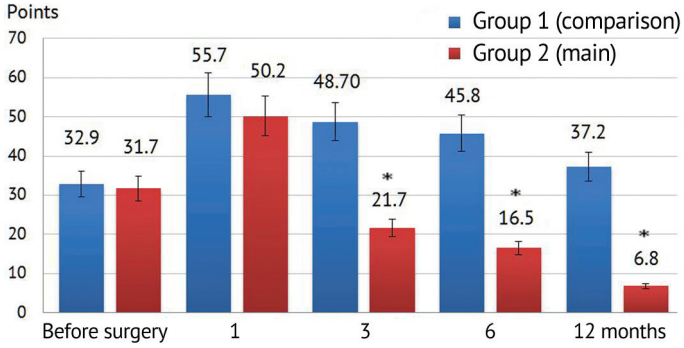

Fig. 5 Quick DASH dynamics, points (M ± m): * – significant differences (at p < 005) relative values in group 1 (comparison group) (Mann-Whitney test)

The analysis of subjective satisfaction of the patients with the results of treatment showed that there were more patients that estimated the results as "excellent" or "good" in the main group and the value was statistically higher (p < 0.05) than in the comparison group (Table 4). Moreover, there were 10 patients (40.0 %) that evaluated the treatment result as "poor" in this group while in group 2 there was only one patient (4.6 %) (p < 0.05).

Таблица 4

Распределение пациентов по степени удовлетворенности функциональным результатом проведенного лечения

Treatment results	Group 1 (comparison), *n* = 25	Group 2 (main research), *n* = 22	Group 1 (comparison), *n* = 25	Group 2 (main research), *n* = 22
	Abs. *n*	%	Abs. *n*	%
Excellent	–	–	**7**	**31.8***
Good	**5**	**20.0**	**11**	**50.0***
Fair	10	40.0	3	13.6
Poor	**10**	**40.0**	**1**	**4.6***

Notes: * – significant differences (at p < 005) relative values in group 1 (comparison group) in χ^2

It should be noted that the main reason of low subjective satisfaction with anatomical, functional and esthetic treatment results is residual asymmetry in comparison with the healthy fingers of the contralateral hand. Absence of bone fragment of the nail phalanx that could support soft tissue of the finger pad also caused lower satisfaction with treatment results in a number of patients. The proportion of such individuals among patients with defects of the fingertip stump, operated on in accordance with the proposed surgical approaches, was statistically lower than in the comparison group.

Skin scar changes were assessed six to 12 months after surgical treatment. Table 5 shows that the Vancouver scar score was statistically lower (p < 0.05) in the main research group than in the comparison group 6 months after treatment. After 12 months post-surgery, the expressiveness of objective components of that scale and values of subjective assessment reduced in most patients. The expressiveness of patients' proper attitude to residual defect of fingers also decreased. A more

expressed decrease in the Vancouver score was characteristic for patients of the main group. In that term of the study, the value of the parameter in the patients treated with the proposed by us method was statistically lower ($p < 0.05$) of the corresponding value of group 1.

Table 5

Dynamics of the Vancouver skin scar scoring, points, $M \pm m$

Post-surgery term	Group 1 (comparison), $n = 25$	Group 2 (main research), $n = 22$
6 months	6.13 ± 1.12	4.12 ± 0.38*
12 months	4.95 ± 0.87	2.43 ± 0.54*

Note: * – significant intergroup differences ($p < 0.05$) in comparison with the corresponding value of group 1 (Mann – Whitney criterion)

DISCUSSION

In general, the comparison of the results achieved in the studied groups showed higher (compared to conventional treatment methods) clinical efficiency of the proposed approach to surgical treatment of fingertip trauma that is based on the plasty of fingertip defects of the peripheral parts of three joint fingers relative to the results obtained in the comparison group.

The results of the study prove that the use of the surgical tactics proposed for the category of patients discussed provides improvement in the treatment results of the patients with injuries to the distal parts of three joint fingers associated with the loss of nail phalanx part and soft tissues of the finger pad.

The results obtained by us are consistent with the results reported in the studies of other authors [15, 16, 23-26]. Thus, Yildirim et al analyzed long-term functional and esthetic outcomes of homodigital neurovascular island flap of fingertip injuries in children when performing reconstruction of extensive pulp defects with bone range of motion, and total finger length over an average follow-up of 7.8 years (range, 2 to 13 years). Eleven patients exposure. Twenty-three children (mean age 4.8 years, range 1 to 10 years) with fingertip injuries underwent reconstruction using a single-digit pedicled flap. The authors assessed finger skin sensitivity, cold intolerance, scar formation, nail deformity, reported cold sensitivity in the operated fingertip, and 15 had a hooked nail deformity. The range of total active movements of the injured finger was significantly lower than that on the uninjured side ($p < 0.001$). However, the approach used in this work demonstrated an effective and reliable method of reconstructive treatment for fingertip injuries in children [15].

Schultz et al in their study, developed and tested a silicone cap that fits over the injured finger, creating a moist chamber surrounding the area of injury. The study analyzed data from patients with full-thickness fingertip injuries for whom simple primary closure of the defect was not possible; patients were randomized into 2 groups; the injured areas were either covered with a bandage or a silicone finger cap was used. The authors included 11 patients aged 2 to 72 years in each of two groups. All patients were satisfied with the cosmetic result of treatment, 88.9 % had no changes in the sensitivity of the skin of the fingers, and 73.7 % had no finger deformity. The duration of epithelization was from 5 weeks. There were no serious side effects observed with the means used in the work. The authors concluded that the tested approach is highly effective [16].

The results of our study confirm the success of the trial of the developed method of fingertip defect coverage of the nail phalanx of three joint fingers by transfer of palmar lateral and dorsal lateral blood supply flaps harvested from the ipsilateral and neighbor fingers without bone stump shortening of the nail phalanges with simultaneous esthetic effect due to visual lengthening of the fingertip phalanges. The obtained data allowed us to offer an algorithm of diagnostic and treatment measures in finger injuries that is presented in Figure 6.

We believe that the diagnosis of the injuries to the structures of the distal phalanx of three joint fingers should be based on the size and severity of injury to both soft tissues and bone component. Thereby, one should also assess the condition of boundary tissues with the level of detachment [23-28].

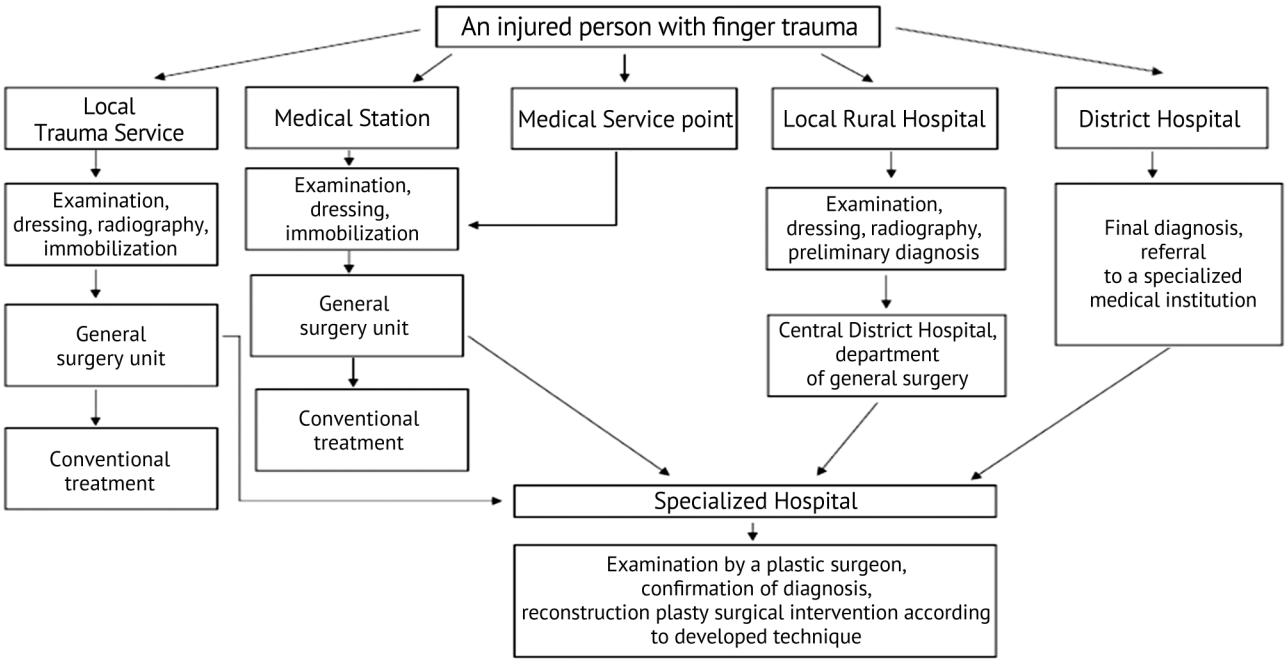

Fig. 6 Diagnosis and treatment algorithm of medical care delivery to injured persons with finger trauma

Crushed character of injuries may set doubt in the success of surgical treatment. In such case, economic primary surgical debridement of the wound and removal of nonviable tissues should be performed. A rich capillary net of the distal phalanx of fingers provides preservation of soft tissues that will be viable enough in 2 to 3 days if corresponding treatment is performed [29-33]. The base of final diagnosis that determines the severity of injuries to the studied structures should be the result of radiographic study that enables to reveal or exclude the presence of bone fragments and their connection with the proximal part of the phalanx bone [25, 34, 35]. If a free bone fragment is detected, it should be removed, as our experience showed, as its viability is minimal and could cause infection in the long term (osteomyelitis). If vascular pathology is detected, it should be treated to provide conditions for reconstructive plastic intervention [36-39].

CONCLUSION

The method for coverage of nail phalanx fingertip defects of fingers 2 to 5 has been developed. Its realization includes formation of a U-shaped cut on the dorsal surface of the neighboring finger at the level of the middle phalanx enabling to cover the defect and create excessive stock of soft tissues by producing the turn of the flap to the side of the recipient finger. The use of the developed method provides a lower (compared with the use of standard surgical treatment methods) pain severity on days 10-21 after the operation, lower values of Quick DASH after 3-12 months, reduction of Vancouver scar score after 6-12 months, higher patients' satisfaction with the results of treatment.

Conflict of interests *Absent.*
Funding source *Absent.*
Ethical approval *Ethical board approval was supplied.*
Informed consent *Not required.*

REFERENCES

1. Kawaiah A, Thakur M, Garg S, et al. Fingertip Injuries and Amputations: A Review of the Literature. *Cureus*. 2020;12(5):e8291. doi: 10.7759/cureus.8291
2. Berezutsky SN. Peculiarities of treatment of traumatic amputations of part of the distal phalanges of the fingers of the hand in children. *Pediatric Surgery*. 2022;26(1):23. (In Russ.)
3. Kokarev VA, Shalin VV. Traumas of hand fingers: amputation or arthroplasty? *Kremlin Medicine Journal*. 2022;(4):81-83. (In Russ.)

4. Malikov MKh, Artykov KP, Karim-Zade GD et al. Delayed reconstructive surgery for severe hand injuries. *Avicenna Bulletin*. 2022;24(3):404-412. (In Russ.) doi: 10.25005/2074-0581-2022-24-3-404-412
5. Petrushin AL. Traumatic hand amputations, the analysis of medical aid on different levels of rural healthcare. *Kazan Medical Journal*. 2013;94(3):327-334. (In Russ.)
6. Jerome JTJ, Malshikare VA. Fingertip Injuries Outcome Score. *Plast Reconstr Surg Glob Open*. 2022;10(6):e4386. doi: 10.1097/GOX.0000000000004386
7. Wang J, Zhou X, Qiang L, Xue M. Thumb fingertip injuries reconstruction using a dorsoulnar flap of the thumb combined with relay V-Y flaps for donor site repair. *J Orthop Surg* (Hong Kong). 2022;30(2):23094990211025089. doi: 10.1177/23094990211025089
8. Reid DBC, Shah KN, Eltorai AEM. et al. Epidemiology of finger amputations in the united states from 1997 to 2016. *J Hand Surg Glob Online*. 2019;1(2):45-51. doi: 10.1016/j.jhsg.2019.02.001
9. Wang K, Sears ED, Shauver MJ, Chung KC. A systematic review of outcomes of revision amputation treatment for fingertip amputations. *Hand* (N Y). 2013;8(2):139-45. doi: 10.1007/s11552-012-9487-0
10. Braga Silva J. Fingernail injury. *Hand Surg Rehabil*. 2023:S2468-1229(23)00027-0. doi: 10.1016/j.hansur.2023.01.002
11. Ng HJH, Yuan J, Rajaratnam V. Management of Fingertip Injuries: A Survey of Opinions of Surgeons Worldwide. *J Hand Microsurg*. 2020;14(1):64-70. German. doi: 10.1055/s-0040-1713072
12. James V, Heng TYJ, Yap QV, Ganapathy S. Epidemiology and Outcome of Nailbed Injuries Managed in Children's Emergency Department: A 10-Year Single-Center Experience. *Pediatr Emerg Care*. 2022;38(2):e776-e783. doi: 10.1097/PEC.0000000000002400
13. Woo SH, Kim YW, Cheon HJ, et al. Management of complications relating to finger amputation and replantation. *Hand Clin*. 2015;31(2):319-38. doi: 10.1016/j.hcl.2015.01.006
14. Samantaray SA, Oommen J, Thamunni CV, et al. Fingertip injury epidemiology: an Indian perspective. *J Plast Surg Hand Surg*. 2022;56(4):224-228. doi: 10.1080/2000656X.2021.1962332
15. Yildirim T, Gunturk OB, Erol K, Toros T. Long-term outcomes of homodigital neurovascular island flap reconstruction of fingertip injuries in children. *J Hand Surg Eur Vol*. 2022;47(8):845-850. doi: 10.1177/17531934221108470
16. Schultz J, Wruck JE, Trips E, et al. Semi-occlusive management of fingertip injuries with finger caps: A randomized controlled trial in children and adults. *Medicine* (Baltimore). 2022;101(27):e29324. doi: 10.1097/MD.0000000000029324
17. Pastor T, Hermann P, Haug L, et al. Semi-occlusive dressing therapy versus surgical treatment in fingertip amputation injuries: a clinical study. *Eur J Trauma Emerg Surg*. 2023;49(3):1441-1447. doi: 10.1007/s00068-022-02193-6
18. Koh SH, Park I, Kim JS, et al. Fingertip reconstruction with a subcutaneous flap and composite graft composed of nail bed and volar pulp skin. *Arch Plast Surg*. 2022;49(1):70-75. doi: 10.5999/aps.2021.01200
19. Mohsen I, Mahmoud M, Shaheen A. Modified Bilateral V-Y Rotation Advancement Flap for Coverage of Fingertip Amputations. *J Hand Surg Asian Pac Vol*. 2022;27(6):1013-1020. doi: 10.1142/S2424835522500977
20. Balde FB, Mukenge T, Benmassaoud Z, et al. Local or distal flap in the management of digital trauma in children. *Afr J Paediatr Surg*. 2022;19(1):5-8. doi: 10.4103/ajps.AJPS_56_21
21. Hao R, Wang H, Huo Y, et al. Fingertip degloving injury coverage with homodactyle bipedicled dorsal island flap. *Hand Surg Rehabil*. 2023;42(2):134-140. doi: 10.1016/j.hansur.2023.01.009
22. Yang S, Li Z. Finger-shaped dressing for fingers and toes after nail surgeries. *J Am Acad Dermatol*. 2023;88(2):e83-e84. doi: 10.1016/j.jaad.2019.07.020
23. Hunt TJ, Powlan FJ, Renfro KN, et al. Common Finger Injuries: Treatment Guidelines for Emergency and Primary Care Providers. *Mil Med*. 2023:usad022. doi: 10.1093/milmed/usad022
24. Xu J, Cao JY, Graham DJ, et al. Clinical Outcomes and Complications of Primary Fingertip Reconstruction Using a Reverse Homodigital Island Flap: A Systematic Review. *Hand* (N Y). 2023;18(2):264-271. doi: 10.1177/15589447211003179
25. Samantaray SA, Kalathingal K, Muhammed H. The Aesthetic Outcomes of Fingertip Amputation Are Better with Proximal Nail Fold Recession. *J Hand Surg Asian Pac Vol*. 2023;28(1):108-112. doi: 10.1142/S2424835523500054
26. Moellhoff N, Throner V, Frank K, et al. Epidemiology of hand injuries that presented to a tertiary care facility in Germany: a study including 435 patients. *Arch Orthop Trauma Surg*. 2023;143(3):1715-1724. doi: 10.1007/s00402-022-04617-9
27. Delle Femmine PF, Bruno E, Tosi D, et al. Reversed distal laterodigital adipofascial flap for nail-bed reconstruction. *Microsurgery*. 2023. doi: 10.1002/micr.31048
28. Ji Z, Nie R, Li S, et al. Clinical effects of resurfacing fingertip amputations in long fingers using homodigital dorsal neurofascial broaden pedicle island flaps. *J Plast Surg Hand Surg*. 2023;57(1-6):453-458. doi: 10.1080/2000656X.2022.2152825
29. Martin-Playa P, Foo A. Approach to Fingertip Injuries. *Clin Plast Surg*. 2019;46(3):275-283. doi: 10.1016/j.cps.2019.02.001
30. Neustein TM, Payne SH Jr, Seiler JG 3rd. Treatment of Fingertip Injuries. *JBJS Rev*. 2020;8(4):e0182. doi: 10.2106/JBJS.RVW.19.00182
31. Venkatesh A, Khajuria A, Greig A. Management of Pediatric Distal Fingertip Injuries: A Systematic Literature Review. *Plast Reconstr Surg Glob Open*. 2020;8(1):e2595. doi: 10.1097/GOX.0000000000002595
32. Golinvaux NS, Maslow JI, Hovis JP, Lee DH. Fingertip Injury and Management. *JBJS Essent Surg Tech*. 2019;9(3):e30. doi: 10.2106/JBJS.ST.19.00008
33. Mak WK, Cheah JM, Chua DT, et al. Outcomes of Surgically Treated Fingertip Injuries in Migrant Workers. *Ann Acad Med Singap*. 2020;49(6):405-407.
34. Gunasagaran J, Sian KS, Ahmad TS. Nail bed and flap reconstructions for acute fingertip injuries - A case review and report of a chemical burn injury. *J Orthop Surg* (Hong Kong). 2019;27(2):2309499019839278. doi: 10.1177/2309499019839278
35. Lam WL, Jordan D. Management of fingertip injuries in Scotland and the United Kingdom. *J Hand Surg Eur Vol*. 2019;44(10):1102-1105. doi: 10.1177/1753193419873555

36. Zhang JF, Wang L, Hao RZ, et al. Treatment of fingertip avulsion injuries using two periposition pedicled flaps. *J Plast Reconstr Aesthet Surg*. 2019;72(4):628-635. doi: 10.1016/j.bjps.2018.12.051
37. Tang JB. Fingertip repair methods: choices for different fingers and sides emphasizing sensation. *J Hand Surg Eur Vol*. 2019;44(10):1109-1111. doi: 10.1177/1753193419876496
38. Petrella G, Tosi D, Sapino G, Adani R. Fingertip defect reconstruction with a modified pivot flap. *J Hand Surg Eur Vol*. 2021;46(1):75-79. doi: 10.1177/1753193420956320

The article was submitted 03.05.2023; approved after reviewing 05.06.2023; accepted for publication 01.12.2023.

Information about the authors:

Ekaterina R. Kalita – postgraduate student, kalita.ekaterina@yandex.ru, https://orcid.org/0009-0000-8794-6656;
Igor V. Chmyrev – Doctor of Medical Sciences, Associate Professor, Head of the Department, chmyrev@mail.ru;
Nikolay G. Gubochkin – Doctor of Medical Sciences, Associate Professor, gubochkin_vto@mail.ru.

Contribution of the authors:

Kalita E.R. – research and writing.
Chmyrev I.V. – data processing, visualization and control.
Gubochkin N.G. – conceptualization and methodology.

Original article
https://doi.org/10.18019/1028-4427-2024-30-1-18-27

Isometry as a predictor of osteosynthesis result in fractures of the posterior acetabulum

A.G. Galkin✉, D.A. Shavyrin, V.P. Voloshin, S.A. Oshkukov, A.A. Glazkov, A.A. Ustinov

Moscow Regional Research and Clinical Institute, Moscow, Russian Federation

Corresponding author: Anatoly G. Galkin, doc_tol@mail.ru

Abstract

Introduction More than 80% of injuries to the acetabulum involve its posterior parts or injuries associated with their destruction. Most poor outcomes of surgical treatment of acetabular fractures manifest themselves in the first 24 months. Surgeons consider accurate anatomical reduction of fragments to be the main predictor of good results. A number of researchers showed good results of its surgical treatment, including those with inaccurate reduction. Poor results also occur in patients with no risk factors and ideal reduction. Thus, inaccurate reduction does not always lead to poor results; the reasons for positive results have not been discussed.

Purpose To evaluate the effect of maintaining hip joint isometry in surgical approach on the outcome of reconstructive operations in the treatment of traumatic destruction of the posterior parts of the acetabulum.

Materials and methods From 2005 to 2021, surgeons from the Moscow Regional Research and Clinical Institute performed 120 reconstructive operations on 120 patients with fractures of the posterior structures of the acetabulum. Of these, 84 patients followed the recommended monitoring regimen, completed the Harris Questionnaire, and had radiographs taken within the specified time frame. From the 84 patients, two groups of 42 patients each were formed that differed in the method of treating the external rotators.

Results During two years of follow-up after reconstructive surgery on the acetabulum, clinical indications for hip replacement were identified or hip replacement was performed in 5 patients in the first group and in 25 patients in the second (11.9 and 59.5%, respectively).

Discussion Accurate reduction of fragments is considered to be the main condition for good results after reconstructive operations for fractures of the posterior part of the acetabulum. Maintaining the isometry in the joint, namely, cutting off and then reinserting external rotators while preserving the attachment sites and length of the muscles, can have a significant impact on the outcome of reconstructive operations for traumatic injuries of the posterior parts of the acetabulum due to maintaining isometry of the hip joint. It seems that the preservation of force vectors centering the femoral head in the acetabulum causes the growth of ossification that forms secondary congruence.

Conclusions Maintaining hip joint isometry in surgical treatment of fractures of the posterior acetabulum by changing the method of treating the external rotators provides significantly better clinical outcomes.

Keywords: acetabulum fracture, osteosynthesis, joint arthroplasty, Kocher – Langenbeck approach, modification

For citation: Galkin AG, Shavyrin DA, Voloshin VP, et al. Isometry as a predictor of osteosynthesis result in fractures of the posterior acetabulum. *Genij Ortopedii*. 2024;30(1):18-27. doi: 10.18019/1028-4427-2024-30-1-18-27

INTRODUCTION

Treatment results of acetabular fractures still may result in dissatisfaction.

More than 80 % of injuries to the acetabulum occur in its posterior parts or injuries associated with their destruction [1, 2]. The most common causes of poor outcomes are the progression of post-traumatic coxarthrosis and avascular necrosis of the femoral head (ANFH) [1, 2].

Most poor outcomes of surgical treatment of acetabular fractures manifest themselves in the first 24 months. Thus, of the total outcomes in ANFH, more than 72 % of cases are diagnosed in the first two years [3]. Of the total number of patients with coxarthrosis that develops in the postoperative period, 87 % were diagnosed in the first 24 months [3]. According to a meta-analysis, osteoarthritis in stages 3 and 4 develops in more than 19 % of patients [1]. According to literature sources, of the total number of conversions to arthroplasty, 79 % happen within the first two years [4]. Thus, the analysis of poor outcomes in the first two years of the postoperative period is an objective way of assessing the results of surgical treatment.

The risk of conversion to arthroplasty after an acetabular fracture, depending on the type of fracture, is 27 % for transverse fractures of a posterior wall fracture, 23 % for T-shaped fractures, 15 % for posterior column and posterior wall fractures, and 12 % for isolated posterior wall fractures [4, 5, 6].

Most researchers assess the results of patients who were operated on in the first 10-14 days after injury [1, 5, 6, 7], as the results tend to worsen with increasing time the injury [2]. A growth in poor outcomes with age of patients has been noted [8]. Age over 46 years old leads to conversion to arthroplasty in 25.7 % of cases, while all patients in the reported study underwent surgical treatment within the first two weeks after injury [8]. Many authors note that the comminuted nature of the fracture results in poor outcomes more frequently [5, 7]. Thus, the analysis of the results of surgical treatment of acetabular fractures identified three main risk factors: the injury is more than three weeks old, the fracture is comminuted, and the patient's age is over 45 years.

Due to risk factors, the failure rate of reconstructive operations may exceed 50 % [9]. In their absence and precise reduction, negative outcomes are approximately 20 % [10]. Surgeons consider accurate anatomical reduction of fragments to be the main predictor of good results [11, 12]. In such cases, the progression of coxarthrosis was 13.2 % [1]. However, in mal-reduction, the probability of coxarthrosis was 43.5 % [1]. E Letournel analyzed the data of 1000 patients with fractures of the acetabulum and identified post-traumatic arthrosis in less than 5 % of cases when anatomical reduction was achieved, and in more than 60 % in cases with mal-reduction [2, 13, 14]. At the same time, an analysis of the results of treatment of 350 injured showed good outcomes of early surgical treatment in 83 % of patients. Thus, it was shown that surgical intervention in the early stages after injury significantly improves treatment results, provided there is good reduction and reliable fixation of bone fragments [1, 2]. Moreover, a number of researchers have shown good results of surgical treatment, including those with inaccurate reduvtion [1, 8, 15]. On the contrary, poor results are often found in patients with no risk factors and ideal reduction [15]. Thus, inaccurate reduction does not always lead to poor results, and the reasons for positive results have not been discussed.

The most common approach for surgical treatment of injuries to the posterior parts of the acetabulum is the Kocher – Langenbeck approach [1], which is also used in hip arthroplasty [16].

We analyzed data from the literature on the use of the Kocher – Langenbeck approach both for fractures of the posterior acetabulum and for hip replacement in order to identify possible common causes of failures.

The main disadvantage of the Kocher – Langenbeck approach for hip replacement is the increased risk of posterior dislocation of the endoprosthesis [17, 18]. This is due to the fact that the standard Kocher – Langenbeck approach involves the intersection of the external rotators (piriformis and triceps muscles) at the point of transition to the tendon part, followed by their end-to-end reinsertion [19, 20]. There are studies that show the low stability potential of this reinsertion method. The failure of rotators with this method of reinsertion, according to researchers, exceeded 70 % [20, 21, 22]. This was the reason for searching and using other methods of refixation of external rotators in arthroplasty.

Based on the literature data indicating a reduction in the risk of endoprosthesis dislocation by changing the method of treating external rotators in the Kocher – Langenbeck approach [16, 17, 18, 23], we made the assumption that the reasons for the increased risk of endoprosthesis dislocation during primary hip replacement using the posterior approach and poor results of reconstructive operations for fractures of the posterior structures of the acetabulum may be identical. That is, failure of the short rotator sutures and/or changes in the site of their reinsertion can lead to disorders in the centering of the femoral head in the acetabulum, thus creating areas of overload of the articular surfaces of the acetabulum and femoral head. This, in turn, may be a starting mechanism for rapid degeneration of cartilage or a cause of impaired blood supply to bone tissue in the overload zone.

The method of treating external rotators using the Kocher – Langenbeck approach with the subsequent failure of the rotator sutures may cause negative results due to changes in the hip joint isometry.

Purpose: to evaluate the effect of maintaining hip joint isometry in surgical approach on the outcome of reconstructive operations in the treatment of traumatic destruction of the posterior parts of the acetabulum.

MATERIALS AND METHODS

Between 2005 and 2021, the surgeon of the orththopaedic department at the Moscow Regional Research and Clinical Institute performed 120 reconstruction operations for fracrures of the posterior structures of the acetabulum. Among them, 84 patients followed the recommended regime of follow-up, filled in the Harris questionnaire and took radiographs at appointed time-points. The criteria for inclusion in the study were age from 18 to 80 years, radiological confirmation of injury to the posterior parts of the acetabulum, the ability to evaluate clinical and radiological results according to the examination schedule (after 3 months, one year and two years). Exclusion criteria were patient's absence or unwillingness to participate in the study, inability to complete the prescribed clinical and radiographic examinations.

In the preoperative period, the injured had radiographs of the pelvis in the direct projection; the injured hip joint was examined in the oblique obturator and iliac projections. A mandatory condition was an RCT examination to assess the nature of the fracture and bone tissue destruction.

In the postoperative period, radiographs in the direct projection were assessed three months, one year and two years after surgical treatment. After one year and two years after surgery, each patient completed the Harris Questionnaire, both if the outcome was good and if the patient had undergone hip replacement. The period for filling out the questionnaire after arthroplasty could exceed 2 years, which is associated with the need for rehabilitation after surgery.

A retrospective analysis of the results of reconstructive operations in the posterior parts of the acetabulum after their traumatic destruction in the first two years after surgery was performed.

Statistical analysis was performed in RStudio 2022.07.2 (RStudioPBC). Since the distribution of most quantitative variables was non-normal, non-parametric methods were used in the analysis. To describe quantitative variables, medians and quartiles (Me [LQ; UQ]) were calculated; to describe qualitative variables, absolute (n) and relative (%) frequencies were calculated. Comparisons of quantitative variables in independent samples were performed using the Mann – Whitney test; quantitative variables were compared using the Chi-square test or Fisher's exact test. A two-factor analysis of the influence of the type of approach (group) and duration of injury on the probability of arthroplasty was carried out using a logistic regression model. The level of error of the first type (α) was taken equal to 0.05. Null hypotheses were rejected at $p < 0.05$.

The groups were formed according to the principle of approach to the acetabulum.

Group 1 were patients who underwent a modified Kocher – Langenbeck approach with cutting off the rotators from the place of their attachment to the greater trochanter and reinserting them to the maternal bed through pre-formed canals in the greater trochanter in the area of their initial attachment ($n = 42$).

Group 2 were patients who underwent the Kocher – Langenbeck approach with standard end-to-end reinsertion of external rotators (n = 42).

In both groups, the majority of patients were under 45 years of age. The groups turned out to be absolutely identical in terms of gender composition. There were 20 patients with comminuted fractures in the first group and 22 in the second group (Table 1).

Table 1

Characteristics of patients included in the study

Parameter		Group 1 (n = 42)		Group 2 (n = 42)		p value
		abs. n	%	abs. n	%	
Age	Under 45 years	26	61.9	28	66.7	0.82[a]
	Over 45 years	16	38.1	14	33.3	
Type of injury	Posterior wall	19	45.2	18	42.9	1[b]
	Posterior column	1	2.4	1	2.4	
	Posterior wall + posterior column	7	16.7	7	16.7	
	Both columns	7	16.7	8	19	
	Both columns + posterior wall	8	19	8	19	
Gender	Male	40	95.2	35	83.3	0.156[b]
	Female	2	4.8	7	16.7	
Comminuted fracture	1-2 fragments	20	47.6	22	52.4	0.827[a]
	3+ fragments	22	52.4	20	47.6	
Injury duration	Less than 3 weeks	30	71.4	13	31	< 0.001[a]
	3 weeks and more	12	28.6	29	69	

[a] – Mann – Whitney test, [b] – Fisher's exact test

Both groups were similar in regard to injury patterns.

The main difference between the groups was the duration of the injury (Table 1). The difference in the number of patients in these groups is due to the fact that in the second group, the operation in the majority of cases (35 subjects) was performed in the conditions of the Moscow Regional Research and Clinical Institute, and the delay was associated with the transfer of the patient from a medical facility in the Moscow region. In the first group, the operations were performed on 32 subjects at a medical facility in the Moscow region by a visiting specialist from the Moscow Regional Research and Clinical Institute.

In both groups, no purulent complications were noted, with the exception of 3 cases of superficial inflammation, which was quickly arrested.

RESULTS

During a two-year follow-up after reconstruction surgery on the posterior acetabulum, hip arthroplasty due to clinical indications for arthroplasty was performed in 5 patients in group 1 and 25 patients in group 2, accounting for 11.9 and 59.5 %, respectively. However, there was a pronounced imbalance in the duration of injury in the groups, which required additional analysis of the results.

Table 2

Functional results of reconstructive operations in patients of groups 1 and 2

Parameter		Group 1 (n = 42)	Group 2 (n = 42)	p value
		Me [*LQ*; *UQ*], *min-max*		
Harris Hip Score at 1 year		83 [79; 87]. 51-91	60.5 [56; 84]. 45-91	0.002[a]
Harris Hip Score at 2 years		87 [85.2; 90]. 81-94	86 [83.2; 89.8]. 75-93	0.122[a]
Harris Hip Score dynamics 2-1 year		3.5 [2; 6.8]. -3-35	23.5 [5; 27.8]. -5-40	< 0.001[a]
THA	No THA, n (%)	37 (88.1)	17 (40.5)	< 0.001[b]
	THA, n (%)	5 (11.9)	25 (59.5)	

[a] – Mann – Whitney test, [b] – Chi-square test

Table 2 shows the obvious negative dynamics of the results of reconstructive operations during the first year in group 2 and the leveling of the results in both groups after hip replacement for negative outcomes of reconstructive operations. It should be noted that there is a significant difference in conversion to arthroplasty in the groups: 11.9 % in group 1 and 59.5 % in group 2 (Fig. 1).

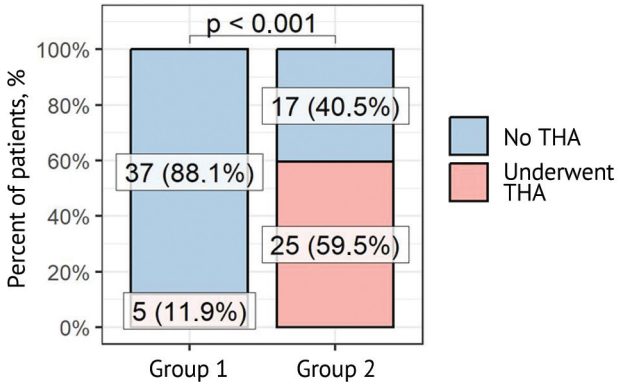

Fig. 1 Patients that needed THA in groups 1 and 2

Analysis of the dynamics of functional treatment results of patients in need of THA and patients satisfied with the results of reconstructive operations is shown in Tables 3, 4 and Figure 2.

Table 3

Functional results of reconstructive operations in patients that needed THA

Parameter	Group 1 (n = 5)	Group 2 (n = 25)	Value p[a]
	Me [*LQ*; *UQ*], *min-max*		
Harris Hip Score at 1 year	57 [53; 59], 51-61	57 [53; 59], 45-63	0.889
Harris Hip Score at 2 years	87 [86; 88], 86-90	84 [83; 86], 75-91	0.023
Harris Hip Score dynamics 2-1 year	29 [29; 34], 29-35	27 [24; 30], 19-40	0.111

[a] – Mann – Whitney test

Table 4

Functional results of reconstructive operations in patients that did not need conversion to THA

Parameter	Group 1 (n = 37)	Group 2 (n = 17)	Value p[a]
	Me [*LQ*; *UQ*], *min-max*		
Harris Hip Score at 1 year	84 [81; 88], 68-91	86 [84; 89], 78-91	0.176
Harris Hip Score at 2 years	87 [85; 91], 81-4	90 [88; 91], 76-93	0.127
Harris Hip Score dynamics 2-1 year	3 [2; 5], -3-17	4 [1; 5], -5-8	0.829

[a] – Mann – Whitney test

Fig. 2 Comparison of Harris Hip Scale in the patients of two groups that needed (a) and did not need (b) THA

The analysis of the characteristics of the groups included in the study revealed statistically significant differences in the duration of injury in patients of both groups (Table 5). Since this could theoretically have an impact on the rate of conversion to arthroplasty, it was decided to conduct

a two-factor analysis with the construction of a logistic regression model. After including the factor of injury duration, the type of approach retained a significant effect on the likelihood of arthroplasty, so we can assume that the type of approach is a predictor independent of how long the injury was.

Table 5

Results of a two-factor analysis of the influence of injury duration and group on the frequency of THA in patients

Parameter		Odds ratio (OR)	95 % CI	*p* value
Duration of injury	Less than 3 weeks	–	–	
	3 weeks and more	2.83	0.95; 8.73	0.064
Group 1		–	–	
Group 2		7.92	2.61; 27.7	< 0.001

Conversion to THA in the standard Kocher – Langenbeck approach happened in 20 out of 29 patients with an injury duration of more than three weeks, which was 69 %. In a modified approach, it was in 2 out of 12 cases, which corresponds to 16.7 %.

In group 1 of patients with a comminuted fracture, arthroplasty was performed in 18.2 % of cases, in group 2 – in 90 % (Fig. 3).

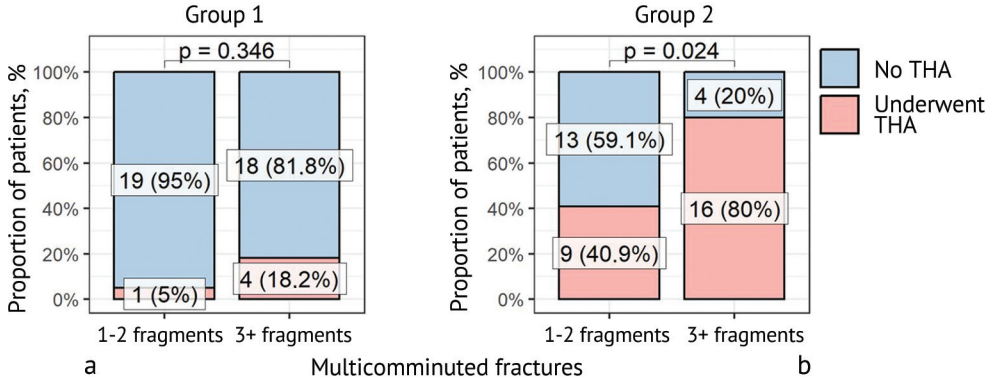

Fig. 3 Proportion of patients in need of THA in multi-comminuted and not multi-comminuted injury in group 1 (a) and group 2 (b)

The majority of patients in group 2 over 45 years of age (12 out of 14, accounting for 85.7 %) required hip replacement; in group 1, it was necessary in 18.75 %.

It should be noted that patients in group 2 were mostly over 45 years old and had comminuted fractures. It is important that the duration of injury in patients in group 2 in most cases exceeded 3 weeks.

The results of reconstructive operations in regard to the injury pattern differed significantly in groups 1 and 2. The largest number of poor outcomes in group 1 occurred in the injuries to the posterior wall, in 4 out of 19; one case out of eight with injury to the posterior wall and posterior column (Table 6). In group 2, the greatest number of failures was observed in patients with posterior wall injury, 13 out of 18 and in combined injuries to the posterior wall and posterior column; 2 out of 8 in posterior column injury, 5 out of 8 in injuries to both columns and the posterior wall (Table 6).

Table 6

Conversion to THA due to injury pattern

Type of injury	Number of operations			
	Group 1, conversion to THA		Group 2, conversion to THA	
	total (*n*)	failure (*n*)	total (*n*)	failure (*n*)
Posterior wall	19	4	18	13
Posterior column	1		1	
Posterior wall + posterior column	6		7	5
Both columns	8		8	2
Both columns + posterior wall	8	1	8	5

A clinical case of surgical treatment outcome in a patient with fractures of both columns and posterior wall of the acetabulum that were treated with a modified approach

Patient I, born in 1979, sustained trauma in a road accident and was operated in 2014.

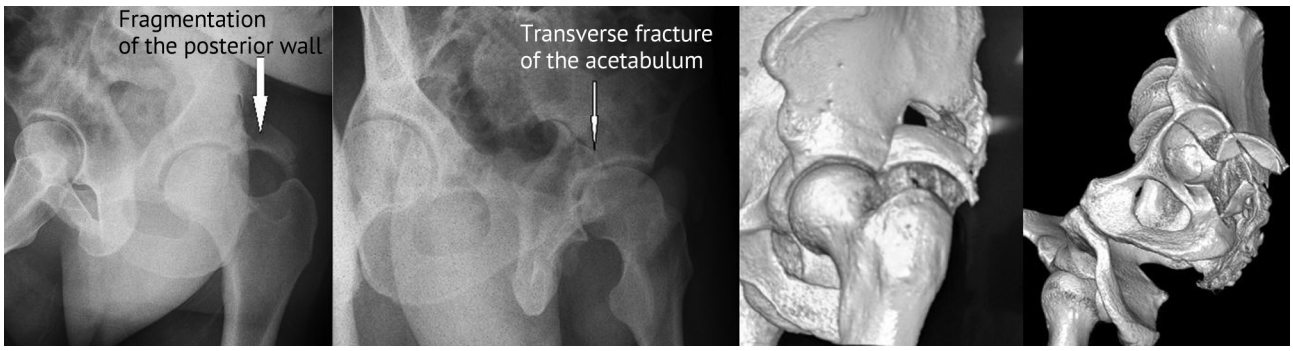

Fig. 4 Transverse fracture of the acetabulum and a comminuted fracture of the posterior wall

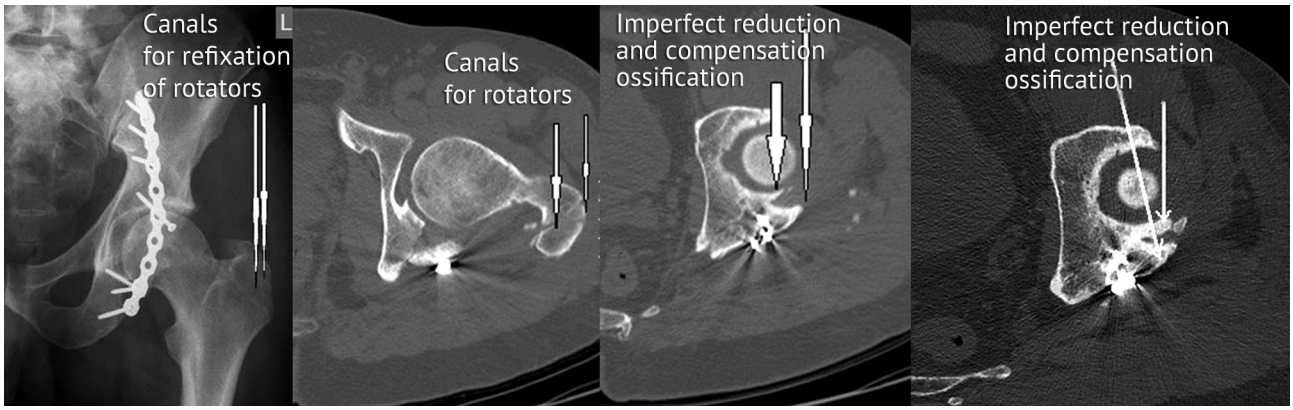

Fig. 5 Canals in the greater trochanter for refixation of short rotators. Ossifications resulting from imperfect reduction, compensating for the articular surface

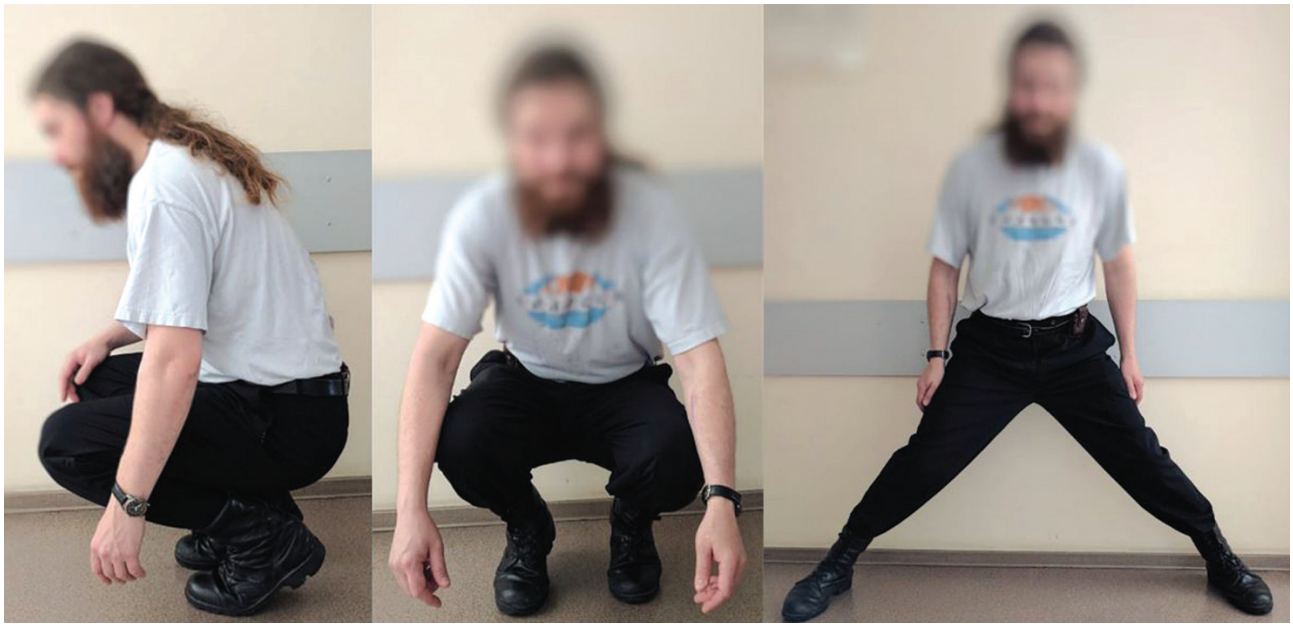

Fig. 6 Patient's photo 2 years after the operation; functional outcome

The patient is in contact and is satisfied with the result.

DISCUSSION

It is known that the main condition for a good result in intra-articular fractures is accurate reduction of fragments [11, 12]. However, it has been shown that a residual displacement of even 6 mm between the fragments results in a good surgical treatment outcome in an intra-articular fracture, provided that this is a displacement in width, that is, a fissure-like displacement between the fragments [24]. A step-like displacement leads to the development of arthrosis [24]. There is no change in the area of the articulating surface if bone is translated in width; in a step-like displacement, the load is concentrated on a smaller surface area.

A number of authors point to the relationship of the magnitude of contact stress between articular surfaces with the development of arthrosis in post-traumatic defects of the articular surface [25, 26]. It has been proven that an increase in contact stress leads to cartilage degeneration [26], that is, the concentration of load on a limited area leads to the progression of post-traumatic arthrosis. The role of the location of the load axis on the formation of excess stress and, as a consequence, cartilage degeneration has also been confirmed [24].

In the standard Kocher – Langenbeck approach, the probability of rotator suture failure exceeds 70 % [20]. The incompetence of the posterior rotators causes a violation of isometry in the hip joint due to inability to antagonize the anterior rotators. As a result, the centering of the femoral head in the acetabulum is violated. This phenomenon can lead to concentration of the contact stress between the articular surfaces even under the conditions of anatomical reduction.

Most studies [1, 2, 11, 12] show that the main reason for failure is an inaccurate reduction of fragments. Almost all authors indicate that residual displacement leads to an increased risk of post-traumatic coxarthrosis. However, the researchers do not explain a phenomenon of a good result in residual displacement of fragments.

We believe that maintaining isometry in the joint, namely, cutting off and reinserting the external rotators while preserving the attachment sites and the length of the muscles, may significantly influence the outcome of reconstructive operations in the treatment of traumatic injuries of the posterior structures of the acetabulum due to maintaining isometry of the hip joint. It is likely that the preservation of force vectors centering the femoral head in the acetabulum causes the growth of ossifications that form secondary congruity.

CONCLUSION

The results obtained show that surgical treatment of acetabular fractures using a modified approach allows for significantly better clinical results in both patients with and without risk factors.

Conflict of interest *Not declared*

Funding *Not declared.*

Ethical expertise *Not required.*

Informed consent *Signed during hospitalization in a hospital within the framework of compulsory medical insurance.*

REFERENCES

1. Giannoudis PV, Grotz MR, Papakostidis C, Dinopoulos H. Operative treatment of displaced fractures of the acetabulum. A meta-analysis. *J Bone Joint Surg Br*. 2005;87(1):2-9. doi: 10.1302/0301-620X.87B1.15605
2. Letournel E. The treatment of acetabular fractures through the ilioinguinal approach. *Clin Orthop Relat Res*. 1993;(292):62-76.
3. Pavelka T, Salášek M, Bárta P, et al. Avascular Necrosis of Femoral Head and Coxarthrosis Progression after Acetabular Fractures. *Acta Chir Orthop Traumatol Cech*. 2019;86(6):381-389.

4. Cichos KH, Spitler CA, Quade JH, et al. Fracture and Patient Characteristics Associated With Early Conversion Total Hip Arthroplasty After Acetabular Fracture Fixation. *J Orthop Trauma*. 2021;35(11):599-605. doi: 10.1097/BOT.0000000000002083
5. Zhi C, Li Z, Yang X, Fan S. Analysis of result and influence factors of operative treatment of acetabular fractures. *Zhongguo Xiu Fu Chong Jian Wai Ke Za Zhi*. 2011;25(1):21-25.
6. Gänsslen A, Frink M, Hildebrand F, Krettek C. Both column fractures of the acetabulum: epidemiology, operative management and long-term-results. *Acta Chir Orthop Traumatol Cech*. 2012;79(2):107-113.
7. Gänsslen A, Hildebrand F, Kretek C. Transverse + posterior wall fractures of the acetabulum: epidemiology, operative management and long-term results. *Acta Chir Orthop Traumatol Cech*. 2013;80(1):27-33.
8. Firoozabadi R, Hamilton B, Toogood P, et al. Risk Factors for Conversion to Total Hip Arthroplasty After Acetabular Fractures Involving the Posterior Wall. *J Orthop Trauma*. 2018;32(12):607-611. doi: 10.1097/BOT.0000000000001327
9. Ankin LN, Ankin NL. *Practice of osteosynthesis and arthroplastyc*. Kyiv: Production edition; 1994:258-284.
10. Morison Z, Moojen DJ, Nauth A, et al. Total Hip Arthroplasty After Acetabular Fracture Is Associated With Lower Survivorship and More Complications. *Clin Orthop Relat Res*. 2016;474(2):392-398. doi: 10.1007/s11999-015-4509-1
11. Mayo KA, Letournel E, Matta JM, et al. Surgical revision of malreduced acetabular fractures. *Clin Orthop Relat Res*. 1994;(305):47-52.
12. Pohlemann T, Tscherne H, Baumgärtel F, et al. Pelvic fractures: epidemiology, therapy and long-term outcome. Overview of the multicenter study of the Pelvis Study Group. *Unfallchirurg*. 1996;99(3):160-167.
13. Giannoudis PV, Grotz MR, Papakostidis C, Dinopoulos H. Operative treatment of displaced fractures of the acetabulum. A meta-analysis. *J Bone Joint Surg Br*. 2005;87(1):2-9.
14. Perry DC, DeLong W. Acetabular fractures. *Orthop Clin North Am*. 1997;28(3):405-417. doi: 10.1016/s0030-5898(05)70298-4
15. Murphy D, Kaliszer M, Rice J, McElwain JP. Outcome after acetabular fracture. Prognostic factors and their inter-relationships. *Injury*. 2003;34(7):512-517. doi: 10.1016/s0020-1383(02)00349-2
16. McLawhorn AS, Potter HG, Cross MB, et al. Posterior Soft Tissue Repair After Primary THA is Durable at Mid-term Followup: A Prospective MRI Study. *Clin Orthop Relat Res*. 2015;473(10):3183-3189. doi: 10.1007/s11999-015-4380-0
17. Kunutsor SK, Barrett MC, Beswick AD, et al. Risk factors for dislocation after primary total hip replacement: meta-analysis of 125 studies involving approximately five million hip replacements. *Lancet Rheumatol*. 2019;1(2):e111-e121. doi: 10.1016/s2665-9913(19)30045-1
18. Robinson RP, Robinson HJ Jr, Salvati EA. Comparison of the transtrochanteric and posterior approaches for total hip replacement. *Clin Orthop Relat Res*. 1980;(147):143-147.
19. Gänsslen A, Grechenig S, Nerlich M, Müller M. Standard Approaches to the Acetabulum Part 1: Kocher-Langenbeck Approach. *Acta Chir Orthop Traumatol Cech*. 2016;83(3):141-146.
20. Kao JT, Woolson ST. Piriformis tendon repair failure after total hip replacement. *Orthop Rev*. 1992;21(2):171-174.
21. Stähelin T, Vienne P, Hersche O. Failure of reinserted short external rotator muscles after total hip arthroplasty. *J Arthroplasty.* 2002;17(5):604-607. doi: 10.1054/arth.2002.32187
22. Stähelin T, Drittenbass L, Hersche O, et al. Failure of capsular enhanced short external rotator repair after total hip replacement. *Clin Orthop Relat Res*. 2004;(420):199-204. doi: 10.1097/00003086-200403000-00028
23. Bottner F, Pellicci PM. Review: posterior soft tissue repair in primary total hip arthroplasty. *HSS J*. 2006;2(1):7-11. doi: 10.1007/s11420-005-0134-y
24. Rosteius T, Rausch V, Pätzholz S, et al. Factors influencing the outcome after surgical reconstruction of OTA type B and C tibial plateau fractures: how crucial is the restoration of articular congruity? *Arch Orthop Trauma Surg*. 2023;143(4):1973-1980. doi: 10.1007/s00402-022-04405-5
25. Townsend KC, Thomas-Aitken HD, Rudert MJ, et al. Discrete element analysis is a valid method for computing joint contact stress in the hip before and after acetabular fracture. *J Biomech*. 2018;67:9-17. doi: 10.1016/j.jbiomech.2017.11.014
26. Anderson DD, Marsh JL, Brown TD. The pathomechanical etiology of post-traumatic osteoarthritis following intraarticular fractures. *Iowa Orthop J*. 2011;31:1-20.

The article was submitted 28.03.2023; approved after reviewing 05.06.2023; accepted for publication 01.12.2023.

Information about the authors:

Anatoly G. Galkin – traumatologist-orthopedist, researcher, https://orcid.org/0000-0001-8227-8492;

Dmitry A. Shavyrin – Doctor of Medical Sciences, Chief Freelance Traumatologist-Orthopedist, Head of Department, Head of Department, https://orcid.org/0009-0002-0069-0155;

Victor P. Voloshin – Doctor of Medical Sciences, Professor of the Department, Leading Researcher, https://orcid.org/0000-0002-2304-8483;

Sergey A. Oshkukov – Candidate of Medical Sciences, Researcher, Associate Professor, https://orcid.org/0000-0003-4898-3416;

Aleksey A. Glazkov – Candidate of Medical Sciences, Senior Researcher, https://orcid.org/0000-0001-6122-0638;

Aleksandr A. Ustinov – Junior Researcher, https://orcid.org/0009-0002-2947-3007.

Contribution of the authors:

Galkin A.G. – surgical treatment, collection and processing of material, analysis and interpretation of the data obtained, preparation of the text.

Shavyrin D.A. – surgical treatment, editing.

Voloshin V.P. – surgical treatment, editing.

Oshkukov S.A. – collection and processing of material, analysis and interpretation of the data obtained, preparation of the text.

Glazkov A.A. – statistical processing, text preparation.

Ustinov A.A. – preparation of the text.

Original article
https://doi.org/10.18019/1028-4427-2024-30-1-28-37

Long-term results and complication following Achilles tendon rupture repair

N.E. Magnitskaya[1]✉, A.N. Logvinov[2], M.S. Ryazantsev[2], P.S. Andreev[2,3], I.A. Vasilyev[2,3], D.A. Bessonov[2,3], D.O. Ilyin[2,3], A.V. Frolov[2,3], A.V. Korolev[2,3]

[1] Medswiss Medical center, Moscow, Russian Federation
[2] European Medical Center, European Clinic of Sports Traumatology and Orthopaedics (ECSTO), Moscow, Russian Federation
[3] Patrice Lumumba Peoples' Friendship University of Russia, Moscow, Russian Federation

Corresponding author: Nina E. Magnitskaya, magnitskaya.nina@gmail.com

Abstract

Introduction Currently, there is no consensus regarding optimal treatment options of Achilles tendon rupture.

The **purpose** of this study was to evaluate long term results of Achilles tendon repair using different surgical techniques, assess complication rate and subjective satisfaction

Methods The study included patients treated for Achilles tendon rupture using minimally invasive and open surgical repair. Complications including re-rupture, infection, deep vein thrombosis and neuropraxia were identified. In order to evaluate the factors influencing the risk of postoperative complications, logistic regression analysis was performed. The Achilles Tendon Rupture Score (ATRS) and the American Orthopedic Foot and Ankle Score (AOFAS) evaluated subjective outcomes.

Results 130 patients with Achilles tendon tear were enrolled (123 primary and 7 revision cases). In primary repairs percutaneous technique was used in 60 % of cases (74/123), *mini open* technique – in 16 % (19/123), and open technique – in 24 % (30/123). Re-rupture occurred in 2.4 % of patients treated with minimally invasive techniques. There were no repeated ruptures following open repairs. Predominant number of infections was registered after open repairs and made 10 %, while minimally invasive techniques had 3.2 % of infections. Logistic regression analyses showed that steroid injection, open repair, application of tapes and autografts increased the risk of infectious complications. There were no significant differences in ATRS and AOFAS scores between different primary Achilles tendon repair techniques ($p > 0.05$).

Discussion Results, obtained in the current study, are consistent with previously published data.

Conclusions Open Achilles tendon repair showed a higher rate of infections, and lower rate of re-ruptures. The anamnesis of steroid injection, open repair, application of tapes and autografts increases the risk of infectious complications.

Keywords: Achilles tendon, minimally invasive suture of the Achilles tendon, open suture of the Achilles tendon, infectious complications, recurrent ruptures

For citation: Magnitskaya NE, Logvinov AN, Ryazantsev MS, et al. Long-term results and complication following Achilles tendon rupture repair. *Genij Ortopedii*. 2024;30(1):28-37. doi: 10.18019/1028-4427-2024-30-1-28-37

INTRODUCTION

The Achilles tendon is the largest and strongest tendon in the human body, formed from the bundles of tendons of the superficial muscles of the posterior group of the lower leg: two heads of the gastrocnemius and soleus muscles. Achilles tendon ruptures are the most common tendon injuries [1-4].

The incidence of Achilles tendon ruptures among professional and amateur athletes is 18 cases per 100,000 people [5], in the general population from 8 to 24 cases per 1,000,000 people, with the incidence rates increasing [6-9]. Thus, according to the Danish National Register the incidence of these injuries has increased significantly from 27 to 31 cases per 100,000 over the past 20 years [10]. Moreover, Achilles tendon ruptures occur 5 times more often in men than in women [11]. According to the Swedish National Register, the incidence of acute Achilles tendon injuries has increased in recent years from 47 to 55.2 cases per 100,000 among men (17 %) and from 12 to 14.7 per 100,000 among women (14.7 %) [10]. For professional athletes, these injuries are of particular importance, since they may disable the athlete for a long time, and in some cases result in completion of a young athlete's career [12-14]. Up to 30 % of athletes do not return to their usual sports activities after surgical treatment [13, 15].

The length of the tendon is about 15 cm (11–26 cm) and the average width is about 6.8 cm (4.5-8.6 cm) [16]. In most cases, ruptures of the Achilles tendon occur in its middle part, 2-6 cm proximal to the point of its attachment to the calcaneal tubercle [17, 18]. Less common are distal avulsions, including avulsion fractures of the calcaneus [19]. Moreover, most distal Achilles tendon injuries are associated with long-term degenerative changes [20].

The analysis of the prevalence of Achilles tendon ruptures among different age groups revealed two main peaks: ages of 40 years and 60-65 years [2, 4, 21]. The first peak is due to sports injuries, while the second is more often characterized by tendon damage due to degenerative changes [7]. The largest number of calcaneal tendon ruptures in the population, according to various literature data, belongs to sports injuries (60-70 %) [22-24]. The most common sports in which Achilles tendon ruptures occur are football, tennis, indoor ball games (basketball, volleyball), jumping and running disciplines of athletics, American football and baseball [25, 26].

To date, there is no consensus in the literature regarding the optimal treatment method for patients with Achilles tendon ruptures [27, 28]. On the one hand, surgical treatment can reduce the risk of re-rupture and achieve higher functional results but, on the other hand, it results in a number of complications, including infectious and neurological ones.

Depending on the type and height of the injury, its duration and concomitant pathology, calcaneal tendon repair can be performed using an open approach, a minimally invasive approach in the projection of the rupture, or percutaneously. Open suturing has remained the gold standard for many years, providing high strength and low risk of re-rupture [29, 30]. The negative factor of this repair method is necrotization of the edges of the postoperative wound and a high risk of infectious complications. Many authors give preference to percutaneous repair, which is characterized by lower infectious risks, but higher risks of developing n. suralis neuropathy.

According to McMahon, the results of open and "mini open" repir techniques are comparable in terms of complications such as repeated ruptures, infection, thrombosis of the lower limb veins, contractures and n. suralis neuropathy. [31] According to Baumfeld et al., subjective results using open and percutaneous suturing techniques are comparable [32].

Purpose of this study was to evaluate long term results of Achilles tendon rupture surgical repair using different surgical techniques, assess complications and subjective satisfaction

MATERIALS AND METHODS

Patients who underwent surgical treatment for calcaneal tendon rupture from October 2010 to April 2020 were included in the study. For Achilles tendon repair, the following methods were used: minimally invasive and open. The minimally invasive method included percutaneous repair by stitching with a transverse mini-approach in the projection of the rupture (*mini open*). All operations were performed with patients in the prone position under spinal anesthesia and intravenous sedation. In the (*mini open*) technique and open repair, a pneumatic tourniquet was used on the proximal third of the thigh.

Indications for minimally invasive repair were acute primary ruptures of the Achilles tendon. The choice between the percutaneous repair and *mini open* technique was made depending on the surgeon's preference. For percutaneous repair, the classic Bunnel – Cuneo suture technique was used with tying and immersion knots through two punctures in the projection of the rupture (Fig. 1). In the *mini open* technique, a transverse approach was performed in the projection of the rupture up to 4 cm long, through which the matching of the ends of the tendon and the immersion of the knots were assessed (Fig. 2).

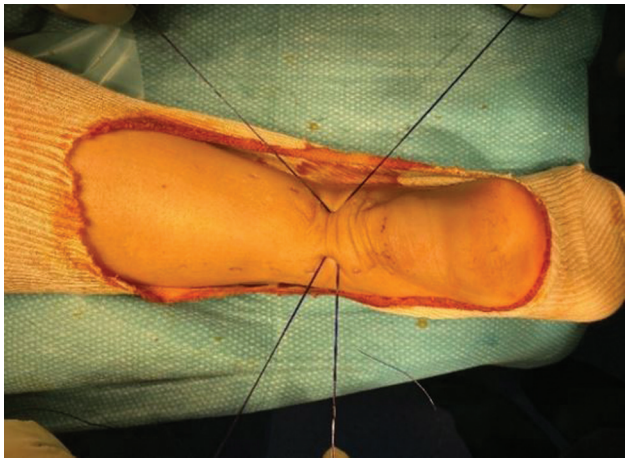

Fig. 1 Percutaneous repair of the Achilles tendon

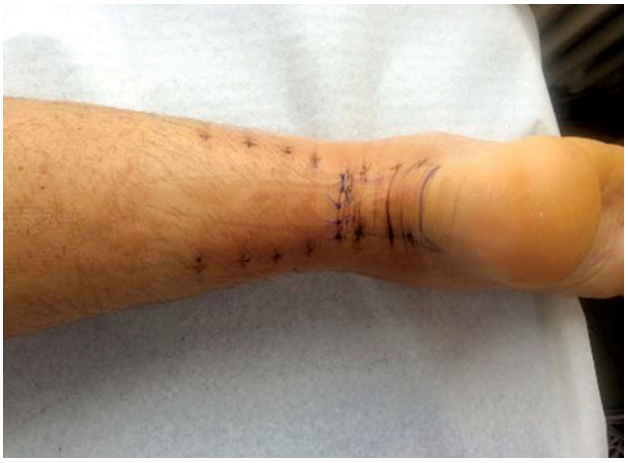

Fig. 2 *Mini open* repair of the Achilles tendon

Indications for open repair of the Achilles tendon were primary ruptures in professional athletes, long-standing ruptures (4-6 weeks or more since the moment of injury), repeated ruptures, degenerative ruptures due to long-term tendinopathy or previous injections of hormonal drugs, tendon evulsions from the calcaneal tubercle. For open repair, S-shaped, medial or midline approaches were used with full visualization of the ends of the torn tendon (Fig. 3). The type of approach for open suturing was determined depending on the height and duration of the rupture, as well as the planned type of reconstruction.

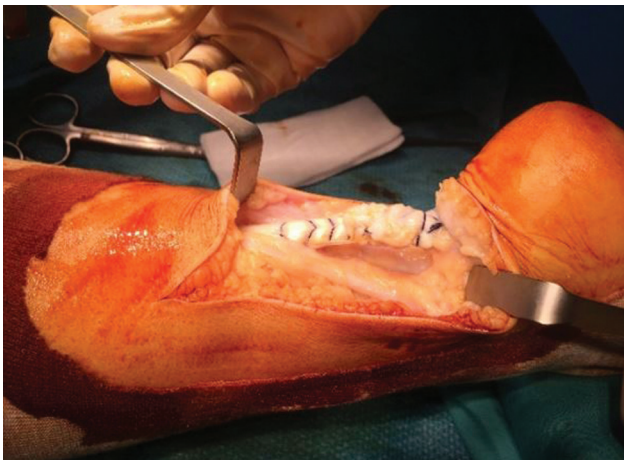

Fig. 3 Primary open repair of the Achilles tendon

If there was a gap between the ends of the tendon of more than 20 mm, reconstruction was performed using Chernavsky, Krasnov or V-Y plasty. If necessary, it was supplemented with an autograft harvested from the tendon of the semitendinosus muscle. When the Achilles tendon was torn off from the calcaneal tubercle, it was refixed to the calcaneus using anchors (Fig. 4).

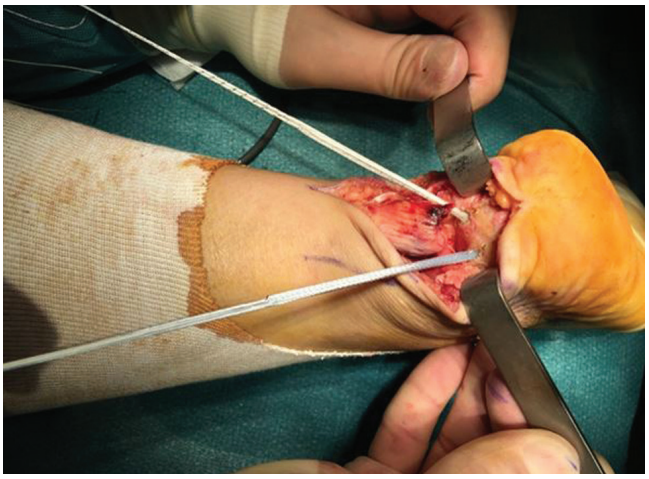

Fig. 4 Reattachment of the Achilles tendon to the calcaneal tubicle with anchor fixators

Postoperative rehabilitation included limited axial load for 6 weeks, immobilization in the equinus position of the foot for 3 weeks, followed by bringing the foot to a neutral position and continued immobilization from week 4 to 6 post-surgery.

Complications were recorded in the postoperative period: re-rupture, infection, thrombosis of the lower limb veins, n. suralis neuropathy.

At the follow-up, the result was assessed using the American Orthopedic Foot and Ankle Society Scale (AOFAS) and The Achilles Tendon Total Rupture Score (ATRS). Patients were also asked to answer the following questions: "Are you satisfied with the results of the operation?", "Would you agree to the operation, knowing in advance about its results?" The answer options were: "definitely yes," "probably yes," "probably no," and "definitely no."

Statistical data processing was carried out using the Statistica 12.0, Stat Soft Inc. To check the normality of data distribution, the Kolmogorov–Smirnov test was used. To assess normal distribution, quantitative data are presented as mean ± error; in a non-normal distribution, quantitative data are presented as median and interquartile range (IQR). Since the manifestations had a distribution other than normal in all groups, the Kruskal–Wallis test was used to test statistical hypotheses in comparing numerical data from several unrelated groups. The critical level of significance was set at 5 % ($p \leqslant 0.05$).

A logistic regression model was used to identify factors influencing the final treatment results and determine cause-and-effect relationships. To form the model, all available factors (signs) were used, and the results obtained were checked by cross-validation. Primary input data were used as factors: age (⩽ 40 years / > 40 years), gender (m/f), body mass index (< 25 / ⩾ 25), time since injury (⩽ 72 hours / > 72 hours), surgeon experience (more than 25 years or less), level of sports activity (professional, amateur, not involved), history of glucocorticosteroid (GCS) injections into the Achilles tendon area (yes/no), type of suture material used (absorbable/non-absorbable), use of autografts (yes/no), type of postoperative immobilization (plaster cast/orthosis), use of a tourniquet intraoperatively (yes/no), type of calcaneal tendon repair (mini-invasive/open). The final result factors were the occurrence of postoperative complications: infection or re-rupture. Several models were built in which the occurrence of different types of postoperative complications was considered either as different events or as one event. Most of the studied features were of a qualitative nature, and in order to conduct a correct statistical analysis, all these features were converted using the binary coding method. Next, the data was normalized and all values were brought to a single scale.

The study was approved by the institutional ethics committee and was conducted in accordance with the ethical standards outlined in the Declaration of Helsinki.

RESULTS

The surgical treatment results of 130 patients with Achilles tendon rupture were analyzed: 123 patients with primary injury and 7 patients with recurrent injury. The median age of patients included in the study was 40 years (IQR 36-48 years). The median follow-up period was 7 years (IQR 5-10 years).

Among patients with a primary rupture, percutaneous repair was performed in 60 % of cases (74/123), *mini open* repair was performed in 16 % (19/123), and open repair of the calcaneal tendon was performed in 24 % (30/123) .

All minimally invasive surgeries were performed for acute Achilles tendon injuries. During the follow-up period, recurrent tendon rupture was detected in 2 patients after percutaneous repair and in 1 patient after the *mini open* technique. Those patients subsequently underwent open calcaneal tendon repair. In the open repair group, 18 operations were performed for acute traumatic injury to the calcaneal tendon, 12 operations were performed for primary degenerative or old rupture. No re-ruptures were diagnosed after open repair. All patients underwent open surgery for re-rupture of the calcaneal tendon. In the follow-up period after percutaneous suture of the Achilles tendon, the following complications were diagnosed: 4.1 % (3/74) of cases – infectious complications, 10.8 % (8/74) – deep vein thrombosis of the lower extremities and in 1.4 % (1/74) – n. suralis neuropathy. After the *mini open* technique in the postoperative period, deep vein thrombosis of the lower extremities was detected in 5.2 % of cases (1/19); no other complications were diagnosed in this group of patients. After the open method for primary ruptures of the Achilles tendon, infectious complications were detected in 10 % of cases (3/30) and neuropathy n. suralis in 3.3 % (1/30). Analysis of anamnestic data showed that among the 3 patients who had infectious complications after open repair, two had previously received injections of hormonal drugs into the Achilles tendon area. In patients with repeated rupture of the Achilles tendon, no infectious or neurological complications were diagnosed; thrombosis of the veins of the lower extremities was detected in 2 cases (Table 1.)

Table 1

Distribution of patients with Achilles tendon ruptures into groups and number of complications

Groups of patients	Number of patients, total	Re-ruptures		Infection		Thrombosis		Neuropathy	
		abs.	%	abs.	%	abs.	%	abs.	%
Primary ruptures	**123**	3	2.4	6	4.8	9	7.3	2	1.6
Mini-invasive repair:	93	3	3.2	3	3.2	9	9.7	1	1.1
Percutaneous suture	74	2	2.7	3	4	8	10.8	1	1.4
Mini open repair	19	1	5	–		1	5	–	
Open repair:	30	–		3	10	–		1	3.3
Acute primary	18	–		–		–		–	
Neglected and degenerative rupture	12	–		3	25	–		1	8.3
Re-ruptures	7	–		–		2	28	–	
Total:	130	3	2.3	6	4.6	11	8.5	2	1.5

We were unable to identify a significant relationship between the studied factors (primary data) and the development of postoperative complications. However, it was found that injection of corticosteroids into the area of the calcaneal tendon, open repair of the calcaneal tendon, and the use of augmentation tapes or autografts increase the likelihood of developing infectious complications.

Subjective questionnaire data were obtained from 32 patients in the percutaneous repair group, 9 patients in the *mini open* repair group, 13 patients in the open repair group with primary ruptures, and 5 patients with recurrent calcaneal tendon rupture (Table 2).

Table 2

Data on subjective satisfaction based on questionnaires

Groups of patients	Number of patients	AOFAS Median (IQR)	ATRS Median (IQR)
Mini-invasive methods:	41	96 (90-98)	95 (90-99)
Percutaneous repair	32	95 (90-98)	96 (89-100)
Mini open repair	9	98 (95-98)	96 (92-97)
Open repair	13	95 (90-100)	95(92-97)
Re-ruptures	5	88 (86-90)	86 (83-96)

In the percutaneous group, the median AOFAS score was 95 points (IQR 90-98) and the ATRS score was 96 points (IQR 89-100). The answer to the question "Are you satisfied with the results of the operation?" was "definitely yes" in the percutaneous group in 69 % (22/32) of patients, 31 % (10/32) of patients chose the option "probably yes"; none of the respondents answered "probably no" or "definitely no". We obtained the following results to the answer to the question "Would you agree to the operation, knowing in advance about its results?": "definitely yes" – 63 % (20/32), "probably yes" – 34 % (11/32), "probably no" – 3 % (1/32); no one answered "definitely no".

In the *mini open* technique group, the median AOFAS score was 98 points (IQR 98-100), and the ATRS score was 95 points (IQR 92-97). When answering the question "Are you satisfied with the results of the operation?" in the *mini open* group, 67 % (6/9) of patients chose the option "definitely yes", 33 % (3/9) of patients "probably yes"; none of the respondents answered "probably no" or "definitely no". The answers to the question "Would you agree to the operation, knowing in advance about its results?, the following results were obtained: "definitely yes" – 78 % (7/9), "probably yes" – 22 % (2/9); none of the respondents answered "probably no" or "definitely no".

After open repair, the median AOFAS score was 95 points (IQR 90-100), and the ATRS score was 95 points (IQR 92-97). When answering the questions "Are you satisfied with the results of the operation?" and "Would you agree to the operation if you knew in advance about its results?", 69 % (9/13) of patients in the group of primary open repair of the Achilles tendon chose the option "definitely yes", 23 % (3/13) of patients "probably yes", one patient (1/13) answered "definitely no" (8 %). There was no statistically significant difference in these subjective questionnaires between the percutaneous, *mini open*, and primary rupture open repair groups ($p > 0.05$) (Fig. 5 and 6).

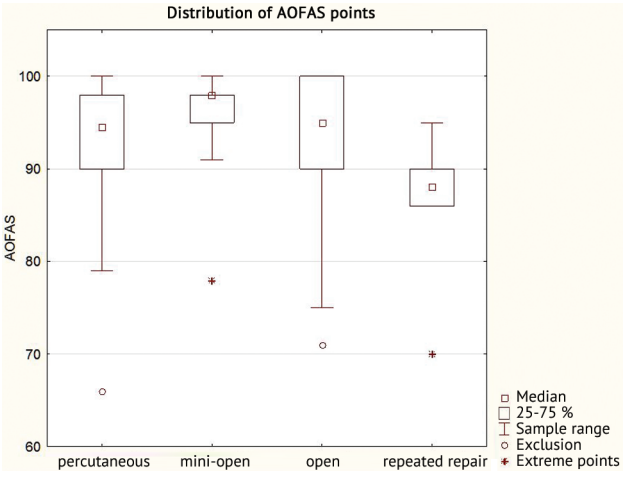

Fig. 5 Distribution of AOFAS points between the groups

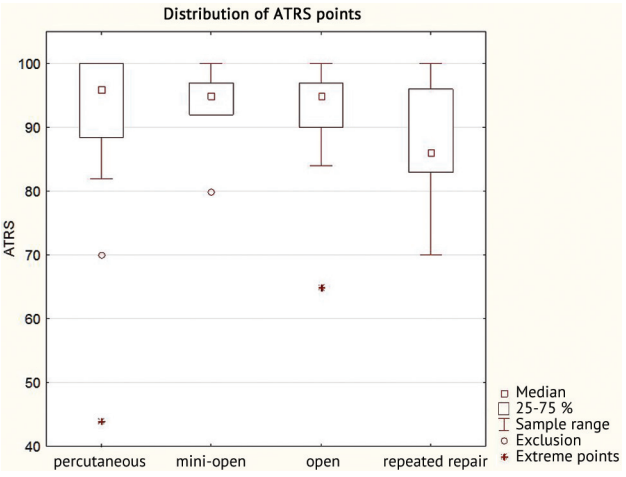

Fig. 6 Distribution of ATRS points between the groups

In the group of repeated rupture repair of the calcaneal tendon, the median AOFAS score was 88 points (IQR 86-90), the ATRS score was 86 points (IQR 83-96), which is lower than after primary repair, but no significant differences were obtained ($p > 0.05$). When answering the question "Are

you satisfied with the results of the operation?" 80 % (4/5) of patients chose the option "definitely yes", 20 % (1/20) of patients answered "probably yes". The answer to the question "Would you agree to the operation, knowing in advance about its results?", 100 % of patients chose the answer "definitely yes."

DISCUSSION

Surgical treatment of Achilles tendon ruptures is aimed at fast functional recovery, return to sports activity, good esthetic effect and subjective patient's satisfaction. The choice of the optimal surgical treatment method raises many contradictions.

The rate of re-ruptures after minimally invasive repair in our study was 3.2 %: 2 cases after percutaneous suture and 1 case after repair using a transverse approach in the projection of the rupture. Our data are comparable with the results of meta-analyses by Yang et al. and Grassi et al., where the incidence of recurrent Achilles tendon ruptures using minimally invasive methods was 3.1 % and from 0 to 4 %, respectively [14, 33]. After open repair, no repeated ruptures were diagnosed in our work. Moreover, in the study of Yang et al. the re-rupture rate after open repair was 2.7 %, in the study of Grassi et al. it ranged from 0 to 6 %. The differences may be explained by a small group for open repair in our study, as well as the inclusion of patients with degenerative and chronic calcaneal tendon ruptures in the analysis of results.

The number of infectious complications in our study was 3.2 % after minimally invasive repair of the calcaneal tendon and 10 % after open repair. Many literature sources indicate a higher risk of infectious complications after primary open repair [14, 34]. Grassi et al. analyzed the results of treatment of more than 350 patients and showed a significantly lower number of infectious complications with application of minimally invasive methods [33]. Moreover, the researchers calculated that every 10 procedures using a minimally invasive Achilles tendon repair instead of an open one avoided one infectious complication. The meta-analysis by Soew et al. showed that the number of infectious complications after percutaneous repair of the Achilles tendon was 2.9 %, which is comparable to the data obtained in our work [35]. For assessing the incidence of postoperative complications, most studies include only acute primary Achilles tendon ruptures. Thus, Fell et al. in 2020 diagnosed infectious complications after open repair in 3 % of cases, which is less than in our work, but the authors did not include old (more than 21 days from the date of injury) injuries in the analysis [36]. All infectious complications after open repair in our study were diagnosed in patients with neglected or degenerative ruptures. Ahmad et al. evaluated the results of open repair for chronic and repeated ruptures of the Achilles tendon and identified superficial infectious complications in 9.4 % of cases and deep ones in 3.1 % [37].

The incidence of thrombosis of lower limb veins after minimally invasive techniques in our work was 9.7 %, while thrombosis was detected in 8.1 % of cases among the patients who underwent open repair at the preoperative stage, which required the implantation of vena cava filters. The detection of thrombosis at the preoperative stage in the open repair group is associated with the inclusion of patients with chronic calcaneal tendon injuries in the analysis. The obtained data are comparable with previously published ones. Thus, Caolo et al. revealed deep vein thrombosis in 8.5 % of cases after minimally invasive suturing of the Achilles tendon and in 9 % after open repair [38].

Many researchers show that percutaneous and minimally invasive techniques have higher risks of n. suralis neuropathy than open techniques of Achilles tendon repair [14, 39]. However, subsequently, several meta-analyses showed no significant differences in the incidence of neurological complications when comparing open and minimally invasive techniques [33, 35]. According to our data, the incidence of sural nerve neuropathy was 1.1 % after minimally invasive techniques and 3.3 % with the open approach; there was also no statistically significant difference ($p > 0.05$).

Most studies indicate comparable subjective results by comparing minimally invasive and open techniques. Mean AOFAS score in Yang et al. meta-analysis was 95.9 points in percutaneous repair and 98.4 in open repair while in the study by Baumfiend (2018), 95.3 and 98.2, respectively [14, 32]. Our data are consistent with previously published ones: in the group of percutaneous repair, the median AOFAS score was 95 points and ATRS score was 96 points; in the group of *mini open* technique, the median AOFAS score was 98 points and ATRS score was 95 points. In the open repair group, the median AOFAS and ATRS scores were 95 and 95 points. After repeated rupture repair, the median AOFAS score was 88 points and ATRS score was 86 points. Our study found high patient satisfaction with the results of surgical treatment.

CONCLUSION

The choice of surgical treatment technique depends on many factors. Open repair techniques have a greater risk of infectious complications, but a lower likelihood of re-rupture. Previous injections of hormonal drugs into the area of the calcaneal tendon, application of augmentation tapes or autografts in Achilles tendon repair increase the risks of infectious complications.

Conflict of interest *Professor Korolev A.V. is an official consultant and lecturer for Arthrex.*

Financing *The study had no sponsor support and external funding.*

Ethical review *The study was approved by the institutional ethics committee and was conducted in accordance with the ethical standards set forth in the Declaration of Helsinki.*

Informed consent *All patients signed informed consents.*

REFERENCES

1. Raikin SM, Garras DN, Krapchev PV. Achilles tendon injuries in a United States population. *Foot Ankle Int*. 2013;34(4):475-480. doi: 10.1177/1071100713477621
2. Huttunen TT, Kannus P, Rolf C, et al. Acute achilles tendon ruptures: incidence of injury and surgery in Sweden between 2001 and 2012. *Am J Sports Med*. 2014;42(10):2419-2423. doi: 10.1177/0363546514540599
3. Clayton RA, Court-Brown CM. The epidemiology of musculoskeletal tendinous and ligamentous injuries. *Injury*. 2008;39(12):1338-1344. doi: 10.1016/j.injury.2008.06.021
4. Owens B, Mountcastle S, White D. Racial differences in tendon rupture incidence. *Int J Sports Med*. 2007;28(7):617-620. doi: 10.1055/s-2007-964837
5. Lemme NJ, Li NY, Kleiner JE, et al. Epidemiology and Video Analysis of Achilles Tendon Ruptures in the National Basketball Association. *Am J Sports Med*. 2019;47(10):2360-2366. doi: 10.1177/0363546519858609
6. Gwynne-Jones DP, Sims M, Handcock D. Epidemiology and outcomes of acute Achilles tendon rupture with operative or nonoperative treatment using an identical functional bracing protocol. *Foot Ankle Int*. 2011;32(4):337-343. doi: 10.3113/FAI.2011.0337
7. Houshian S, Tscherning T, Riegels-Nielsen P. The epidemiology of Achilles tendon rupture in a Danish county. *Injury*. 1998;29(9):651-654. doi: 10.1016/s0020-1383(98)00147-8
8. Leppilahti J, Puranen J, Orava S. Incidence of Achilles tendon rupture. *Acta Orthop Scand*. 1996;67(3):277-279. doi: 10.3109/17453679608994688
9. Maffulli N, Waterston SW, Squair J, et al. Changing incidence of Achilles tendon rupture in Scotland: a 15-year study. *Clin J Sport Med*. 1999;9(3):157-160. doi: 10.1097/00042752-199907000-00007
10. Ganestam A, Kallemose T, Troelsen A, Barfod KW. Increasing incidence of acute Achilles tendon rupture and a noticeable decline in surgical treatment from 1994 to 2013. A nationwide registry study of 33,160 patients. *Knee Surg Sports Traumatol Arthrosc*. 2016;24(12):3730-3737. doi: 10.1007/s00167-015-3544-5
11. Vosseller JT, Ellis SJ, Levine DS, et al. Achilles tendon rupture in women. *Foot Ankle Int*. 2013;34(1):49-53. doi: 10.1177/1071100712460223
12. Malvankar S, Khan WS. Evolution of the Achilles tendon: The athlete's Achilles heel? *Foot* (Edinb). 2011;21(4):193-197. doi: 10.1016/j.foot.2011.08.004
13. Zellers JA, Carmont MR, Grävare Silbernagel K. Return to play post-Achilles tendon rupture: a systematic review and meta-analysis of rate and measures of return to play. *Br J Sports Med*. 2016;50(21):1325-1332. doi: 10.1136/bjsports-2016-096106
14. Yang B, Liu Y, Kan S, et al. Outcomes and complications of percutaneous versus open repair of acute Achilles tendon rupture: A meta-analysis. *Int J Surg*. 2017;40:178-186. doi: 10.1016/j.ijsu.2017.03.021

15. Trofa DP, Miller JC, Jang ES, et al. Professional Athletes' Return to Play and Performance After Operative Repair of an Achilles Tendon Rupture. *Am J Sports Med*. 2017;45(12):2864-2871. doi: 10.1177/0363546517713001
16. Carmont MR, Silbernagel KG, Mathy A, et al. Reliability of Achilles tendon resting angle and calf circumference measurement techniques. *Foot Ankle Surg*. 2013;19(4):245-249. doi: 10.1016/j.fas.2013.06.007
17. Campbell P, Lawton JO. Spontaneous rupture of the Achilles tendon: pathology and management. *Br J Hosp Med*. 1993;50(6):321-325.
18. Reinherz RP, Granoff SR, Westerfield M. Pathologic afflictions of the Achilles tendon. *J Foot Surg*. 1991;30(2):117-121.
19. Beavis RC, Rourke K, Court-Brown C. Avulsion fracture of the calcaneal tuberosity: a case report and literature review. *Foot Ankle Int*. 2008;29(8):863-866. doi: 10.3113/FAI.2008.0000
20. Kannus P, Józsa L. Histopathological changes preceding spontaneous rupture of a tendon. A controlled study of 891 patients. *J Bone Joint Surg Br*. 1991;73(10):1507-1525. doi: 10.2106/00004623-199173100-00009
21. Möller A, Astron M, Westlin N. Increasing incidence of Achilles tendon rupture. *Acta Orthop Scand*. 1996;67(5):479-481. doi: 10.3109/17453679608996672
22. Longo UG, Salvatore G, Risi Ambrogioni L, et al. Epidemiology of Achilles tendon surgery in Italy: a nationwide registry study, from 2001 through 2015. *BMC Musculoskelet Disord*. 2020;21(1):687. doi: 10.1186/s12891-020-03688-2
23. Plecko M, Passl R. Ruptures of the Achilles tendon: causes and treatment. *J Finn Orthop Traumatol*. 1991;14:201-204
24. Sereda A. P. *Surgical treatment of Achilles tendon ruptures*: Kand. Dis. Moscow; 2015:324. Available at: https://www.dissercat.com/content/khirurgicheskoe-lechenie-razryvov-akhillova-sukhozhiliya. Accessed Aug 29, 2023.
25. Chan JJ, Chen KK, Sarker S, et al. Epidemiology of Achilles tendon injuries in collegiate level athletes in the United States. *Int Orthop*. 2020;44(3):585-594. doi: 10.1007/s00264-019-04471-2
26. Efimenko NA, Gritsyuk AA, Sereda AP. Diagnosis of Achilles tendon ruptures. *Clinical medicine*. 2011;89(3):64-70. (In Russ.)
27. Wu Y, Lin L, Li H, et al. Is surgical intervention more effective than non-surgical treatment for acute Achilles tendon rupture? A systematic review of overlapping meta-analyses. *Int J Surg*. 2016;36(Pt A):305-311. doi: 10.1016/j.ijsu.2016.11.014
28. Wilkins R, Bisson LJ. Operative versus nonoperative management of acute Achilles tendon ruptures: a quantitative systematic review of randomized controlled trials. *Am J Sports Med*. 2012;40(9):2154-2160. doi: 10.1177/0363546512453293
29. Maffulli G, Buono AD, Richards P, et al. Conservative, minimally invasive and open surgical repair for management of acute ruptures of the Achilles tendon: a clinical and functional retrospective study. *Muscles Ligaments Tendons J*. 2017;7(1):46-52. doi: 10.11138/mltj/2017.7.1.046
30. Gritsyuk AA, Sereda AP. *Achilles tendon*. Moscow: Academy of natural Sciences; 2010:25-30. (In Russ.)
31. McMahon SE, Smith TO, Hing CB. A meta-analysis of randomised controlled trials comparing conventional to minimally invasive approaches for repair of an Achilles tendon rupture. *Foot Ankle Surg*. 2011;17(4):211-217. doi: 10.1016/j.fas.2010.11.001
32. Baumfeld D, Baumfeld T, Spiezia F, et al. Isokinetic functional outcomes of open versus percutaneous repair following Achilles tendon tears. *Foot Ankle Surg*. 2019;25(4):503-506. doi: 10.1016/j.fas.2018.03.003
33. Grassi A, Amendola A, Samuelsson K, et al. Minimally Invasive Versus Open Repair for Acute Achilles Tendon Rupture: Meta-Analysis Showing Reduced Complications, with Similar Outcomes, After Minimally Invasive Surgery. *J Bone Joint Surg Am*. 2018;100(22):1969-1981. doi: 10.2106/JBJS.17.01364
34. Gatz M, Driessen A, Eschweiler J, et al. Open versus minimally-invasive surgery for Achilles tendon rupture: a meta-analysis study. *Arch Orthop Trauma Surg*. 2021;141(3):383-401. doi: 10.1007/s00402-020-03437-z
35. Seow D, Yasui Y, Calder JDF, et al. Treatment of Acute Achilles Tendon Ruptures: A Systematic Review and Meta-analysis of Complication Rates With Best- and Worst-Case Analyses for Rerupture Rates. *Am J Sports Med*. 2021;49(13):3728-3748. doi: 10.1177/0363546521998284
36. Fell D, Enocson A, Lapidus LJ. Surgical repair of acute Achilles tendon ruptures: a follow-up of 639 consecutive cases. *Eur J Orthop Surg Traumatol*. 2020;30(5):895-899. doi: 10.1007/s00590-020-02650-1
37. Ahmad J, Jones K, Raikin SM. Treatment of Chronic Achilles Tendon Ruptures With Large Defects. *Foot Ankle Spec*. 2016;9(5):400-408. doi: 10.1177/1938640016640895
38. Caolo KC, Eble SK, Rider C, et al. Clinical Outcomes and Complications With Open vs Minimally Invasive Achilles Tendon Repair. *Foot Ankle Orthop*. 2021;6(4):24730114211060063. doi: 10.1177/24730114211060063
39. Aibinder WR, Patel A, Arnouk J, et al. The rate of sural nerve violation using the Achillon device: a cadaveric study. *Foot Ankle Int*. 2013;34(6):870-875. doi: 10.1177/1071100712473097

The article was submitted 30.05.2023; approved after reviewing 21.09.2023; accepted for publication 01.12.2023.

Information about the authors:

Nina E. Magnitskaya – Candidate of Medical Sciences, orthopedic traumatologist, magnitskaya.nina@gmail.com, https://orcid.org/0000-0002-4336-036X;

Alexey N. Logvinov – Candidate of Medical Sciences, orthopedic traumatologist, logvinov09@gmail.com, https://orcid.org/0000-0003-3235-5407;

Mikhail S. Ryazantsev – Candidate of Medical Sciences, traumatologist-orthopedist, Ryaz.doc@yandex.ru; https://orcid.org/0000-0002-9333-5293;

Pavel S. Andreev – orthopedic traumatologist, graduate student, pandreev@emcmos.ru; https://orcid.org/0000-0002-5750-626X;

Ivan A. Vasiliev – orthopedic traumatologist, graduate student, dr.vasilyev.ivan@gmail.com, https://orcid.org/0000-0002-1163-950X;

Dmitry A. Bessonov – orthopedic traumatologist, graduate student, Bessonovdmitry96@gmail.com, https://orcid.org/0000-0002-0532-9847;

Dmitry O. Ilyin – Doctor of Medical Sciences, orthopedist-traumatologist, ilyinshoulder@gmail.com, https://orcid.org/0000-0003-2493-4601;

Alexander V. Frolov – Candidate of Medical Sciences, orthopedic traumatologist, Associate Professor of the Department, a.frolov1980@gmail.com; https://orcid.org/0000-0002-2973-8303;

Andrey V. Korolev – Doctor of Medical Sciences, Chief Physician, Professor of the Department, akorolev@emcmos.ru, https://orcid.org/0000-0002-8769-9963.

Contribution of the authors:

Magnitskaya N.E. – conceptualization, methodology, formal analysis, investigation, review and editing, visualization and research project management.

Logvinov A.N. – methodology, validation, formal analysis, research, reviewing and editing.

Ryazantsev M.S. – conceptualization, methodology, research, visualization, review and editing of the study.

Andreev P.S. – formal analysis, research, data processing, writing the initial version of the manuscript.

Vasiliev I.A. – research, data processing, writing the initial version of the study.

Bessonov D.A. – formal analysis, research, data processing, writing the initial version of the manuscript.

Ilyin D.O. – conceptualization, methodology, research, control over the implementation of the study.

Frolov A.V. – conceptualization, methodology, research, control over the implementation of the study.

Korolev A.V. – conceptualization, methodology, research, reviewing and editing, supervision and management of the research project.

Original article
https://doi.org/10.18019/1028-4427-2024-30-1-38-45

Limb lengthening and deformity correction in patients with severe fibular hemimelia: experience of the children's university hospital in Belgrade

M. Lazović[1], S.S. Leonchuk[2]✉, S. Ducić[1], Sh.A. Imomov[2], D.A. Popkov[2]

[1] University Children's Hospital, Belgrade, Serbia
2 Ilizarov National Medical Research Centre for Traumatology and Orthopedics, Kurgan, Russian Federation

Corresponding author: Sergey S. Leonchuk, leon4yk@mail.ru

Abstract

Background Fibular hemimelia (FH) is a congenital disease manifested by valgus deformity and instability of the knee joint, shortening and deformity of the tibia, hypoplasia and deformities of the foot and ankle.

The aim of this paper was to determine the efficacy of the strategy of separate reconstruction of the foot along with correction of tibia deformity, and then tibial lengthening in patients with FH of types 3 and 4 according to Paley.

Methods This retrospective study is based on an analysis of the treatment of 12 children with severe FH. The patients, aged no older than 24 months, were treated for foot reconstruction along with correction of tibial deformity followed by a separate stage of tibial lengthening. Tibial lengthening was performed in the age 4.6 ± 1.2 years. The long-term result of treatment was evaluated at least 1 year after the end of tibial lengthening. Evaluation criteria after tibia lengthening were external osteosynthesis index, amount of lengthening, assessment of outcomes according to Lascombes. Walking ability was assessed using Gillette questionnaire.

Results The approach we used gave excellent and good results in 83 % of cases after the first reconstructive stage. Complications and recurrences of deformities encountered during the first stage were eliminated during subsequent planned limb lengthening. The average magnitude of lengthening was 6.4 ± 2.4 cm (37.2 ± 12.4 % of the initial segment length). The index of external osteosynthesis was 22.9 ± 12.2 days/cm. Monofocal distraction osteosynthesis was used in 9 cases and bifocal osteosynthesis in three cases. The results of lengthening were classified by Lascombes as IA in 7 cases, IB in four cases, 2B in one case.

Discussion In severe FH, the question of reconstruction or early amputation remains open. There are two opinions on the staging of reconstructive orthopedic surgery and tibial lengthening in young children with severe FH.

Conclusion The strategy of reconstruction of the foot and ankle joint at an early age (16-24 months) in children with severe FH followed by lengthening of the lower leg (at the age of 4-6 years) proved to be effective and can be used when it is chosen by the patient's parents. In 3C type cases, the use of external fixation to correct the deformity and simultaneously lengthen the tibia at the first stage is an alternative reasonable strategy option.

Keywords: fibular hemimelia; reconstruction; limb lengthening; Ilizarov method

For citation: Lazović M, Leonchuk SS, Ducić S, Imomov ShA, Popkov DA. Limb lengthening and deformity correction in patients with severe fibular hemimelia: experience of the children's university hospital in Belgrade. *Genij Ortopedii*. 2024;30(1):38-45. doi: 10.18019/1028-4427-2024-30-1-38-45

INTRODUCTION

Fibular hemimelia (FH) is a congenital malformation where part or all of the fibula is hypoplastic, dysplastic, or absent, and this is associated with dysplasia or hypoplasia of the tibia and foot. FH refers to the so-called postaxial anomalies, in contrast to tibial hemimelia (preaxial type of longitudinal anomaly). The incidence of FH varies between 1:40,000 and 1:50,000 newborns [1, 2]. The etiology of this anomaly remains unknown in most cases, usually classified as embryopathy [3, 4]. The main orthopedic problems in fibular hemimelia are length discrepancy of the lower limbs, instability and valgus deformity of the knee joint, tibial deformity, deformities and abnormalities of the foot and ankle joint [5, 6]. In severe FH forms, the question of reconstruction or early amputation remains open [7-10]. There is a consensus that the success of reconstructive treatment is due to the achievement of a weight-bearing position of the foot and the elimination of deformities of the ankle joint and lower leg [10, 11]. The age of the child when indications for the first stage of reconstruction (correction of deformities of the foot, ankle and tibia) are optimal is between 18-24 months [6].

Surgical treatment provides the correct foot position, ensures the function of the ankle joint, achieves vertical posture of the child, and develops independent walking with orthoses that compensate for the difference in length [12]. The operation can be combined with leg lengthening [6, 12], which, however, is accompanied by a long period of wearing an external fixation device. The decision on both the treatment strategy and the scope of primary intervention should consider the opinion of the parents [9]. Thus, the first stage of elongation can be delayed until the age of 4-8 years [13-15]. So, there are two opinions about the combination and stages of reconstructive orthopedic intervention on the limbs and leg lengthening in young children with severe FH.

This retrospective study analyzed the results of reconstructive surgical treatment and tibial lengthening in patients with severe FH (Paley types 3 and 4), when parents preferred tibial lengthening delayed for several years after primary surgical reconstruction of the foot and ankle.

Purpose To determine the effectiveness of the strategy of separate implementation of the foot reconstruction stage combined with correction of the tibial deformity and tibial lengthening stage in patients with Paley FH types 3 and 4.

MATERIALS AND METHODS

This retrospective study included 12 patients with fibular aplasia (7 boys and 5 girls).

The inclusion criteria were that the stage of foot reconstruction and correction of the tibial deformity be performed separately from the stage of the first tibial lengthening due to the choice of this treatment strategy by child's parents. Other inclusion criteria were severe FH, classified as types 3 and 4 according to Paley [15], completion of the first stage of treatment in patients no older than 24 months, completion of the second stage of treatment (tibial lengthening), the ability to evaluate the result at least 1 year after the completion of leg lengthening.

This study did not include patients with milder FH, patients whose reconstructive treatment was started at a later age, as well as cases where it was not possible to evaluate the result of lengthening one year or more after removal of the Ilizarov apparatus.

The features of the first (reconstructive) stage of surgical treatment were the following mandatory elements of the intervention: correction of tibial deformity using the resection type of closed-wedge osteotomy, corrective osteotomy through the area of the talocalcaneal coalition of the foot, resection

of the rudiment of the fibula, lengthening of the triceps using the type of aponeurotomy of the calf muscles, Z-lengthening of the peroneal tendons (or single muscle), ankle capsulotomy, internal osteosynthesis (bone locking plates or threaded pins) for fixation of tibial fragments, threaded immersion wires or external diafixation wires for fixation of the position of hindfoot and ankle joint fragments (not changing the relationship between the tibia and talus), as well as plaster immobilization. The duration of plaster fixation was 6-8 weeks; removal of the plaster cast was accompanied by the removal of the diafixation wires (in this type of fixation). Subsequently, before performing the leg lengthening stage, patients used devices with hinges inserted into shoes (AFO – ankle-foot orthosis type); walking with full load in shoes with compensation for shortening was allowed.

Tibial lengthening (the second stage of treatment) was performed using the Ilizarov apparatus in all cases, at one or two levels. Simultaneously with the application of the Ilizarov apparatus, the previously applied osteosynthesis material was removed if it interfered with external osteosynthesis. Elastic reinforcement was used in 9 cases. Lengthening of the tibia was combined with correction of deformities if necessary; osteosynthesis was carried out with protection of the knee and ankle joints, taking into account the instability of adjacent joints inherent in these severe forms.

The evaluation criteria after the first stage of treatment were the parameters of anatomical X-ray angles of orientation of the articular surfaces in the frontal (lateral distal tibial angle – aLDTA) and sagittal (anterior distal tibial angle – aADTA) planes, deviation of the biomechanical axis from the center of the knee joint (mechanical axis deviation – MAD) [16, 17], as well as the tibiotalar (TT) and tibiocalcaneal (TCC) angles in the standing position under limb loading. A clinical assessment of the position of the foot, the supportability of the foot and the ability to weight-bearing walking, and the child's motor activity was also carried out. Walking ability was examined using the Gillette questionnaire [18].

The evaluation criteria after lengthening the tibia were the index of external osteosynthesis, the amount of lengthening (cm and %). In general, the evaluation of the elongation stage was carried out according to the criteria of P. Lascombes [19]. The complications encountered, the treatment/measures applied to them and the consequences of the complications were also assessed.

Statistical assessment included descriptive parameters (mean values, standard deviations); the Attestat 12.0.5 software was used.

RESULTS

The first stage of treatment was carried out in the age from 16 to 24 months. FH cases according to the Paley classification were: type 3A (3 patients, 25 %), type 3B2 (4 patients, 33.3 %), type 3C (4 patients, 33.3 %), type 4 (1 patient, 8.3 %). In all cases, shortening of the femur was less than 1 cm, while in 3 cases there was a valgus deformity of the knee joint of no more than 10°, caused by hypoplasia of the lateral condyle of the femur.

After the first stage, the treatment goals were achieved in 10 cases (Fig. 1). Two cases had foot equinus and relapse of the hindfoot deformity and did not allow achieving good treatment results (Table 1). Among other complications of the first stage, there was local skin necrosis in three cases, which required conservative treatment for wound healing by secondary intention, and one case of superficial infection in the area of the diafixation wire.

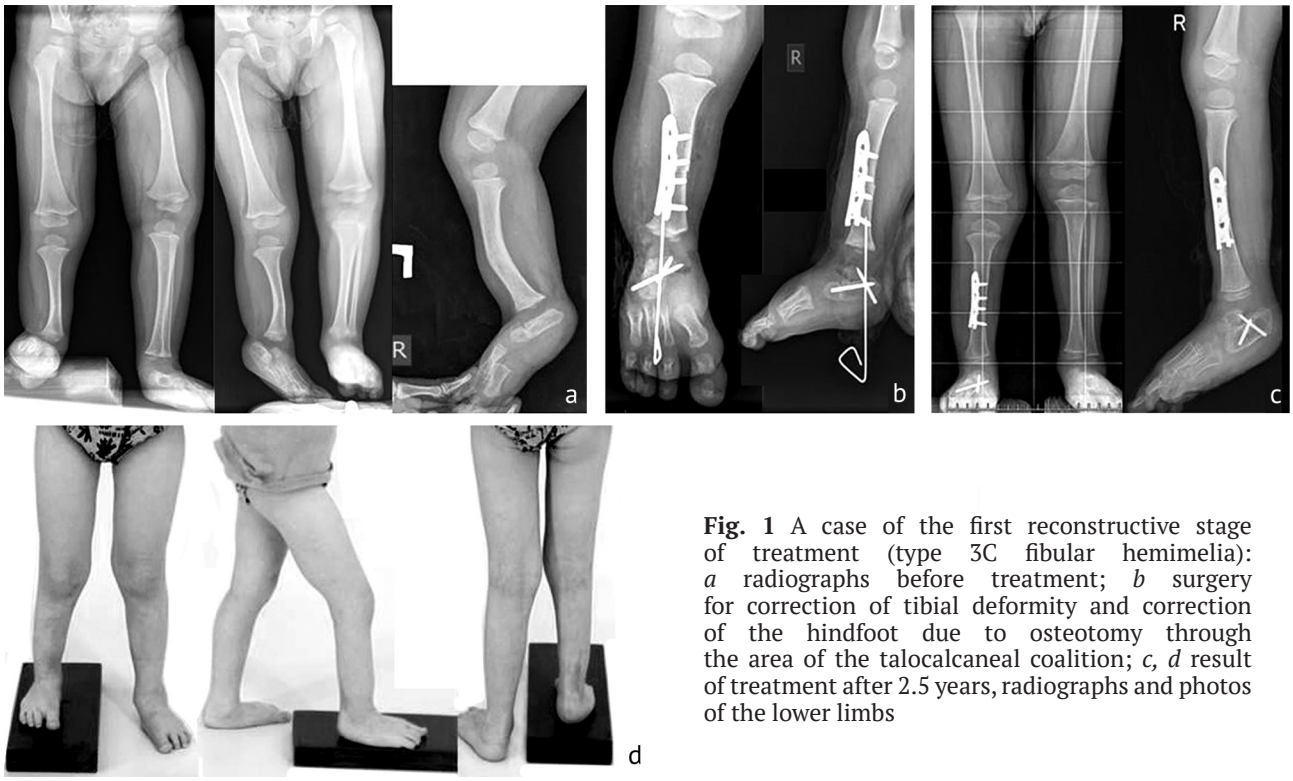

Fig. 1 A case of the first reconstructive stage of treatment (type 3C fibular hemimelia): *a* radiographs before treatment; *b* surgery for correction of tibial deformity and correction of the hindfoot due to osteotomy through the area of the talocalcaneal coalition; *c, d* result of treatment after 2.5 years, radiographs and photos of the lower limbs

Table 1

Results of radiographic studies after correction of lower limb deformities in FH patients

Patients	LDTA; °		ADTA; °		MAD; mm		TTA; °		TCCA; °	
1	68	84	84	83	12	4	120	97	80	117
2	69	86	85	83	14	3	119	97	74	105
3	74	88	84	84	12	0	117	95	69	110
4	84	87	83	82	15	3	123	99	68	106
5	83	85	84	84	15	4	130	98	70	107
6	82	85	83	87	16	5	125	95	78	99
7	84	87	85	85	18	2	130	95	67	106
8	71	85	86	85	21	2	130	111*	66	72*
9	73	90	89	84	11	0	141	98	58	108
10	72	84	85	85	18	3	134	145*	64	55*
11	68	83	89	82	22	4	142	97	65	105
12	66	86	87	84	18	6	139	99	64	116

Note: * – cases of hindfoot deformity recurrence and foot equinus

According to the Gillette questionnaire, the assessment of walking ability, which was influenced not only by anomalies of the limb development but also by age, before treatment was: level 3 – 3 patients, level 4 – 7 patients, level 5 – 2 patients. One year after the first stage of reconstructive treatment: level 7 – 6 patients, level 8 – 5 patients, level 9 – 1 patient.

The second stage of treatment to lengthen the tibia (Fig. 2) was performed in patients aged 3.5-6 years (mean age, 4.6 ± 1.2 years). The average lengthening was 6.4 ± 2.4 cm (37.2 ± 12.4 % of the initial segment length). The external osteosynthesis index averaged 22.9 ± 12.2 days/cm. Monofocal distraction osteosynthesis was used in 9 cases, bifocal in three cases. Correction of foot equinus and gradual correction of the hindfoot deformity due to osteotomy of the calcaneus were carried out simultaneously with monofocal lengthening of the tibia (Fig. 3; Fig. 4).

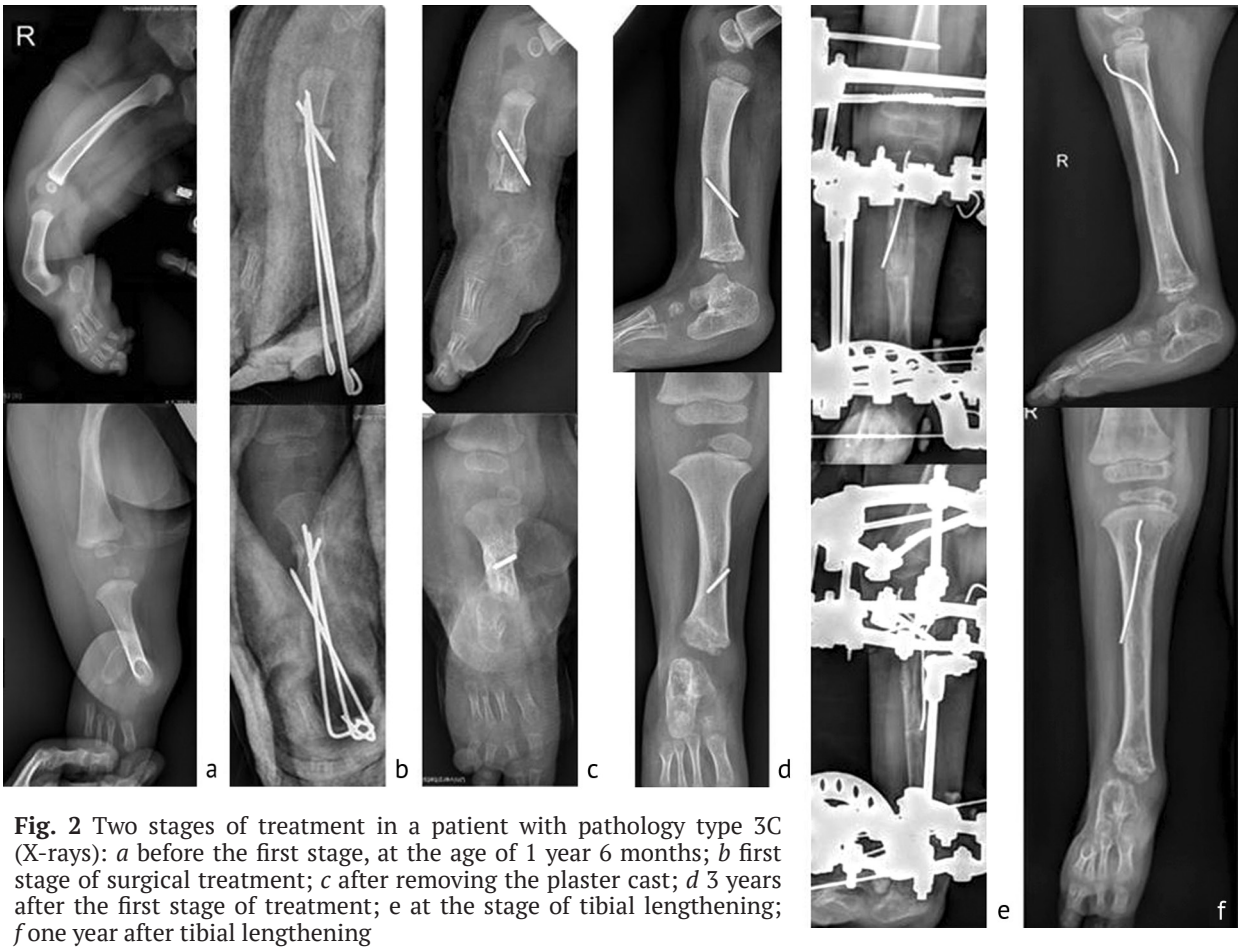

Fig. 2 Two stages of treatment in a patient with pathology type 3C (X-rays): *a* before the first stage, at the age of 1 year 6 months; *b* first stage of surgical treatment; *c* after removing the plaster cast; *d* 3 years after the first stage of treatment; e at the stage of tibial lengthening; *f* one year after tibial lengthening

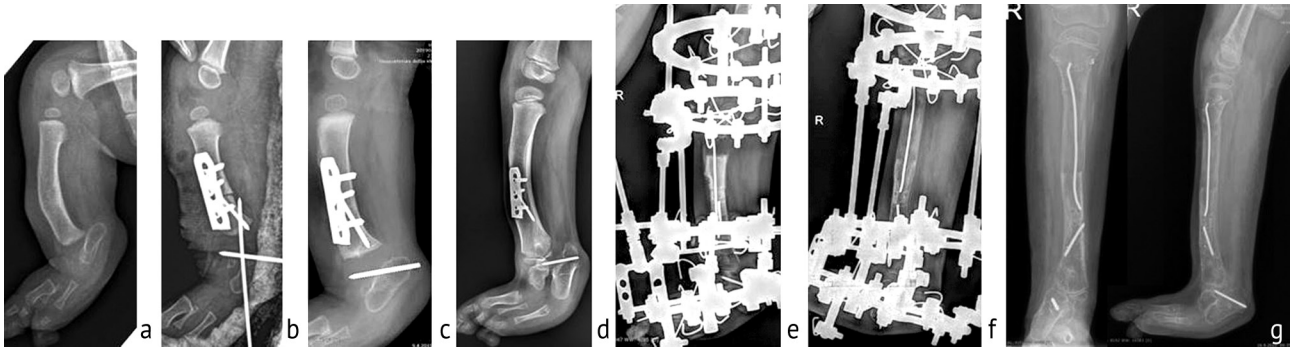

Fig. 3 A case of developed foot equinus and its correction (X-rays): *a* before surgery; *b* first stage of deformity correction; *c* after removing the plaster cast; *d* equinus of the hindfoot 2 years after surgery; *e* second stage of treatment, lengthening with simultaneous gradual closed elimination of foot deformity using the Ilizarov apparatus; *f* before removing the Ilizarov frame; *g* after removing the frame, the foot remains in a satisfactory position, close to full weight bearing

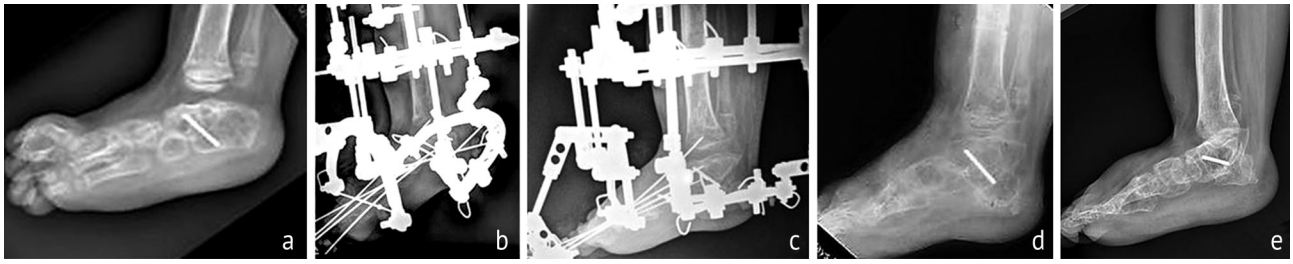

Fig. 4 Correction of recurrent deformity of the calcaneus, radiographs (FH type 3C): *a* the foot before the lengthening stage, tibial-calcaneal angle 72°; *b* at the beginning of foot deformity correction; *c* after correction of the deformity achieved, the angular divergence of the calcaneal fragments is clearly visible; *d* after removal of the Ilizarov apparatus; *e* follow-up after 1.5 years, the treatment result is maintained

Among the complications of the second stage of treatment (tibial lengthening), there was one case of a tibial fracture after removal of the Ilizarov apparatus, which required fixation of the limb in a plaster cast and was completed without loss of lengthened magnitude and secondary deformities. Four children had superficial infection near the wires. In such cases, antibiotic therapy was used, and regular dressings were effective. Thus, the results of limb lengthening using the Ilizarov apparatus were classified according to P. Lascombes as 7 cases of category IA, four cases of IB, and one case of 2B.

DISCUSSION

The most severe forms of congenital fibular hemimelia (types 3 and 4 according to the Paley classification) are accompanied by deformities of the tibia, ankle dysplasia, absence of several rays of the foot, tarsal coalition, usually in a pronounced valgus or varus position of the foot [6, 20]. The disorders are so pronounced already at an early age that they complicate or completely hinder wearing orthotic devices and become the main reason for the delay or complete absence of walking function in children [21, 22].

Therefore, early amputations and prosthetics are an alternative treatment option: Syme and Boyd methods are common interventions [23, 24]. Studies of motor activity and quality of life conducted in groups of adolescents and adults after amputation (followed by prosthetic fitting) and after reconstructive treatment showed the absence of statistically significant total indicators of gait analysis, as well as comparable socio-psychological adaptation, quality of life and physical activity [7].

We emphasize that surgical treatment in this pathology should be aimed at achieving the highest possible functional result, and may include corrective osteotomies, lengthening, and complex reconstruction of soft tissues in the treatment plan. The treatment strategy depends on both the severity of the anomaly and the family's choice [9].

If reconstructive strategy is chosen, the most important element of treatment is correction of deformities of the lower leg, ankle joint area and functional position of the foot [25]. An interesting study by EJ Morris et al. [10] compared the functional results of a 6-minute walk test between the patients who underwent foot and ankle reconstruction and a group that underwent both reconstruction and subsequent tibial lengthening. The first group showed the best functional results.

From the same point of view, we also consider the conclusions that the lack of success of reconstructive surgery in severe FH is due to residual or recurrent deformities of the ankle, foot and leg, and not to the difference in the length of the lower extremities [11, 26, 27].

Therefore, the first stage of surgical treatment, performed at an early age, determines the success of all subsequent staged surgery.

The results of our study are concordant with the above conclusions about the importance of the functional result of the first intervention. The approach we used ensured excellent and good results in 83 % of cases after the first reconstructive stage. It should be noted that the complications encountered and recurrences of stage 1 deformities were eliminated during the subsequent planned limb lengthening. However, both patients who had recurrent foot deformities had limited functional abilities (walking and wearing shoes) between treatment phases.

The reason for the recurrence of foot deformities, in our opinion, lies in the complexity of the surgical technique. Due to deficiency in the length of soft tissues, correction of tibial deformity and foot deformity requires a shortening osteotomy of the tibia, which can be significant and is not always possible under the conditions of internal osteosynthesis.

The insufficient amount of resection in our series, combined with the limited time and effectiveness of fixation with a plaster cast and diafixation wires, caused pronounced soft tissues tension, which led to a relatively rapid relapse of the foot deformity. It is obvious that the use of external fixation, when reconstructive treatment and simultaneous lengthening of the lower leg are combined, does not pose the risk of excessive shortening of the segment, short-term fixation of the foot and lower leg, and can be recommended for the most severe FH types (3C), accompanied by severe deformities of the foot and lower leg [6, 12].

We consider another disadvantage of the applied approach to be the need to remove the osteosynthesis material (as a separate stage during the tibia lengthening operation), which limits the possibilities of distraction osteosynthesis or increases the surgical burden on the patient. It is obvious that the use of transphyseal intramedullary osteosynthesis elements during the first stage of surgical treatment, over which lengthening can be carried out subsequently, may be the most rational solution [28].

However, our small series of cases showed the rationality of the approach of separating the reconstructive stage of treatment (correction of tibial and foot deformities) in children aged 16-24 months and the stage of leg lengthening with the Ilizarov apparatus. This is important both from the point of view of restoration and development of limb function, and transferring the stage of lengthening with an external fixation device, which is difficult for a child, to an older, but preschool age.

CONCLUSION

The strategy of foot and ankle reconstruction at an early age (16-24 months) in children with severe FH, followed by lengthening of the tibia at the age of 4-6 years, has proven to be effective and is used when chosen by the patient's parents. In case of significant shortening osteotomy planned at the first treatment stage to correct tibial deformity, external fixation to correct the deformity and simultaneously lengthen the tibia is an alternative reasonable strategy.

Conflict of interest *Not declared.*
Funding *Not declared.*

REFERENCES

1. Froster UG, Baird PA. Congenital defects of lower limbs and associated malformations: a population based study. *Am J Med Genet*. 1993;45(1):60-64. doi: 10.1002/ajmg.1320450116
2. Rogala EJ, Wynne-Davies R, Littlejohn A, Gormley J. Congenital limb anomalies:frequency and aetiological factors. Data from the Edinburgh Register of the Newborn (1964-68). *J Med Genet*. 1974;11(3):221-233. doi: 10.1136/jmg.11.3.221
3. Georgescu T, Ionescu O, Toader OD, Bacalbasa N, Pop LG. Fibular hemimelia. *J Med Life*. 2022;15(4):587-588. doi: 10.25122/jml-2021-0397
4. Fordham LA, Applegate KE, Wilkes DC, Chung CJ. Fibular Hemimelia: More than just an absent bone. *Semin Musculoskelet Radiol*. 1999;3(3):227-238. doi: 10.1055/s-2008-1080068
5. Popkov A, Aranovich A, Popkov D. Prevention of recurrence of tibia and ankle deformities after bone lengthening in children with type II fibular hemimelia. *Int Orthop*. 2015;39(7):1365-1370. doi: 10.1007/s00264-015-2752-4
6. Fuller CB, Shannon CE, Paley D. Lengthening Reconstruction Surgery for Fibular Hemimelia: A Review. *Children* (Basel). 2021;8(6):467. doi: 10.3390/children8060467
7. Birch JG, Paley D, Herzenberg JE, et al. Amputation Versus Staged Reconstruction for Severe Fibular Hemimelia: Assessment of Psychosocial and Quality-of-Life Status and Physical Functioning in Childhood. *JB JS Open Access*. 2019;4(2):e0053. doi: 10.2106/JBJS.OA.18.00053
8. Elmherig A, Ahmed AF, Hegazy A, et al. Amputation Versus Limb Reconstruction for Fibula Hemimelia: A Meta-analysis. *J Pediatr Orthop*. 2020;40(8):425-430. doi: 10.1097/BPO.0000000000001510

9. Nossov SB, Hollin IL, Phillips J, Franklin CC. Proximal Femoral Focal Deficiency/Congenital Femoral Deficiency: Evaluation and Management. *J Am Acad Orthop Surg*. 2022;30(13):e899-e910. doi: 10.5435/JAAOS-D-21-01186
10. Morris EJ, Tofts L, Patterson M, et al. Physical performance of children with longitudinal fibular deficiency (fibular hemimelia). *Disabil Rehabil*. 2022 Jun;44(12):2763-2773. doi: 10.1080/09638288.2020.1849420
11. Patel M, Paley D, Herzenberg JE. Limb-lengthening versus amputation for fibular hemimelia. *J Bone Joint Surg Am*. 2002;84(2):317-319. doi: 10.2106/00004623-200202000-00021
12. Kulkarni RM, Arora N, Saxena S, et al. Use of Paley Classification and SUPERankle Procedure in the Management of Fibular Hemimelia. *J Pediatr Orthop*. 2019;39(9):e708-e717. doi: 10.1097/BPO.0000000000001012
13. Herzenberg JE, Shabtai L, Standard SC. Fibular hemimelia: principles and techniques of management. In: Sabharwal, S. (eds) *Pediatric lower limb deformities*. Springer, Cham. 2016:427-454. doi: 10.1007/978-3-319-17097-8_23
14. Popkov AV, Aranovich AM, Popkov DA. Features of surgical treatment of children with congenital fibular hemimelia. *Genij Ortopedii*. 2013;(1):55-60. (In Russ.)
15. Paley D. Surgical reconstruction for fibular hemimelia. *J Child Orthop*. 2016;10(6):557-583. doi: 10.1007/s11832-016-0790-0
16. Paley D, Herzenberg JE, Tetsworth K, et al. Deformity planning for frontal and sagittal plane corrective osteotomies. *Orthop Clin North Am*. 1994;25(3):425-465.
17. Popkov D, Lascombes P, Berte N, et al. The normal radiological anteroposterior alignment of the lower limb in children. *Skeletal Radiol*. 2015;44(2):197-206. doi: 10.1007/s00256-014-1953-z
18. Novacheck TF, Stout JL, Tervo R. Reliability and validity of the Gillette Functional Assessment Questionnaire as an outcome measure in children with walking disabilities. *J Pediatr Orthop*. 2000;20(1):75-81.
19. Lascombes P, Popkov D, Huber H, et al. Classification of complications after progressive long bone lengthening: proposal for a new classification. *Orthop Traumatol Surg Res*. 2012;98(6):629-637. doi: 10.1016/j.otsr.2012.05.010
20. Leonchuk SS, Neretin AS, Muradisinov SO, et al. Radiographical features of foot in patients with congenital fibular hemimelia. *REJR*. 2021; 11(2):219-226. (In Russ.) doi: 10.21569/2222-7415-2021-11-2-219-226
21. Hefti F. Malformations of the lower extremities. *Orthopade*. 2008;37(4):381-402. (In German) doi: 10.1007/s00132-008-1250-4
22. Tonbul M, Adas M, Keris I. Combined fibular and tarsal agenesis in a case of lower extremity hemimelia. *J Foot Ankle Surg*. 2007;46(4):278-82. doi: 10.1053/j.jfas.2007.03.005
23. Osebold WR, Lester EL, Christenson DM. Problems with excessive residual lower leg length in pediatric amputees. *Iowa Orthop J*. 2001;21:58-67.
24. Calder P, Shaw S, Roberts A, et al. A comparison of functional outcome between amputation and extension prosthesis in the treatment of congenital absence of the fibula with severe limb deformity. *J Child Orthop*. 2017;11(4):318-325. doi: 10.1302/1863-2548.11.160264
25. Johnson CE, Haideri NF. Comparison of functional outcome in fibular deficiency treated by limb salvage versus Syme's amputation. In: Herring JA, Birch JG (eds) *The child with a limb deficiency.* Rosemont: American Academy of Orthopaedic Surgeons Publ.; 1998:173-177.
26. Cheng JC, Cheung KW, Ng BK. Severe progressive deformities after limb lengthening in type-II fibular hemimelia. *J Bone Joint Surg Br*. 1998;80(5):772-776. doi: 10.1302/0301-620x.80b5.8475
27. Naudie D, Hamdy RC, Fassier F, et al. Management of fibular hemimelia: amputation or limb lengthening. *J Bon Joint Surg Br*. 1997;79(1):58-65. doi: 10.1302/0301-620x.79b1.6602
28. Mingazov E, Gvozdev N, Popkov A, et al. Preliminary Results of Bone Lengthening over Telescopic Titanium Intramedullary Rod. *Case Rep Orthop*. 2023;2023:4796006. doi: 10.1155/2023/4796006

The article was submitted 26.04.2023; approved after reviewing 26.05.2023; accepted for publication 01.12.2023.

Information about the authors:

Mikan Lazović – MD, Pediatric Surgery Resident, mikanlazovic@gmail.com, https://orcid.org/0000-0003-0936-5236;

Sergey S. Leonchuk – Candidate of Medical Sciences, Head of Department, leon4yk@mail.ru, https://orcid.org/0000-0003-0883-9663;

Siniša Ducić – MD, orthopedic traumatologist, sinisaducic@gmail.com, https://orcid.org/0000-0002-6496-2220;

Shokhbek Imomov – clinical resident, shoh777123@gmail.com;

Dmitry A. Popkov – Doctor of Medical Sciences, Head of the Clinic, Professor of the Russian Academy of Sciences, Corresponding Member of the French Academy of Medical Sciences, dpopkov@mail.ru, https://orcid.org/0000-0002-8996-867X.

Original article
https://doi.org/10.18019/1028-4427-2024-30-1-46-58

Surgical treatment of nonunion of the lateral humeral condyle in children using combined methods of bone grafting and the Ilizarov fixation

P.U. Urinbaev[1], Sh.M. Davirov[2]✉, I.P. Urinbaev[2]

[1] Samarkand State Medical University, Samarkand, Uzbekistan
[2] Samarkand branch of the Republican Specialized Scientific and Practical Medical Center for Traumatology and Orthopedics, Samarkand, Uzbekistan

Corresponding author: Sharof M. Davirov, sharofd1976@mail.ru

Abstract

Introduction Elbow trauma is common accounting for 40-50 % of all musculoskeletal injuries in children. From them, lateral condyle fractures are the second most common fractures in the pediatric elbow with complications ranging from 3.3 to 54.8 %.

The objective was to determine the effectiveness of nonunion of the lateral humeral condyle (LHC) treated with bone grafts harvested from the patient's fibular shaft and the Ilizarov apparatus.

Material and methods We report surgical treatment of bone defect repaired with bone graft and the Ilizarov apparatus in 57 children with nonunion of the LHC. Maintained articulation between the non-united bone and the radial head, magnitude and direction of displacement, visible resorption of the epimetaphysis, bone deficiency, malaligned upper limb, late ulnar neuritis were the parameters used for outcome assessment. Depending on the type of surgical treatment the patients were divided into 3 groups: Group 1 (n = 13) included patients who underwent open osteosynthesis and bone fixation using 2-3 Kirschner wires; Group 2 (n = 30) consisted of patients who underwent surgery to repair the bone defect between the humerus metaphysis and an non-united fragment of the LHC fixed with wires and immobilized with a cast; Group 3 (n = 12) included patients who were treated with bone graft followed by fixation of the bone and the graft using Ilizarov wires and frame. Two patients underwent supracondylar osteotomy.

Results The outcomes were evaluated based on criteria to include non-union consolidation, joint function, limb alignment and condition of the growth plate. Long-term results were explored in 49 (85.9 %) patients out of 57 over a period of 6 months to 10 years. The results were rates as good in 39 (79.6 %) patients, as fair in 9 (18.36 %) and poor in one (2.04 %) case.

Discussion Various types of operations are reported for non-united fractures and non-unions of the cervical spine to include surgeries from open osteosynthesis to complicated reconstructions.

Conclusion Surgeries aimed at repair of bone defects using fibular autograft facilitated consolidation of non-unions and engraftments.

Keywords: children, humerus fracture, elbow joint, head of the humeral condyle, lateral condyle, non-union, surgical treatment, bone grafting, Ilizarov method

For citation: Urinbaev PU, Davirov ShM, Urinbaev IP. Surgical treatment of nonunion of the lateral humeral condyle in children using combined methods of bone grafting and the Ilizarov fixation. *Genij Ortopedii*. 2024;30(1):46-58. doi: 10.18019/1028-4427-2024-30-1-46-58

INTRODUCTION

Impaired long bone healing of pediatric fracture occurs in 10 %. Unreasonable refusal of surgical treatment can result in complicated and slow fracture healing [1]. Injuries to the elbow joint are common, accounting for 40-50 % of all pediatric musculoskeletal injuries [2, 3]. Despite significant advances in the diagnosis and treatment of elbow injuries in children, poor results account for 16-28 % [4, 5]. Lateral condyle fractures of the elbow are associated with higher rates of complications ranging between 3.3 and 54.8 % [6-9]. Nonunions of the capitellum are observed in 28 % of the fractures [10]. Outcomes of non-united capitellum fractures of the remain disappointing: surgical treatment of non-united fractures of the capitellum [11] can result in poor outcomes ranging between 18 and 26.6 % [12]. Surgical treatment of intra-articular nonunions is challenging [13-18]. With use of many methods, restoration of the lost bone of the lateral condyle, replacement of the bone defect of the central lateral epimetaphysis, being typical for nonunions of the capitellum with valgus alignment of the forearm, are not considered. A bone defect in the central lateral portion of the humeral epiphysis and metaphysis can be seen in patients with long-term nonunions of the capitellum. A surgical procedure offered by the authors included bone grafting of the nonunion and replacement of the bone defect using bone grafts harvested from the fibular shaft of the patients and fixed with the Ilizarov frame [19].

The objective was to determine the effectiveness of nonunion of the lateral humeral condyle (LHC) treated with bone grafts harvested from the patient's fibular shaft and the Ilizarov apparatus.

MATERIAL AND METHODS

Our study includes outcomes of surgical treatment of 57 patients treated with bone grafting using autografts harvested from the fibular shaft and the Ilizarov external fixation. Treatment was performed between 2009 and 2022. Characteristics of the patients at the time of admission are shown in Table 1. Microsoft Excel was used for statistical data processing. The mean value of the parameter and standard deviation were used for descriptive statistics. The differences were considered significant at $p < 0.05$.

Table 1

Characteristics of patients

Description	Number of patients	
	abs.	%
Distribution by gender:		
boys	36	63
girls	21	37
Distribution by age:		
under 5 years	10	18
5-8 years	24	42
8-14 years	16	28
14 years and greater	7	12
Distribution by duration of injury:		
1-6 months	25	44
6 months - 1 year	18	32
1-12 years	14	24

The study received a favourable opinion from the relevant research ethics committee of the Samarkand branch of the Republican Specialized Medical Center for Trauma and Orthopaedics No. 2/12 dated May 17, 2009. The study was performed in accordance with ethical principles for medical research involving human subjects stated in the Declaration of Helsinki developed by the World Medical Association as revised in 2000. Written informed consent was obtained from all patients for publication of the findings without identifying details.

Based on clinical and radiological findings, patients with nonunion of the capitellum were divided into the following groups:

Group 1 included patients with nonunion with articulation preserved between the nonunion and the radial head, with a slight (up to 3 mm) displacement of the non-united fragment in the lateral direction, without visible resorption of the epimetaphysis;

Group 2 included patients with nonunons with articulation preserved between the nonunion and the radial head, with the nonunion displaced by more than 4-5 mm in several projections: lateral, anterior, posterior, proximal, and visible epimetaphyseal resorption, malaligned limb, with possible late ulnar neuritis;

Group 3 included patients with nonunons with impaired articulation between the nonunion and the radial head, subluxation, dislocation of an nonunited fragment from the joint cavity, impaired axis of the arm, and possible late neuritis of the ulnar nerve.

Physical examination included range of motion (ROM) in the joint, alignment of the upper limb, and innervation of the ulnar nerve.

RESULTS

Joint contracture. Five (8.8 %) patients had a full range of motion and the rest developed contracture with ROM measuring 30° (*n* = 15; 26.3 %), 50° (*n* = 11; 19.3 %), 70 ° (*n* = 12; 21.1 %), 90° (*n* = 5; 8.8 %), 120° (*n* = 9; 15.8 %).

Malaligned forearm bones. Valgus alignment of the forearm bones was observed in 27 (47.3 %) patients: measuring not greater than 10° (*n* = 11; 19.3 %), 15-25° (*n* = 10; 17.5 %) and 30-40° (*n* = 6; 10.5 %) (Fig. 1).

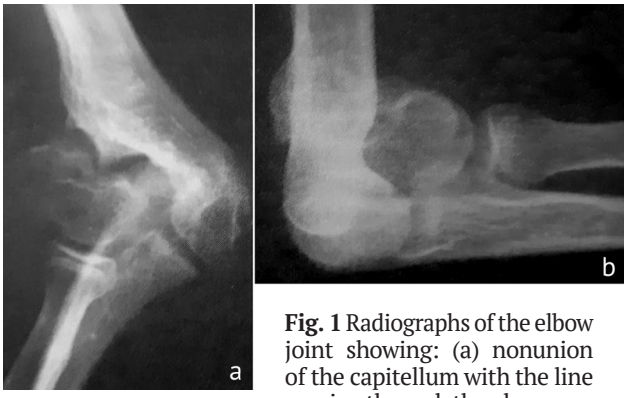

Fig. 1 Radiographs of the elbow joint showing: (a) nonunion of the capitellum with the line passing through the olecranon fossa on the AP view, severe cubitus valgus, osteoporotic bone; (b) anterior displacement of the fragment can be seen on the lateral view with poor proximal alignment

Cubitus valgus result from the bone displaced laterally + proximally, laterally + anteriorly + proximally and epiphyseal and metaphyseal resorption of the shoulder. Severe valgus deformity was seen in patients with unstable nonunions, non-united lateral humeral condyle (LHC) fractures with impaired articulation of the radial head. Varus deformity (*n* = 2) was characteristic of stable nonunions and nonunited fractures with posterior displacement of the LHC (Fig. 2a).

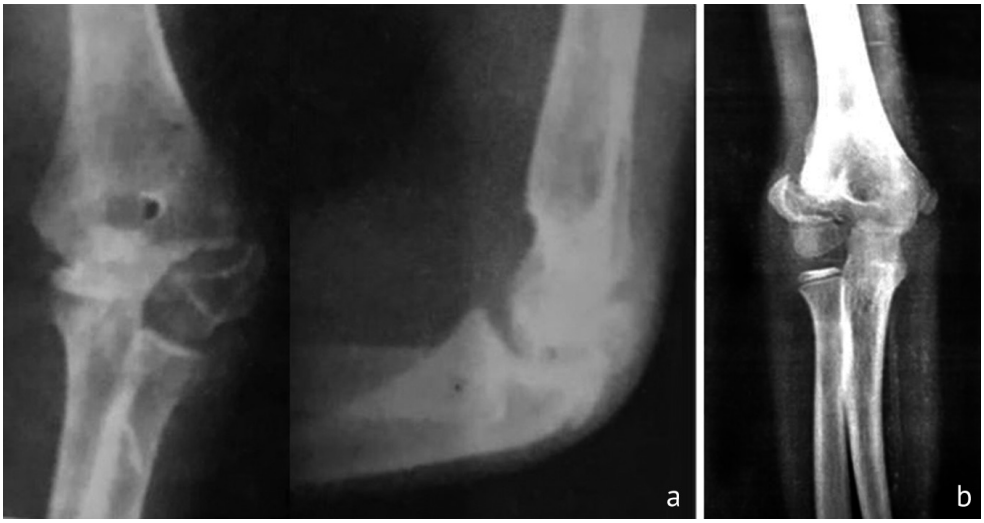

Fig. 2 Radiographs of the upper limb of patients with nonunions of the LHC: (a) without bone defect, osteoporosis of the LHC with cubitus varus; (b) nonunion of the LHC fragment

Late neuritis of the ulnar nerve. There was malalignment between the olecranon process and the medial epicondyle due to valgus alignment of the joint. There was narrowing of the sulcus ulnaris in the condyle, excursion of the nerve during flexion and extension and perineuritis and neuritis due to injury. The external deviation of the forearm bones measured 20-25° in 5 out of 6 patients with impaired ulnar nerve function and 35° in one patient.

Radiological examination. Anteroposterior and lateral views of the elbow joint were practical for evaluation of a fracture pattern (epiphysiolysis, osteoepiphysiolysis), location of the start of the fracture line (often in the trochlea), direction of the fracture in relation to the long axis of the shoulder (< 45°, > 45°), bone displacement (lateral + proximal, lateral + anterior + proximal),

amount of displacement (< 2 mm, > 2 mm), presence of a gap-diastasis, rotation, rotation of the fragment, preserved articulation with the radial head, protrusion of the fragment (subluxation, dislocation), bone resorption, bone deficiency of the epiphysis, metaphysis, bone defect of the nonunion, engraftment, fusion of the nonunion, restoration of the anatomical structure and the condition of the growth zone and the articular ends of the elbow joint.

Nonunion of the condylar head can develop because of different reasons. In our series, 13 (23 %) patients had nonunited fractures, and 44 (77 %) had pseudarthrosis. Among 44 patients with pseudarthrosis, 9 (20.5 %) had lateral displacement with bone rotation, subluxation, dislocation of the fragment, lacking contact of the fracture surfaces and impaired articulation of the lateral head. The resulting regenerate on the fracture plane cannot provide consolidation due to the rotation of the planes in different directions. One patient had successful reduction during the previous stage of treatment with secondary displacement, 3 patients had poor reduction, 5 patients were treated with plaster immobilization for 2-3 weeks.

Among 35 patients, 6 (17 %) had a fracture of the epiphysiolysis pattern, the rest had an epimetaphyllary fracture: the fracture line originated in the trochlear groove, crossed the growth zone, passed along the metaphysis and ended above the epicondyle. The fracture surface consisted of heterogeneous cartilage and bone tissue. For this group of patients, the bone displacement of fragments could be termed as lateral + proximal by 4-5 mm with resultant gap-diastasis of 2-3-4 mm or greater seen between the fragments. At the previous stage, 6 patients underwent closed reduction, which was successful in two cases, but with repeated secondary displacement in a plaster cast; 4 had failures and the rest were treated with a plaster cast. A few years later, nonunions that developed after ununited fractures with slight displacement with preserved articulation with the radial head were associated with delayed development of the central trochlea and the lateral condyle, resorption, epiphyseal and metaphyseal defects (Fig. 8), disappearing olecranon fossa, the forearm bones being displaced laterally at an angle of 20-40°. Post-traumatic late neuritis of the ulnar nerve could occur due to overstretching and pressing against the medial epicondyle with resultant secondary contracture of the joint. Some patients showed radiological signs of osteoporosis (Fig. 1, 3).

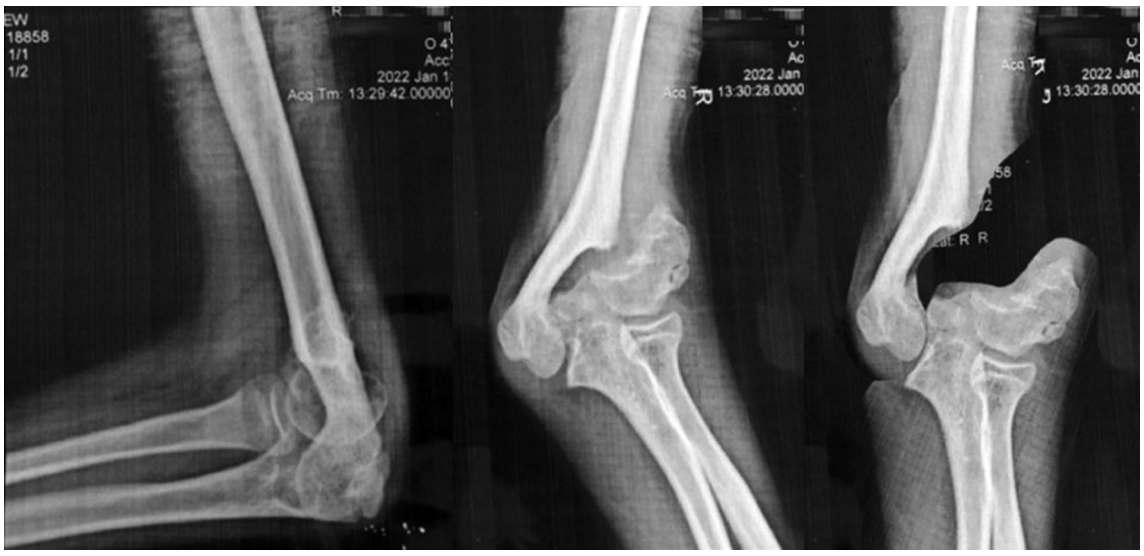

Fig. 3 Radiographs of the elbow joint showing nonunion of the capitellum (left). Dimensions of the defect formed after realignment could be visualized in the figure on the right

For such a pathology, surgical treatment should be aimed at stimulating reparation, filling the bone defect, achieving fusion of the nonunion, realigning the axis of the arm, creating anatomical conditions for restoring joint function and eliminating signs of late post-traumatic neuritis.

A method of surgical treatment of pseudoarthrosis of the lateral humeral condyle has been proposed with use of two diaphyseal bone grafts taken from the patient's fibular shaft, between metaphysis and the fragment replacing the bone defect formed at the site of the false joint. This technology

helps stimulate the repair of an osteoporotic bone, fusion of the nonunion, restoration of the impaired olecranon fossa, elimination of valgus alignment of the arm, avoiding supracondylar osteotomy and creating anatomical conditions for the elbow function.

The grafts were taken subperiosteally. The grafts length equated the size of the diastasis between the metaphysis and the nonunited fragment, measured intraoperatively to eliminate cubitus valgus. Grafts of 0.5-0.7 cm, about 1 cm, about 1.5-2 cm were normally used. The inside graft placed in the diastasis was shorter than the outside graft. One graft was used first in isolated cases to be followed by the use of two grafts (Fig. 4).

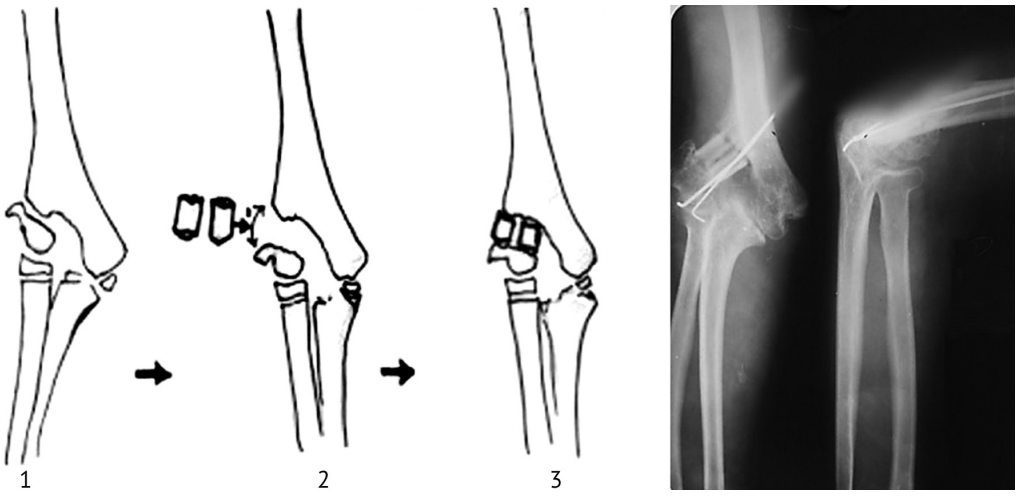

Fig. 4 Diagram of the operation and radiographs of the patient's elbow joint after bone grafting (clinical observation of the authors)

Depending on the surgical treatment used, our patients were grouped as follows (Table 2):

Group 1 included patients who underwent open osteosynthesis and bone fixation using 2-3 Kirschner wires (n = 13);

Group 2 included patients who had a bone defect repaired between the humeral metaphysis and a nonunited fragment of the LHC using wires and external immobilization with a plaster cast (n = 30);

Group 3 included patients who were treated with fixation of bone fragments and grafts using wires and Ilizarov frame after bone grafting (n = 12). The Ilizarov external fixation was used at the second stage after bone grafting in cases of the graft – metaphysis fusion with no fusion of the graft and the capitellum (n = 6).

Table 2

Distribution of patients by type of surgical intervention

Types of surgical interventions used for patients with non-united fractures and nonunions of LHC	Number of patients	
	abs.	%
Open metal osteosynthesis, fixation with wires	13	22.81
Bone grafting, fixation with wires	30	52.63
Bone grafting, fixation with wires and the Ilizarov frame	12	21.05
Supracondylar osteotomy	2	3.51
Total	57	100

Supracondylar osteotomy was performed for two patients.

Clinical instance of nonunion of the capitellum with a history of 9 years (Fig. 5).

We report a clinical example showing fusion of the medial graft and nonunited lateral graft over a period of 3 months of immobilization with a plaster cast that fused after application of the Ilizarov apparatus. Patient K.N., born in 2005, her clinical appearance and radiographs dated 2018.12.10 and 2019.01.29 (Fig. 6).

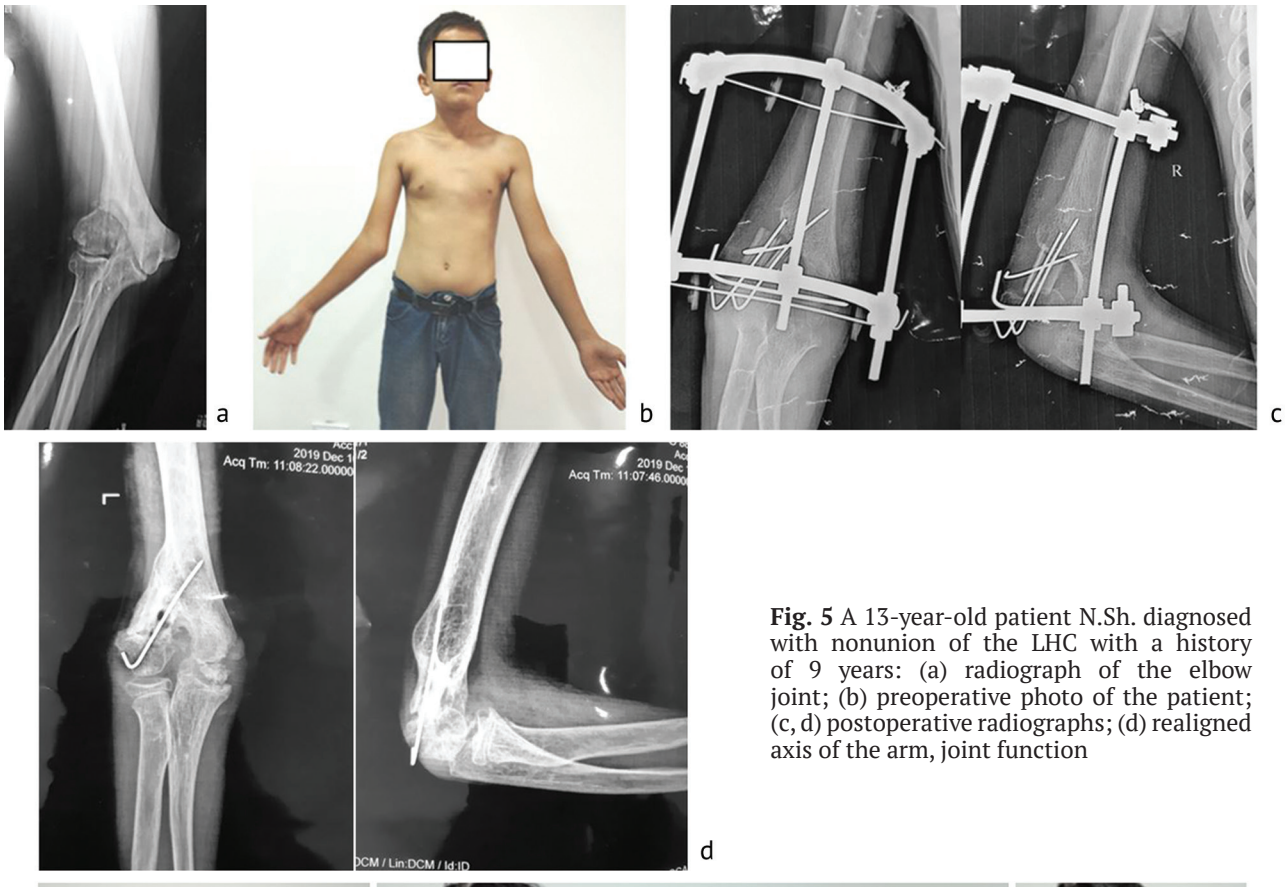

Fig. 5 A 13-year-old patient N.Sh. diagnosed with nonunion of the LHC with a history of 9 years: (a) radiograph of the elbow joint; (b) preoperative photo of the patient; (c, d) postoperative radiographs; (d) realigned axis of the arm, joint function

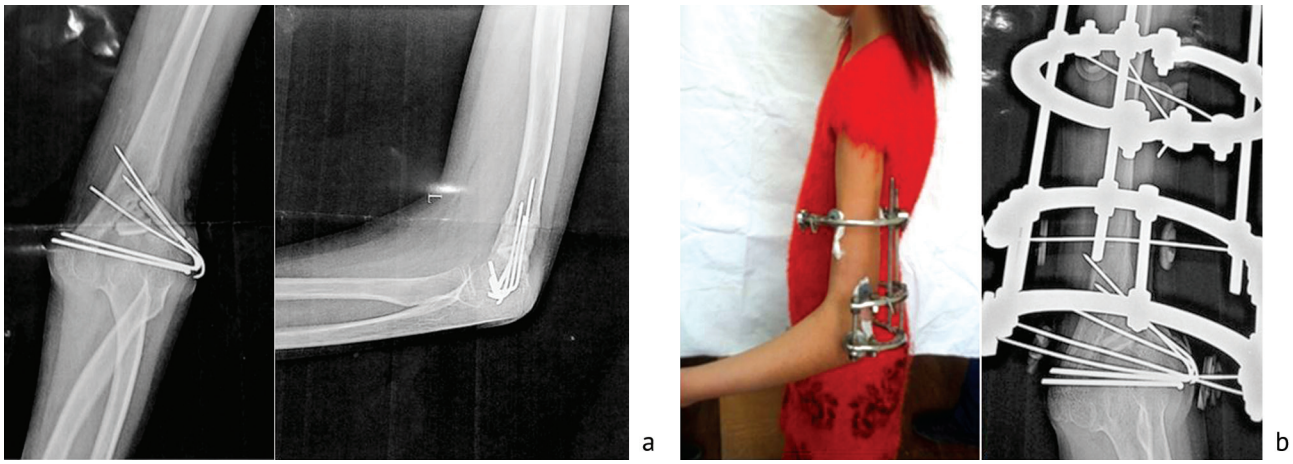

Fig. 6 Patient K.N.: (a) radiographs of the elbow joint dated October 12, 2018; (b) clinical appearance and a radiograph dated January29б 2019 during treatment with the Ilizarov apparatus

A supracondylar osteotomy was performed for two patients of group 3 with nonunions of the LHC developed after a fracture and dislocation of a fragment from the joint cavity, with impaired articulation with the radial head. The end of the central fragment shaped as a tent was deepened, the surface of the distal fragment adapted, the bone reduced and fixed with Ilizarov wires and the frame (Fig. 7).

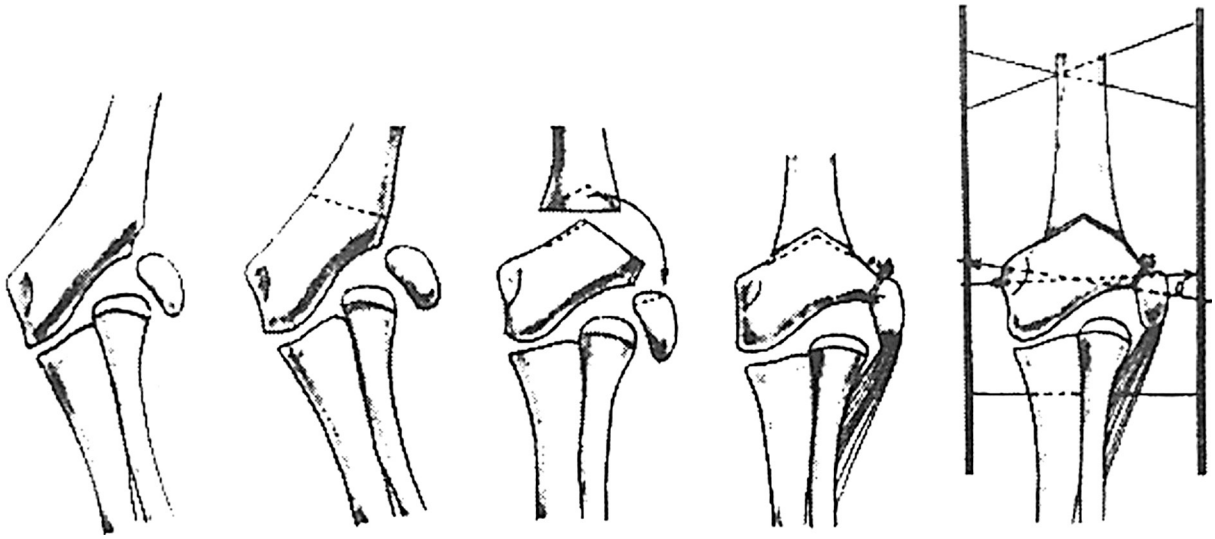

Fig. 7 Diagram of the operation performed for the patients of the third group with nonunions of the LHC and impaired articulation of nonunited fragment, the radial head and cubitus valgus

Results of bone grafting performed for nonunions of the capitellum

Long-term results must be evaluated in a differential manner, taking into account the severity of the fracture (nonunion, pseudarthrosis) based on objective criteria for assessing long-term outcomes. The fusion of pseudarthrosis, joint function, the arm axis, and the growth zone were assessed (Table 3).

Table 3

Criteria for assessing long-term results of non-union fractures, pseudarthrosis of the head of the humeral condyle in children

Criteria	Score
According to the bone fusion or non-union:	
1. The fusion is well aligned, but there is a uniform thickening of the condyle with olecranon fossa partially filled with bone tissue	4
2. Fusion is malaligned, the bone being rotated in the sagittal plane at least 20-25 degrees, laterally displaced, proximally at least 5 mm	3
3. Nonunion (resorption) of a fragment of the head of the condyle	2
Joint function (range of motion (ROM):	
1. ROM from 110 to 130° (N – 140-145°)	4
2. ROM from 80 to 110°	3
3. ROM up to 80°	2
Alignment of the upper limb:	
1. Straight elbow, valgus alignment of the forearm bones of at least 5° from physiological valgus	4
2. Valgus alignment 6-15° from physiological valgus	3
3. Valgus alignment of 20° or greater from physiological valgus	2
Impaired growth of the condyle and other components of the elbow joint:	
1. Premature closure of the growth plate in children older than 14 years	4
2. Premature closure of the growth plate in children aged 8-13 years; deformation of the epiphysis capitulum humeri, relative enlargement of the radial head and the coronoid process	3
3. Premature physeal closure in children aged 5-8 years, significant enlargement of the radial head, coronoid process, filling of anatomical fossae with bone tissue, narrowing of the joint space	2

The resulting sum of scores was divided by the number of characteristics and an average score was measured to rate the result as good, fair or poor. The outcome was evaluated as good with 15-16 scores in 4 criteria. For example: 15:4 = 3.75 (4 + 4 + 4 + 3). The outcome was evaluated as fair with a score of 11-14. For example: 12:4 = 3.0 (3 + 3 + 3 + 3). Poor result scored less than 10. For example: 10:4 = 2.5 (3 + 3 + 2 + 2).

The 12 patients who underwent bone grafting and Ilizarov external developed bone union. Out of 30 operations of bone grafting, fixation with 3-4 wires and external immobilization with a plaster cast, union was achieved in 24 (80 %) patients. The fusion period was 2-3 months, was obtained on the side of the Metaphyseal union was achieved in 6 (20 %) patients with weak consolidation noted on the side of the LHC and radiological nonunion. Pseudarthrosis consolidated in the patients with closed application of the Ilizarov apparatus at the second stage.

Resorption of bone grafts on the side of the LHC was observed in two patients who underwent reoperation. Bone grafting using the Ilizarov apparatus was performed in one patient who developed fusion of pseudarthrosis. Another patient had a recurrent nonunion. Long-term treatment results were examined in 49 (85.9 %) out of 57 patients over a period of 6 months to 10 years. Good results were obtained in 39 (79.6 %) patients, 9 (18.36 %) had fair outcomes and one result (2.04 %) was rated as poor. An operation to transpose the ulnar nerve, anterior to the medial epicondyle was performed for 7 patients with very long follow-up periods of 10 to 17 years, with late post-traumatic neuritis of the ulnar nerve and good elbow function, satisfactory alignment of the nonunited fragment and a small cubitus valgus.

DISCUSSION

Nonunion of the elbow fractures can be caused by localization (intra-articular injury), osteochondral involvement, instability, conservative treatment of displaced injury (lateral + proximal), with diastasis between the fragments and lack of external immobilization for an appropriate period. The period of external immobilization required for the healing of an acute fracture can range from 4 weeks according to G.M. Ter-Egiazarov et al. [20] to 4-6 weeks as reported by KS Song [21]; JM Weiss [22]; S Yuxi [23]; to 8-12 weeks according to JC Flyn [24].

Specific localization of the fracture, the fracture line, a small (up to 3-5 mm) lateral bone displacement without rotation prove diastasis along the fracture. This leads to a polycyclic course of the reparative regeneration process and requires longer immobilization. An outward + proximal displacement can be observed with peculiar direction of the fracture line with the fragment sliding laterally and rising upwards along the fracture plane. It can be suggested that the cartilaginous surface of the fracture at the epiphysis partially outstands the osseous portion of the fracture at the metaphysis (Fig. 8).

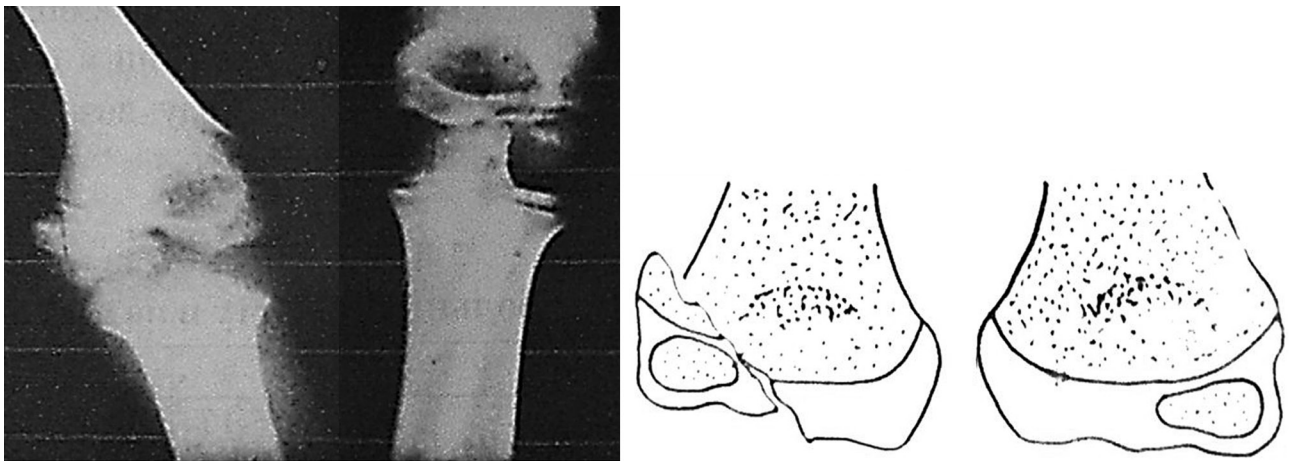

Fig. 8 Photo of radiographs and a diagram of a LHC fracture with lateral + proximal displacement, contact of heterogeneous tissues: the cartilaginous surface of the epiphysis is located opposite the osseous wound of the metaphysis

There is a contact of dissimilar tissues, which apparently slows down the formation of the regenerate that fails to be solid over the usual period of immobilization. Nonunion may occur in the cases with early exercising of the joint. The lateral condylus fragment and the fracture surface consist mainly of cartilaginous tissue. (Fig. 9).

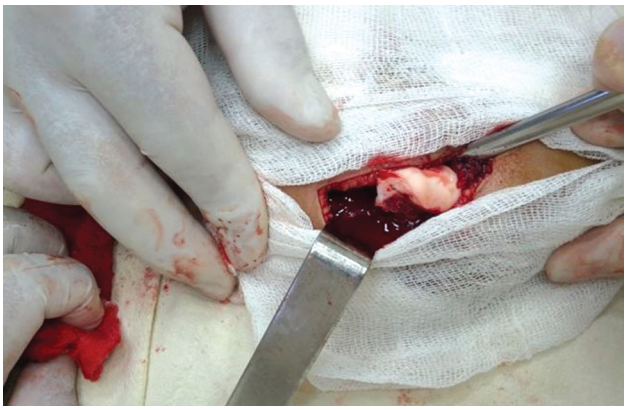

Fig. 9 Intraoperative photograph of a fragment of the lateral condyle of the humerus in a four-year-old child. The fragment consists of cartilage tissue

The fracture surface consists of bone tissue in the metaphyseal part and of the cartilage tissue in the epiphyseal portion. Regeneration processes occur with different intensity in the tissues. This was confirmed by the experiments reported by G.I. Lavrishcheva [25]. Despite the fact that most favorable conditions were created for osteochondral healing, "uneven" healing of wounds was noted in several experiments. There was no cartilaginous fusion in 25 % of the rabbits after 14-16 days and in 33 % after 19-21 days and in 50 % after 30 days with healing seen in the bone wound.

Fractures of the lateral epimetaphysis of the distal articular end of the humerus are often referred to as "fractures of the head of the humeral condyle" (LHC) (capitulum humeri).

The term fracture of the lateral condyle of the humerus describes more accurately the fracture pattern based on clinical and radiological findings of pseudarthrosis of capitellum. Various surgeries used to treat nonunited fractures and pseudarthrosis of the LHC include modalities from open osteosynthesis to complex reconstructive operations. The surgical strategy would be dependent on the position of the fragment: with the fragment being well aligned, the arm axis mainly maintained, joint contracture not seen, the surgery are not indicated due to a possible deterioration in the range of motion in the joint. Open reduction and bone fixation is indicated for pseudarthrosis of the LHC without pronounced valgus alignment of the forearm bones. Wires, a cortical bone graft in the form of a screw, screws are used to fix the bone fragment. Cubitus valgus can be corrected with supracondylar osteotomy. Plaster cast, skeletal traction, Ilizarov apparatus are used for external fixation. Transposition of the ulnar nerve anterior to the joint can be employed when needed.

Delayed consolidation at various stages of long bone repair and bone regeneration is termed differently: slowly healing fractures, non-uniting and non-united fractures, post-traumatic pseudarthrosis and long bone defects of. Each of the above terms can be a portion of a phase complicated by failed fracture consolidation and pathological process of reparative bone regeneration. The timing for transition from one stage of nonunion to another is different and depends on several factors including localization of injury; child's age; the extent of impaired regeneration processes; microcirculatory disorders; the presence or absence of osteoporosis and the treatment strategy. The results of treatment of non-united capitellum fractures remain disappointing. The rate of poor outcomes ranges from 18 to 26.6 % after surgical treatment of non-united LHC fractures. Insufficient knowledge of the causes of failed consolidation and the lack of comprehensive examination is one of the significant problems in the diagnosis and treatment of LHC fractures with a complicated course [26]. Imaging is the main diagnostic method of pediatric fractures and their consequences; computed tomography, thermography, laser Doppler flowmetry, and ultrasonography are also practical.

Surgical treatment of intra-articular pseudarthrosis is a difficult procedure. A variety of surgical treatments including osteosynthesis, supracondylar osteotomy, transposition of the ulnar nerve were

offered for treatment of capitellum based on the anatomical and functional changes of the elbow joint [3, 6, 18, 27-30]. Wires, screws [31-35] in combination with a bone graft, screws [36-38], and compression osteosynthesis [39, 40] were used to fix the bone. Autospongy bone tissue [41], homoplasty of the articular end [42] and joint replacement were treatment options [43]. Removal of the fragment [44] was not supported.

It has been suggested that nonunited fractures with good fracture position do not require surgical treatment but should be delayed until adulthood or until the when the deformity requires surgical correction [45, 46]. Other authors believe that surgical treatment can result in fusion with the risk of greater limitation in joint function, and extra-articular surgery can be offered using supracondylar osteotomy for valgus alignment of the forearm bones [7, 47, 48]. Early surgical treatment can be considered for nonunion with minor displacement and no noticeable limitation of elbow function. In case of significantly displaced bone fragment, the role of surgical treatment is questionable, because of a risk of early epiphyseal closure [49].

SI Stamatin et al. reported a case of homoplasty of the distal humerus in a 9-year-old child for valgus deformity associated with a defect in the articular end due to a fracture of the lateral condyle of the humerus [42]. At a long term, the forearm bones are set in a position of lateral deviation at an angle of 20-40°, patients can develop secondary contracture and late post-traumatic ulnar nerve neuritis.

GM Ter-Egiazarovs reported surgical intervention for the deformity using nonunited fragment to be placed in the bed and fixed with bone grafts; supracondylar osteotomy to be followed by skeletal traction [50]. The procedure could be added by bone fixation using Ilizarov wires and the frame [28, 29].

NA Ovsyankina et al. reported fixation of the fragment of the condylar head to the anatomical bed using a metal screw with the false joint to be covered with a bone autograft harvested from the distal humerus, with the brachioradialis muscle with vessels and nerves [51]. Patients with nonunited fractures and pseudarthrosis can be successfully treated with open osteosynthesis, conventional debridement of the false joint, bone reduction and fixation to the metaphysis with 3 or 4 wires. Bone replacement is indicated for patients with pseudarthrosis and a significant epimetaphyseal defect. It is common knowledge that replacement of diaphyseal bone defect was historically produced with the bone grafting developed by Lexer, described by VD Chaklin [11] regarding pseudarthrosis, a diaphyseal defect, tumor removal of processes using match stick grafts [6]; regarding bone defects after open injuries [12]. According to the researchers, an 11 cm long free autograft taken from the patient's fibula and transplanted onto a bone defect in the ulna showed good survival rate. This is consistent with the opinion of GI Lavrishcheva that the process of reconstruction or assimilation of the graft occurs most quickly with the transplantation of fresh autoplastic bone, and somewhat slower with homoplastic bone [25].

We filled the diastasis with bone grafts taken from the patient's fibula to achieve fusion by replacing the bone defect. Grafts with a length of 0.5-0.7 cm, about 1 cm, 1.5-2 cm were required. The internal graft placed in the diastasis was shorter than the external graft. Fixation was produced with 4-5 wires. External immobilization with a plaster cast facilitated fusion of the pseudarthrosis in 80 % of patients. Fusion was achieved from the metaphysis and grafts in 20 % of patients. The Ilizarov apparatus was practical for providing healing of the fragment and the grafts at the second stage of the procedure. The bone fusion occurred within 2-3 months of the Ilizarov application. All the grafts survived with the exception of 2 patients who could achieve fusion with repeated bone grafting. These clinical observations serve to understand the feasibility of bone grafting for nonunion of the capitellum/LHC. The procedure has greater indications for patients with severe osteoporosis of the nonunited fragment.

CONCLUSION

An intra-articular injury, a risk of impaired blood supply, bone instability (tendency to displacement), the cartilaginous surface of the epiphyseal part, a contact with the metaphyseal bone wound, and the polycyclic course of regeneration with failed callosity expected to develop within an appropriate timing are important factors affecting non-union of LHC fractures.

Patients with pseudarthrosis of the LHC, a bone defect at the pseudarthrosis can benefit from a surgery aimed to replace the bone defect with bone grafts taken from the fibula. The transplants have shown good survival rates, with the exception of a few cases. The valgus alignment of the forearm bones can be addressed with the anatomical prerequisites created for restoring ROM in the joint, eliminating osteoporosis of the LHC fragment. The use of the Ilizarov apparatus facilitates fusion of the pseudarthrosis in all cases. Postoperative immobilization with a plaster cast ensures fusion of the pseudarthrosis in 80 % of patients.

Conflict of interest *Not declared.*
Funding *Not declared.*

REFERENCES

1. Ter-Egiazarov GM, Struzhina VT, Mironov SP. Treatment of post-traumatic deformities and movement restrictions in the elbow joint in children. *Topical issues of traumatology and orthopedics*. 1977;15:68-71.
2. Mironov SP. *Post-traumatic deformities and contractures of large joints in children and adolescents and their treatment*. Dokt. Dis. Moscow; 1984:365. (In Russ.)
3. Antipov DI, Nikolaev AV, Morozov DA, Turkovskij VB. The use of compression metal osteosynthesis in the treatment of fractures of the distal metaepiphysis of the humerus in children. *Pediatric surgery*. 1998;3:35-37. (In Russ.)
4. Drozdov AS. *Fractures of the capitate eminence of the humerus in children*. Kand. Dis. Minsk: 1966. (In Russ.)
5. Sysa N.F. On the treatment of false joints of the head of the condyle of the shoulder in children. *Rehabilitation treatment of children with diseases and injuries of the musculoskeletal system*. Collection of scientific papers. Sankt-Peterburg: 1991:134-137. (In Russ.)
6. Bagomedov G.G. Errors in treatment of humeral condyle head fractures in children. *Actual problems of children's traumatology and orthopaedics*: Materials of conference. Sankt-Peterburg: 2005;15-16. (In Russ.)
7. Plasejchuk YuA. On the treatment of some chronic intra-articular fractures of the distal epimetaphysis of the humerus in children. *Collection of scientific papers of the Sverdlovsk NIITO and Leningrad NIITO*. 1973;2:208-211. (In Russ.)
8. Bohler J. Crossed boring wires, a simple principle of osteosynthesis. *Arch Orthop Unfallchir*. 1955;47(2):242-254. (In German)
9. Song KS, Kang CH, Min BW, et al. Closed reduction and internal fixation of displaced unstable lateral condylar fractures of the humerus in children. *J Bone Joint Surg Am*. 2008;90(12):2673-81. doi: 10.2106/JBJS.G.01227
10. Kuptsova OA, Baindurashvili AG, Nikitin MS. Underlying causes of poor outcomes in the treatment of children with fractures of the capitulum of the distal humeru. *Pediatric Traumatology, Orthopaedics and Reconstructive Surgery*. 2016;4(1):11-16. (In Russ.) doi: 10.17816/PTORS4111-16
11. Chaklin VD. *Fundamentals of operative orthopedics and traumatology*. Moscow: Meditsina Publ.; 1964:738. (In Russ.)
12. Davirov ShM, Urinboev PU. Repair of an open forearm fracture and extensive bony loss (case report). *Genij Ortopedii*. 2021;27(1):87-91. doi: 10.18019/1028-4427-2021-27-1-87-91
13. Bairov GA, Ul'rih EV. *Proceedings of the II All-Russian Congress of Traumatologists-Orthopedists, 1971*. Leningrad: 1973:223-227. (In Russ.)
14. Ovsyankin NA, Nikityuk IE. Treatment of children with false joints of the head of the condyle of the humerus. In: *Materials of the meeting of the main pediatric orthopedists and traumatologists of Russia "Topical issues of pediatric traumatology and orthopedics"*; Saint Peterburg; 2002:6-77. (In Russ)
15. Watson-Jones R. *Fractures and joint injuries*. Moscow: Meditsina Publ.; 1972:672. Available at: https://www.forens-med.ru/book.php?id = 555. Accessed Dec 25, 2023.
16. Eamsobhana P, Kaewpornsawan K. Should we repair nonunion of the lateral humeral condyle in children? *Int Orthop*. 2015;39(8):1579-85. doi: 10.1007/s00264-015-2805-8
17. Jakob R, Fowles JV, Rang M, Kassab MT. Observations concerning fractures of the lateral humeral condyle in children. *J Bone Joint Surg Br*. 1975;57(4):430-6.
18. Lang C. The treatment methodology and clinical outcomes of fractures of the lower end of the humerus. *Arch. Orthop* trauma surgeon. 1935;35(H-2):129-146

19. Urinbaev PU, Eranov NF, Urinbaev IP. Surgical treatment of pseudoarthrosis of the head of the condyle of the humerus using bone grafting. *Materials of the IX Congress of Traumatologists and Orthopedists. Uzbekistan actual problems of traumatology and orthopedics*. Tashkent; 2017:96-97. (In Russ)
20. Ter-Egiazarov GM, Struzhina VT, Urinbaev PU. Misunited and nonunited fractures of the head of the condyle and trochlea of the humerus in children. *Materials of the reports of the III Inter-Republican Congress of Traumatologists and Orthopedists of Transcaucasia*. Tbilisi; 1976:195-198. (In Russ)
21. Song KS, Kang CH, Min BW, et al. Closed reduction and internal fixation of displaced unstable lateral condylar fractures of the humerus in children. *J Bone Joint Surg Am*. 2008;90(12):2673-2681. doi: 10.2106/JBJS.G.01227
22. Weiss JM, Graves S, Yang S, et al. A new classification system predictive of complications in surgically treated pediatric humeral lateral condyle fractures. *J Pediatr Orthop*. 2009;29(6):602-605. doi: 10.1097/BPO.0b013e3181b2842c
23. Su Y, Chen K, Qin J. Retrospective study of open reduction and internal fixation of lateral humeral condyle fractures with absorbable screws and absorbable sutures in children. *Medicine* (Baltimore). 2019;98(44):e17850. doi: 10.1097/MD.0000000000017850
24. Flynn JC. Nonunion of slightly displaced fractures of the lateral humeral condyle in children: an update. *J Pediatr Orthop*. 1989;9(6):691-6. doi: 10.1097/01241398-198911000-00012
25. Lavrishcheva GI, Onoprienko GA. *Morphological and complex aspects of reparative classification of supporting organs and tissues*. Moscow: Meditsina Publ.; 1996:208. (In Russ)
26. Shamsiev AM, Urinbaev PU. *Treatment of chronic fractures of the distal end of the humerus in children*. Tashkent 2000:162. (In Russ)
27. Levitsky S.F. *Fractures of the head of the condyle of the humerus in children and their treatment: Autoref. Kand. Dis*. Kharkov; 1988. (In Russ)
28. Urinbaev PU. *Treatment of fractures and their consequences of the distal end of the humerus in children*: Doct. Diss. Samarkand; 1995. (In Russ)
29. Urinbaev PU. *Improperly fused, non-fused, fractures and pseudoarthrosis of the capitate eminence of the humerus in children*. Autoref. Kand. Dis. Moskva; 1977. (In Russ)
30. Klima J, Klima T. Pseudarthrosis of condyle of the humerus and its significance in Working capacity. *Cas Lek Cesk*. 1953;92(41-42):1133-1134.
31. Flynn JC, Richards JF Jr, Saltzman RI. Prevention and treatment of non-union of slightly displaced fractures of the lateral humeral condyle in children. An end-result study. *J Bone Joint Surg Am*. 1975;57(8):1087-1092.
32. Flynn JC. Nonunion of slightly displaced fractures of the lateral humeral condyle in children: an update. *J Pediatr Orthop*. 1989;9(6):691-696. doi: 10.1097/01241398-198911000-00012
33. Gajdobranski D, Marić D, Tatić M, et al. Osteosynthesis with Kirschner pin fixation in treatment of fractures with dislocation of the lateral condyle of the humerus in a pediatric population. *Med Pregl*. 2004;57(1-2):60-66. (In Serbian) doi: 10.2298/mpns0402060g
34. Knight DM, Alves C, Alman B, Howard A. Percutaneous screw fixation promotes healing of lateral condyle nonunion in children. *J Pediatr Orthop*. 2014;34(2):155-160. doi: 10.1097/BPO.0000000000000077
35. Tan SHS, Dartnell J, Lim AKS, Hui JH. Paediatric lateral condyle fractures: a systematic review. *Arch Orthop Trauma Surg*. 2018;138(6):809-817. doi: 10.1007/s00402-018-2920-2
36. Abzug JM, Dua K, Kozin SH, Herman MJ. Current Concepts in the Treatment of Lateral Condyle Fractures in Children. *J Am Acad Orthop Surg*. 2020;28(1):e9-e19. doi: 10.5435/JAAOS-D-17-00815
37. Espino AMJ, Nualart L, Capdevila R. Pseudoarthrosis of distal fractures of the humerus in children, clinical and radiological correlation. *Rev Mex Ortop Ped*. 2005;7(1):24-29. (In Spanish)
38. Toh S, Tsubo K, Nishikawa S, et al. Long-standing nonunion of fractures of the lateral humeral condyle. *J Bone Joint Surg Am*. 2002;84(4):593-598. doi: 10.2106/00004623-200204000-00013
39. Lavrishcheva GI, Onoprienko GA. *Morphological and evolutionary aspects of reparative certification of supporting organs and tissues*. Moscow: Meditsina Publ.; 1996:208. (In Russ)
40. Shapiro MS. Features of diagnosis and surgical treatment of chronic brain fractures in children. *Diseases and injuries of the upper limbs in children. Collection of scientific works*. Leningrad 1988:120-123. (In Russ)
41. Moroz PF. Treatment of fractures of the distal epimetaphysis of the humerus in children. *Orthopedics, traumatology and prosthetics*. 1976;4:70-72.
42. Stamatin S.I., Merin I.M., Yakunina L.N. Homoplasty of the articular ends of long tubular bones. *Arthroplasty of large joints: Mater. All-Union. symposium*. Moscow: Medicine, 1974:129-134. (In Russ)
43. Peterson HA. *Epiphyseal Growth Plate Fractures*. Berlin: Springer-Verlag, 2007. doi: 10.1007/978-3-540-33802-4
44. Blasche J. *Lateral joint fracture of the elbow joint*. 1962:1657-1665.
45. Hardacre JA, Nahigian SH, Froimson AI, Brown JE. Fractures of the lateral condyle of the humerus in children. *J Bone Joint Surg Am*. 1971;53(6):1083-1095.
46. Jeffery CC. Non-union of the epiphysis of the lateral condyle of the humerus. *J Bone Joint Surg Br*. 1958;40-B(3):396-405. doi: 10.1302/0301-620X.40B3.396

47. Akhundov AA, Boyarinova NV, Ovsyankin NA. Unfavorable consequences of an unrepaired fragment occur with fractures in the area of the elbow joint in children. *Proceedings of the II All-Russian Congress of Traumatologists-Orthopedists, 1971*. Leningrad: 1973:236-237. (In Russ.)
48. Bogdanov FR. *Reparative processes in intra-articular fractures and principles of treatment of these fractures*. Sverdlovsk-Moscow; 1937. (In Russ.)
49. Flynn JC, Richards JF Jr. Non-union of minimally displaced fractures of the lateral condyle of the humerus in children. *J Bone Joint Surg Am*. 1971;53(6):1096-1101.
50. Ter-Egiazarov GM, Struzhina VT, Urinbaev PU. Misunited and nonunited fractures of the head of the condyle and trochlea of the humerus in children. *Materials of the reports of the III Inter-Republican Congress of Traumatologists and Orthopedists of Transcaucasia*. Tbilisi 1976:195-198. (In Russ.)
51. Ovsjankin NA, Malenkov NN, Nikitjuk IE. *Method for treating false joints of condyle head and humerus*. Patent RF, no. 2158114, 2000. Available at: https://patents.google.com/patent/RU2158114C2/ru. Accessed Aug 18, 2023.

The article was submitted 12.04.2023; approved after reviewing 07.08.2023; accepted for publication 01.12.2023.

Information about the authors:

Payzulla U. Urinboev – Doctor of Medical Sciences, Professor;
Sharof M. Davirov – Orthopedic Traumatologist, sharofd1976@mail.ru;
Ikrom P. Urinbaev – Orthopedic Traumatologist.

Original article
https://doi.org/10.18019/1028-4427-2024-30-1-59-66

Pathogenetic and clinical significance of fungal infection of the palmar aponeurosis in Dupuytren's contracture

T.A. Stupina✉, N.A. Shchudlo, T.N. Varsegova, D.A. Ostanina

Ilizarov National Medical Research Centre for Traumatology and Orthopedics, Kurgan, Russian Federation

Corresponding author: Tatyana A. Stupina, StupinaSTA@mail.ru

Abstract

Introduction Among the generally accepted theories of the etiology and pathogenesis of palmar fascial fibromatosis, the role of infectious factors has not been considered; however, there are references to fungal skin lesions in patients with advanced contractures and several studies that identified fungal infection in surgical material from such patients.

The purpose of the work was to assess the pathogenetic and clinical significance of fungal infection of the palmar fascia in Dupuytren's contracture.

Materials and methods We studied 41 medical records of patients operated on for Dupuytren's contracture in stages II-IV. The surgical material was examined at the light-optical level (hematoxylin-eosin and methenamine-silver PASM stains) and with scanning electron microscopy.

Results Fungal infection of the palmar aponeurosis was detected in 20 out of 41 patients; various types of tissue reaction to the introduction of fungi into the palmar aponeurosis and the blood vessels perforating it were found. Groups of patients without signs of fungal invasion (n = 21) and with signs of fungal infection of the palmar aponeurosis (n = 20) were comparable in clinical and demographic characteristics, but significantly differed in the rate of early relapses, 0 versus 25 % in the group with fungal infection (p = 0.02).

Discussion The immunogenetic characteristics of patients with palmar fascial fibromatosis and characteristic skin lesions create general and local conditions for the introduction of fungal flora.

Conclusion Histological detection of pseudohyphae of the genus Candida in the palmar aponeurosis and the lumens of blood vessels in patients with Dupuytren's contracture verifies invasive candidiasis; the relationship between fungal infection of the aponeurosis and an increased rate of early relapses of contracture has been statistically proven. To increase the duration of the relapse-free period and potentially the life expectancy of patients, consultations with infectious disease mycologists and correction of modifiable risk factors for candidiasis are necessary.

Keywords: palmar fascial fibromatosis, Dupuytren's contracture, mycoses, relapses

For citation: Stupina TA, Shchudlo NA, Varsegova TN, Ostanina DA. Pathogenetic and clinical significance of fungal infection of the palmar aponeurosis in Dupuytren's contracture. *Genij Ortopedii*. 2024;30(1):59-66. doi: 10.18019/1028-4427-2024-30-1-59-66

INTRODUCTION

Dupuytren's disease or palmar fascial fibromatosis (PFF) refers to fibroproliferative diseases of connective tissue which is characterized by an increased content of myofibroblasts, hyperproduction of collagen types III and I, thickening and contraction of the palmar-digital fascia and dermis of the skin [1]. Changes in fascial structures and integumentary tissues lead to restrictions in finger extension, and then to contractures and fixed deformity of the metacarpophalangeal and interphalangeal joints, and a decrease in hand grip strength [2]. These changes inevitably reduce the quality of life of patients, disrupting professional skills, daily activities and social contacts [3]. Despite the development of many methods for conservative, surgical and minimally invasive treatment of Dupuytren's contracture [4], fascial fibromatosis is considered incurable, since it has infiltrative growth and recurs [5].

Among the generally accepted theories of the etiology and pathogenesis of Dupuytren's disease, the main ones are genetic, microtraumatic, immunological, toxic, ischemic [6], and metabolic [7]. Fibromatous nodes are characterized by microvascular changes, primarily occlusion of capillaries and proliferation of pericytes, and presence of macrophages, the number of which correlates with the number of myofibroblasts; lymphocytes are localized around the nodes [8].

Despite the identification of inflammatory cells in most patients, the role of infectious factors in the development of fascial fibromatosis is not traditionally considered. However, a case of phlegmonous infection in the first stage of the disease was described [9], and the development of skin mycoses was mentioned in severe contractures [10]. Skin retractions that form in some patients in the early stages of the disease [11] can facilitate deeper penetration of the infectious agent [12]. Using scanning electron microscopy in patients with Dupuytren's contracture, budding fungal flora was established in the areas of the pathologically altered aponeurosis excised during fasciectomy [13]. Diagnosis of mycoses is critical not only for full postoperative rehabilitation, but also for the future life of patients; however, the pathogenetic and clinical significance of mycotic invasion into the fascial structures of the hand remains unclear.

Purpose: to evaluate the pathogenetic and clinical significance of fungal infection of the palmar fascia in Dupuytren's contracture.

MATERIALS AND METHODS

In the period from 2017 to 2020, interventions were performed in 153 patients with Dupuytren's contracture at the Ilizarov National Medical Research Center for Traumatology and Orthopaedics. Using a random selection method, a sample of 41 patients with contracture of the Tubiana degrees II-IV [14] was formed who underwent partial fasciectomy. Among them there were 39 men and 2 women aged from 39 to 77 years.

Inclusion criteria were clinically evident and histologically confirmed palmar fascial fibromatosis. Exclusion criteria were hand contractures of another etiology.

For histological examination, tissue samples, after fixation in a 10 % neutral formaldehyde solution, were embedded in paraffin according to standard methods. Paraffin sections (5-7 μm thick) were prepared using an HM 450 Thermo Scientific microtome (USA) and were stained with hematoxylin and eosin; PASM methenamine-silver staining was used to identify fungal mycelium. Light-optical study and digitization of images of histological sections were carried out using an AxioScope.A1 microscope with an AxioCam digital camera and Zen Blue Edition software (Carl Zeiss MicroImaging GmbH, Germany).

Tissue samples (size, 3 × 5 mm) fixed in formalin for examination in a scanning electron microscope (SEM) "JSM-840" (Jeol, Japan) were washed in distilled water, then dehydrated in ethanol (from 70 to 96 %) and soaked in 3 ,3-dimethyl-2-methylenebicyclo[2,2,1]heptane (camphene) [15]. The samples were dried in a thermostat at 37 °C, then mounted on polished clean aluminum disks

using conductive glue and sputtered with silver in an IB-6 ion sputter (Eiko, Japan). The conductive paste was used to remove the charge from the sputtered surface of the sample.

The patients were divided into two groups for subsequent clinical and statistical analysis, based on the results of studying the surgical material at the light-optical level and SEM: Dupuytren's contracture without signs of mycotic invasion (group 1, n = 21) and Dupuytren's contracture with signs of mycotic lesions of the palmar aponeurosis (group 2, n = 20). For the comparative analysis, the following parameters were used: age at the start of PFF, the male-to-female ratio, age at the time of surgery, PFF imcidene in both hands, degree of contracture, number of fingers with impaired function, frequency of primary operations and operations for relapses, frequency of visits for relapses.

Statistical processing of quantitative data was carried out in the Attestat software (version 9.3.1, developer I.P. Gaidyshev, Rospatent certificate No. 2002611109). Hypotheses about the normality of distribution were tested using the Shapiro–Wilk test. For some samples, the hypothesis of normality was rejected; table data are presented in the form of medians and quartiles, as well as minimum and maximum values (Me (Q1÷Q3)) (min-max). To test hypotheses about differences between the compared groups, the Mann–Whitney test and Fisher's exact test were used.

RESULTS

Light microscopy of paraffin sections revealed signs of mycotic lesions of palmar aponeurosis in four out of 41 patients (9.76 %). Pseudomycellar structures (budding yeast cells and pseudohyphae) were located in foci of chronic inflammation with signs of activation of lymphocytes and macrophages, as well as deposits of amorphous eosinophilic substance (Fig. 1 a, b). PASM stain revealed silver-positive yeast cells and pseudohyphae in the perivascular spaces and in the lumens of blood vessels (Fig. 1 c, d). In one patient out of four, giant multinucleated macrophages of the foreign body type cells and degenerative eosinophils were found in the foci of chronic inflammation, along with lymphocytes and macrophages (Fig. 1 e).

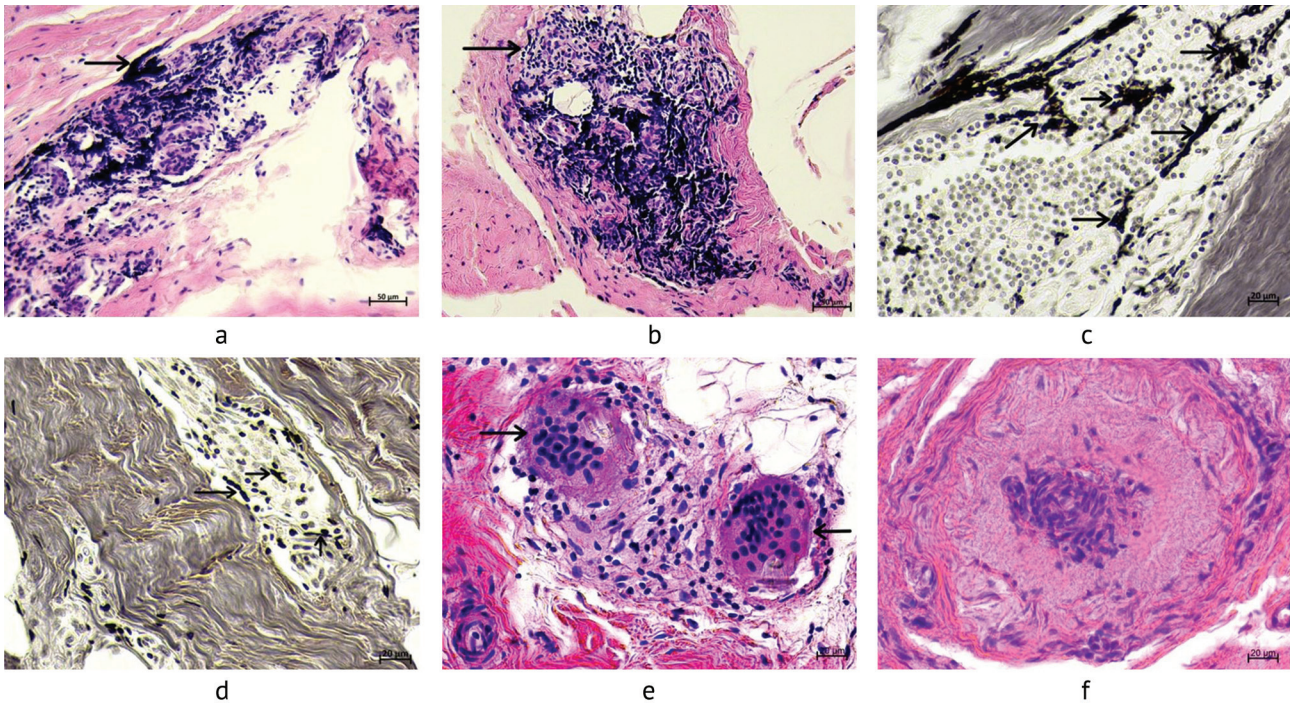

Fig. 1 Fragments of the palmar aponeurosis in Dupuytren's contracture with signs of fungal invasion: *a* pseudomicellar structures (arrow); *b* focus of chronic inflammation (arrow); *c, d* pseudohyphae in the lumen of blood vessels (arrows); *e* giant multinucleated macrophages of the foreign body cell type (arrows); *f* obliterated arteriole. Paraffin sections, stained with hematoxylin and eosin (*a, b, e, f*), methenamine-silver PASM (*c, d*). Magnification 200× (*a, b*) and 400× (*c, d, e, f*)

Few yeast cells and short pseudohyphae along with crystalline inclusions were located in the cytoplasm of giant multinucleated macrophages, such as foreign body cells. There were obliterated arterioles (Fig. f), in which degenerating yeast cells were detected along with dying cells of the vascular wall and inflammatory cells.

The SEM method detected fungal flora (Fig. 2 a-d) in 20 patients out of 41 (43.9 %). In 18 out of those 20 patients, budding yeast cells and pseudohyphae were found (Fig. 2 a, b, c), and pseudohyphae with blastospores were detected in two patients (Fig. 2 d).

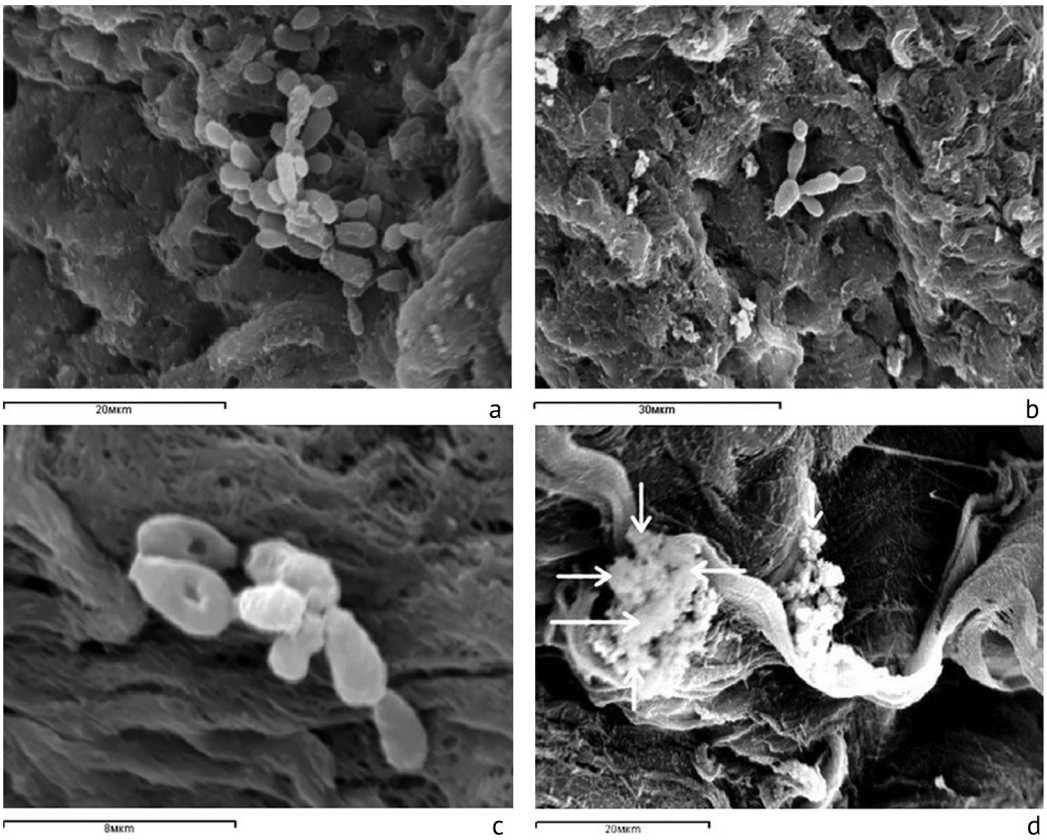

Fig. 2 Fragments of a pathologically altered palmar aponeurosis. SEM: *a* single and budding yeast cells; *b* pseudohypha; *c* pseudohypha and blastospores; *d* yeast cells (horizontal arrows) forming blastospores (vertical arrows). ×2300 (*a*), ×1700 (*b*), ×6000 (*c*), ×1800 (*d*)

Yeast cells had a round, round-oval, pear-like or slightly elongated shape; their sizes varied from 2 to 7 μm. Along with separately lying yeast cells, budding cells were also found. Some cells had a brightly contrasted depression in the center (Fig. 2 c). Both in intact and destroyed intercellular contacts, a ring-shaped girdle was evident at one end of the cell and a bud at the other. The thickness of the intercellular contact zone was no more than 0.5 μm. Blastospores were located on the surface of yeast cells in the form of clusters, immersed in the intercellular matrix in some places (Fig. 2 d), had a spherical shape, and were heterogeneous in size. Cavities were formed around the budding yeast cells as the connective tissue fibers loosened, exfoliated and lysed (Fig. 2 a-c).

Comparison of clinical and statistical indicators of patients (Table 1), divided into groups based on the absence or presence of fungal flora, found that the groups were comparable in age, gender composition, duration of fascial fibromatosis and the frequency of damage to both hands, degree of contracture, number of fingers with impaired function, the ratio of primary operations and operations for relapses, as well as the frequency of visits for late relapses (11-18 years after the primary operation) – $p > 0.05$.

Table 1

Clinical and statistical indicators of patients with Dupyuitren's contracture

Parameter	Group 1, *n* = 21		Group 2, *n* = 20		*P*[1,2]
	Me (Q1÷Q3)	(min-max)	Me (Q1÷Q3)	(min-max)	
Age at the onset of PFF, years	51 (40÷55)	(39-66)	48 (42÷59)	(38-69)	0.92[1]
Males:Females	21:1		19:1		0.74[2]
Age at surgery, years	57 (54.5÷63.5)	(45-71)	59 (55÷65)	(39-77)	0.57[1]
Duration of fascial fibromatosis	5 (3÷7.5)	(1-15)	6 (2.25÷10)	(1.5-18)	0.67[1]
Rate of fascial fibromatosis in both hands, %	57.14		50.0		0.76[2]
Contracture severity	3 (2.75÷3)	(1-4)	3 (2.5÷3.75)	(2-4)	0.52[1]
Number of finger with functional disorders	2 (1÷3)	(1-6)	2 (1÷3.5)	(1-7)	0.99[1]
Ratio of the studied material from primary operations and operations for relapse	19:2		16:4		0.41[2]
Rates of contracture recurrence at long term (11-18 years), %	9.52		5.00		0.52[2]
Rate of early recurrence (4-15 months after primary operation), %	0		25		0.02[2]*

[1] – Mann – Whitney test; [2] – Fisher's exact test; * – differences are significant $p < 0.05$

However, there were no complaints about early recurrence (4-15 months after the primary operation) in group 1, and in group 2 their rate was 25 % ($p < 0.05$).

DISCUSSION

Invasive fungal infections remain an underestimated cause of morbidity and mortality to this day [16], even in immunocompetent carriers [17].

We previously established the presence of fungal flora in the surgical material of patients with Dupuytren's contracture; we showed a higher resolution of SEM compared to light microscopy in detecting fungi and determining their taxonomic affiliation [13].

This study, carried out on a larger material, not only confirmed the difficulty of detecting fungal flora at the light-optical level and the frequent occurrence of fungal flora in the palmar aponeurosis with Dupuytren's contracture, but also could identify various options for tissue reactions to the introduction of fungi into the palmar aponeurosis, as well as the penetration of yeast cells and pseudohyphae into vessels perforating the palmar aponeurosis. The penetration of fungal flora through the epithelial and endothelial barriers may be facilitated by impaired blood supply [18, 19].

The lymphocytic-histiocytic chronic inflammatory infiltrate that forms in the invasion zone, giant multinucleated cells, degenerating eosinophils, crystal formation and damage to blood vessels are characteristic, but nonspecific for fungal infections, as they can occur with bacterial and parasitic lesions [20].

Pseudohyphae, dimorphism (yeast cells and blastospores), as well as features of the ultrastructure of intercellular contacts of fungal cells [21] are characteristic of Candida albicans, the most common representative of the opportunistic fungal flora, the various stages of morphogenesis of which have different effects on immune recognition [22]. Cutaneous candidiasis caused by other species of the genus Candida is rare in the clinic, as it is unusual for humans [23]. Since other species of the genus Candida may exhibit increased resistance to drugs, in recent years there has been intensive development of molecular and genetic methods for species identification, which have higher sensitivity and specificity compared to traditional microbiological methods [24].

The role of histological examination in the diagnosis of mycoses is great, since the presence of fungi, as well as signs of their invasion into tissues and blood vessels in histological preparations, is reliable evidence of a deep fungal infection [25]. If the presence of fungal flora is suspected and even with clinical manifestations of mycoses, microbiological methods frequently show false-negative results and do not allow differentiating contamination, colonization and infection, and polymerase chain reaction (PCR) methods and immunohistochemical reactions are not available in all laboratories, therefore scanning electron microscopy is regarded as an important diagnostic method [26], which can detect fungal lesions [27].

The work contains a comparative clinical and statistical analysis of two groups of patients with Dupuytren's contracture for the first time: without signs of fungal invasion and with damage to the palmar aponeurosis by fungi of the genus Candida. The groups are comparable in clinical and demographic characteristics, but significantly differ in the frequency of early Dupuytren's contracture recurrence, which indicates the pathogenetically significant role of fungal invasion as a damaging factor initiating the activity of fascial fibromatosis. The immunogenetic features that are characteristic of Dupuytren's disease [28] form general (systemic) risk factors for fungal invasion. Involvement of the skin in the fibromatous process [29] violates its barrier properties and creates local conditions for the introduction of infectious agents into deeper tissues. On the other hand, first of all, in the study of Candida albicans, and then other species of this genus of fungi, different authors identified the peptide toxin candidalysin, which perforates cell membranes and inhibits the complement system [30].

Candida fungi are known as representatives of the normal microbiota of the mucous membranes and skin of most healthy people; however, commensals are transformed into pathogens under the influence of general and local factors. Cutaneous candidiasis is characterized by superficial localization; lesions of the dermis and subcutaneous tissue are rare [31]. Our study revealed the introduction of Candida pseudohyphae into deep tissues (palmar aponeurosis), as well as into the bloodstream, which refers to the criteria for invasive candidiasis, which, as a rule, develops as a result of increased colonization in combination with impaired factors of general and local defense of the patient's body [32]. Candida fungi that have entered the bloodstream can be successfully eliminated from the body of a healthy person; however, in elderly patients with chronic diseases, candidemia frequently leads to hematogenous dissemination of the pathogen and fatal complications [33].

The limitations of the study are its monocenter nature and the average sample size.

Further comprehensive studies using immunohistochemical analysis, PCR, microbiological cultures of blood and wound fluid would be promising for the development of rational antimycotic therapy and anti-relapse therapy for fascial fibromatosis. Consultation of patients with Dupuytren's contracture by an infectious disease mycologist and the prescription of etiotropic therapy does not eliminate the need to correct modifiable risk factors for candidiasis, which include malnutrition and micronutrient deficiency, obesity, diabetes mellitus, irrational antibiotic therapy and corticosteroids [34].

CONCLUSION

Histological detection of pseudohyphae of the genus Candida in the palmar aponeurosis and the lumens of blood vessels in patients with Dupuytren's contracture verifies invasive candidiasis; the relationship between fungal infection in the aponeurosis and an increased rate of early relapses of contracture has been statistically proven. To increase the duration of the relapse-free period and, potentially, the life expectancy of patients, consultations with infectious disease mycologists and correction of modifiable risk factors for candidiasis are necessary.

Conflict of interest *Not declared.*

Financing *The work was supported by the program of the Ministry of Health of the Russian Federation within the framework of the state task for the Federal State Budgetary Institution Ilizarov National Medical Research Center for Traumatology and Orthopaedics for 2021-2023.*

Ethical expertise *The study was performed in accordance with the ethical standards of the Declaration of Helsinki (revised in October 2013) and was approved by the ethics committee (protocol No. 4 (68) of 11/11/2020).*

Informed consent *Patients gave voluntary informed consent to publish the study results without disclosing their identity.*

REFERENCES

1. Wade R, Igali L, Figus A. Skin involvement in Dupuytren's disease. *J Hand Surg Eur Vol*. 2016;41(6):600-608. doi: 10.1177/1753193415601353
2. Grazina R, Teixeira S, Ramos R, et al. Dupuytren's disease: where do we stand? *EFORT Open Rev*. 2019;4(2):63-69. doi: 10.1302/2058-5241.4.180021
3. Wilburn J, McKenna SP, Perry-Hinsley D, Bayat A. The impact of Dupuytren disease on patient activity and quality of life. *J Hand Surg Am*. 2013;38(6):1209-1214. doi: 10.1016/j.jhsa.2013.03.036
4. Dutta A, Jayasinghe G, Deore S, et al. Dupuytren's Contracture - Current Concepts. *J Clin Orthop Trauma*. 2020;11(4):590-596. doi: 10.1016/j.jcot.2020.03.026
5. Soreide E, Murad MH, Denbeigh JM, et al. Treatment of Dupuytren's contracture: a systematic review. *Bone Joint J*. 2018;100-B(9):1138-1145. doi: 10.1302/0301-620X.100B9.BJJ-2017-1194.R2
6. Bobiński R. Etiologia przykurczu Dupuytrena [Etiology of Dupuytren's contracture]. *Chir Narzadow Ruchu Ortop Pol*. 2008;73(4):232-5. (In Polish.)
7. Rydberg M, Zimmerman M, Löfgren JP, et al. Metabolic factors and the risk of Dupuytren's disease: data from 30,000 individuals followed for over 20 years. *Sci Rep*. 2021;11(1):14669. doi: 10.1038/s41598-021-94025-7
8. Andrew JG, Andrew SM, Ash A, Turner B. An investigation into the role of inflammatory cells in Dupuytren's disease. *J Hand Surg Br*. 1991;16(3):267-71. doi: 10.1016/0266-7681(91)90051-o
9. Unglaub F, Loos B, Schwarz S, et al. Phlegmonous-infection in first degree Dupuytren's disease. *Arch Orthop Trauma Surg*. 2009;129(4):445-8. doi: 10.1007/s00402-008-0589-7
10. Dumitrescu-Ionescu D. A New Therapeutic Approach to Dupuytren's Contracture/Disease (DD). *Adv Plast Reconstr Surg*. 2017;1(5):129-136.
11. Trojian TH, Chu SM. Dupuytren's disease: diagnosis and treatment. *Am Fam Physician*. 2007;76(1):86-89.
12. Wylock P, Vansteenland H. Infection associated with a palmar skin pit in recurrent Dupuytren's disease. *J Hand Surg Am*. 1989;14(3):518-520. doi: 10.1016/s0363-5023(89)80015-2
13. Stupina TA, Migalkin NS, Shchudlo NA, Shchudlo MM. Detection of Fungi in the Palmar Aponeurosis in Patients with Dupuytren's Contracture by Scanning Electron Microscopy. *Traumatology and Orthopedics of Russia*. 2020;26(1):147-152. doi: 10.21823/2311-2905-2020-26-1-147-152
14. Tubiana R. Dupuytren's disease of the radial side of the hand. *Hand Clin*. 1999;15(1):149-159.
15. Silant'eva TA, Gorbach EN, Ir'janov JuM, et al. *Method of preparing biological tissue samples for analysis in scanning electron microscope*. Patent RF, no. 2397472. 2010. Available at: https://www.fips.ru/registers-doc-view/fips_servlet?DB=RUPAT&DocNumber=2397472&TypeFile=html. Accessed Nov 15, 2023. (In Russ.)
16. Firacative C. Invasive fungal disease in humans: are we aware of the real impact? *Mem Inst Oswaldo Cruz*. 2020;115:e200430. doi: 10.1590/0074-02760200430
17. Badiee P, Zare M. Consideration of Invasive Fungal Infections in Immunocompetent Hosts. *Arch Clin Infect Dis*. 2017;12(4):e66111. doi: 10.5812/archcid.66111
18. Dolganova TI, Shchudlo NA, Shabalin DA, Kostin VV. Assessment of hemodynamics of the hand arteries and skin microcirculation in Dupuytren's contracture stages 3 to 4 of before and after surgical treatment with the use of Ilizarov transosseous fixation. *Genij Ortopedii*. 2019;25(1):86-92. doi: 10.18019/1029-4427-2019-25-1-86-92
19. Shchudlo N.A., Varsegova T.N., Stupina T.A., Shchudlo M.M. Types and stages of vascular remodeling in Dupuytren's contracture (analysis of 506 arteries in the surgical material of 111 patients). *Genij Ortopedii*. 2020;26(2):179-184. doi: 10.18019/1028-4427-2020-26-2-179-184
20. Ghosh A, Gharti Magar D, Thapa S, et al. Histopathology of important fungal infections – a summary. *J Pathol Nep*. 2019;9(1):1490-1496. doi: 10.3126/jpn.v9i1.23377
21. Staniszewska M, Bondaryk M, Swoboda-Kopec E, et al. Candida albicans morphologies revealed by scanning electron microscopy analysis. *Braz J Microbiol*. 2013;44(3):813-21. doi: 10.1590/S1517-83822013005000056
22. Mukaremera L, Lee KK, Mora-Montes HM, Gow NAR. Candida albicans Yeast, Pseudohyphal, and Hyphal Morphogenesis Differentially Affects Immune Recognition. *Front Immunol*. 2017;8:629. doi: 10.3389/fimmu.2017.00629
23. Farzeen I, Muzammil S, Rafique A, et al. Cutaneous Candidiasis. In book: Askun T, ed. Candida and Candidiasis. *IntechOpen*; 2023. doi: 10.5772/intechopen.100869
24. Eghtedar Nejad E, Ghasemi Nejad Almani P, Mohammadi MA, Salari S. Molecular identification of Candida isolates by Real-time PCR-high-resolution melting analysis and investigation of the genetic diversity of Candida species. *J Clin Lab Anal*. 2020;34(10):e23444. doi: 10.1002/jcla.23444
25. Guarner J, Brandt ME. Histopathologic diagnosis of fungal infections in the 21st century. *Clin Microbiol Rev*. 2011;24(2):247-80. doi: 10.1128/CMR.00053-10
26. Yue X, Wang A, Li Q. The Role of Scanning Electron Microscopy in the Direct Diagnosis of Onychomycosis. *Scanning*. 2018;2018:1581495. doi: 10.1155/2018/1581495
27. Yuping R, Kaiwen Z, Wenying H, et al. Observation of Fungi, Bacteria, and Parasites in Clinical Skin Samples Using Scanning Electron Microscopy. In book: Janecek M, Kral R, eds. Modern Electron Microscopy in Physical and Life Sciences. *InTech*; 2016. doi: 10.5772/61850

28. McCarty S, Syed F, Bayat A. Role of the HLA System in the Pathogenesis of Dupuytren's Disease. *Hand* (N Y). 2010;5(3):241-250. doi: 10.1007/s11552-009-9255-y
29. Wade R, Igali L, Figus A. Skin involvement in Dupuytren's disease. *J Hand Surg Eur Vol*. 2016;41(6):600-608. doi: 10.1177/1753193415601353
30. Russell CM, Rybak JA, Miao J, et al. Candidalysin: Connecting the pore forming mechanism of this virulence factor to its immunostimulatory properties. *J Biol Chem*. 2023;299(2):102829. doi: 10.1016/j.jbc.2022.102829
31. Talapko J, Juzbašić M, Matijević T, et al. Candida albicans-The Virulence Factors and Clinical Manifestations of Infection. *J Fungi* (Basel). 2021;7(2):79. doi: 10.3390/jof7020079
32. Pappas PG, Lionakis MS, Arendrup MC, et al. Invasive candidiasis. *Nat Rev Dis Primers*. 2018;4:18026. doi: 10.1038/nrdp.2018.26
33. Barchiesi F, Orsetti E, Mazzanti S, et al. Candidemia in the elderly: What does it change? *PLoS One*. 2017;12(5):e0176576. doi: 10.1371/journal.pone.0176576
34. Martins N, Ferreira IC, Barros L, et al. Candidiasis: predisposing factors, prevention, diagnosis and alternative treatment. *Mycopathologia*. 2014;177(5-6):223-240. doi: 10.1007/s11046-014-9749-1

The article was submitted 20.02.2023; approved after reviewing 09.11.2023; accepted for publication 01.12.2023.

Information about the authors:

Tatyana A. Stupina – Doctor of Biological Sciences, leading researcher, StupinaSTA@mail.ru, https://orcid.org/0000-0003-3434-0372;

Natalia A. Shchudlo – Doctor of Medical Sciences, leading researcher, nshchudlo@mail.ru;

Tatyana N. Varsegova – Candidate of Biological Sciences, senior researcher, varstn@mail.ru, https://orcid.org/0000-0001-5430-2045;

Daria A. Ostanina – orthopedic traumatologist, https://orcid.org/0000-0002-4399-2973.

Contribution of the authors:

Stupina T.A. – development of the concept and design of the study; collection, analysis and interpretation of data, writing the text;

Shchudlo N.A. – development of the concept and design of the study, writing the text;

Varsegova T.N. – collection, analysis and interpretation of data, writing the text;

Ostanina D.A. – data collection, writing a fragment of the text.

Original article
https://doi.org/10.18019/1028-4427-2024-30-1-67-75

Comparison of bone age assessment methods using a hand radiography in patients with active growth plate and anteromedial knee instability

Ia.A. Ivanov✉, D.S. Minninkov, D.A. Gushchina, A.G. Yeltsin

National Medical Research Center for Traumatology and Orthopedics named after N.N. Priorova, Moscow, Russian Federation

Corresponding author: Iaroslav A. Ivanov, docyaroslav@gmail.com

Abstract

Background Bone age is essential for pediatric patients with active growth zones and anteromedial instability to facilitate optimal treatment strategy and minimize postoperative complications. However, many people are unaware of various tools for determining bone age, including classical methods and modern machine learning techniques.

The objective was to show and compare different methods for calculating bone age and determining surgical strategy for patients with anteromedial instability of the knee joint.

Material and methods All-Inside anterior cruciate ligament reconstruction was performed for 20 patients. Wrist radiographs were performed for bone age assessment using the "point scoring system" of Tanner and Whitehouse and the "atlas matching" method of Greulich and Pyle. Machine learning programs were used in addition to standard bone age assessments.

Results The findings showed an average difference of 21 months (80 %) in a group of 20 individuals with bone age ahead of the passport age and an average difference of 18 months (20 %) in patients with retarded bone age.

Discussion The findings showed the difference between chronological and bone age and could be encountered in scientific articles on endocrinology and pediatrics. No scientific studies on the use of the methods could be found in the specialty “trauma and orthopaedics”.

Conclusion Bone age assessment, prediction of children's target height are essential for surgical treatment of patients with open growth plates.

Keywords: bone age, children, all-inside, ACL reconstruction, active growth plate, artificial intelligence

For citation: Ivanov IaA, Minninkov DS, Gushchina DA, Yeltsin AG. Comparison of bone age assessment methods using a hand radiography in patients with active growth plate and anteromedial knee instability. *Genij Ortopedii*. 2024;30(1):67-75. doi: 10.18019/1028-4427-2024-30-1-67-75

INTRODUCTION

Anterior cruciate ligament reconstruction (ACLR) in children with open growth plates is an area of controversy [1]. The incidence of pediatric injury is increasing due to increased sports participation and recreational activities [2, 3]. Issues associated with ACL ruptures are the choice of surgical or conservative treatment [4]; a risk of intraoperative injury to the growth plates [5] and, as a consequence, the search for the optimal surgical technique. The article is based on the dissertation of Ivanov Y.A. "Damage to the pediatric anterior cruciate ligament. Diagnosis and treatment", 05.26.2022 FSBI National Medical Research Center for Traumatology and Orthopaedics named after. N.N. Priorov, Ministry of Health of the Russian Federation.

The objective was to show and compare different methods for calculating bone age and determining surgical strategy for patients with anteromedial instability of the knee joint.

MATERIAL AND METHODS

The patients and volunteers who participated in the clinical study gave written consent. The study was performed in accordance with the principles of the Declaration of Helsinki of the World Medical Association (as amended in 2013). The study was approved by the ethics committee (02/04/2021, No. 1-2021). The following criteria were identified for selecting patients for surgical treatment using the all-inside method: age from 10 to 16 years, complete ACL rupture first identified with imaging, severe anteromedial instability. The study did not include patients with additional injuries to the posterior cruciate ligament (PCL), collateral ligaments, or fracture of the intercondylar tubercle.

The gender information was reported with no obvious correlations or differences found with the parameter. There were 6 (30 % of the total) female patients. Our clinical department provides surgical treatment for patients with ACL ruptures using all-inside all epiphyseal and all-inside partial transphyseal techniques. The main difference of this technique is that the channels are formed up to the growth zone in both bones (all-inside all epiphyseal) or in the femur up to the growth zone, and in the tibia through the growth zone (all-inside partial transphyseal).

An all-inside, all-epiphyseal ACL reconstruction technique involves drilling bone tunnels contained completely within the epiphyses of the skeletally immature knee. Partial transphyseal anterior cruciate ligament (ACL) reconstruction suggests the femoral tunnel placed in the distal femoral epiphysis whereas the tibial tunnel placed in a transphyseal fashion medial to the tibial tubercle. There have been 20 patients treated for anteromedial instability. Radiography of the hand was produced for the patients to determine bone age [6]. The Knee Injury and Osteoarthritis Outcome Score for Children (KOOS-Child) and the Pediatric International Knee Documentation Committee (Pedi-IKDC) Subjective Knee Evaluation Form were used to evaluate functional status. The Tanner and Whitehouse method, a bone-specific scoring system (TW2.1975) [7] and the Atlas of Greulich and Pyle (Greulich W.W. and Pyle S.I., 1959) [8] were used to evaluate skeletal age (Fig. 1).

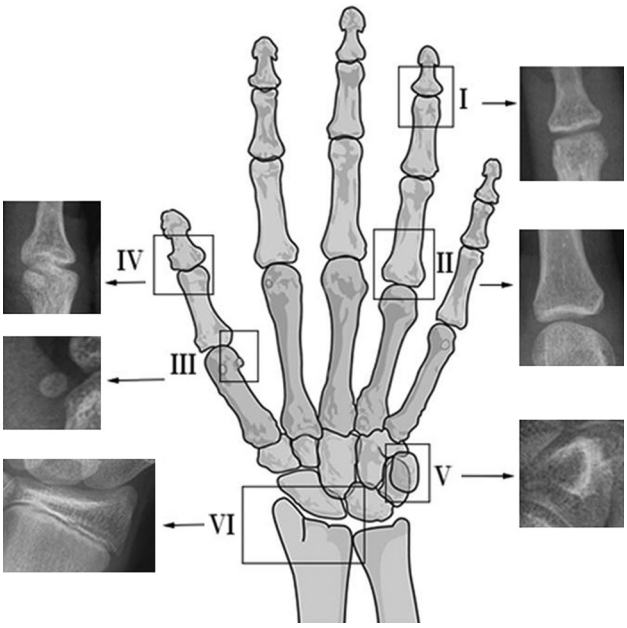

Fig. 1 Growth plates closing at different times in males (can be used as a reference manual): I – 15.5 years, II – 16 years, III – 13 years, IV – 15 years, V – 12.5 years, VI – 14 years old (author's drawing)

In addition to conventional standard methods bone age assessment can be produced using machine learning techniques [9, 10]. There are combined algorithms for bone age assessment based on the use of various neural network models, which helps improve the accuracy of assessment [10, 11]. The data

obtained from the neural network analysis were consistent with the data of the BoneXpert© [12], Auxology© (Pfizer) reconstruction and manual calculations using the Greulich – Pyle Atlas and the Tanner – Whitehouse method.

RESULTS

Patient data analysis was conducted to compare different methods of bone age assessment and expected height, major differences were identified. These data may be useful for orthopaedic surgeons when choosing a surgical treatment technique for patients with open growth plates (Table 1).

Table 1

Data for determining bone age and expected height of patients using machine learning programs

Patient	Software	Gender	Age	Height, cm	Mother's height, cm	Father's height, cm	Bone age	Expected height
1	TW2	m	11	161	170	183	12	183
	Auxology						13.1	183
	BoneXpert						13.6	182.8
	BAA						13.9	180.8
2	TW2	m	12.1	170	164	186	13	181.5
	Auxology						14.8	181.5
	BoneXpert						13.83	187.1
	BAA						13.11	184.5
3	TW2	f	13.3	150	154	178	14.5	159.5
	Auxology						13.9	159.5
	BoneXpert						15.36	152.3
	BAA						13.1	153.4
4	TW2	m	13.5	170	162	168	14	171.5
	Auxology						15.3	171.5
	BoneXpert						14.25	180.9
	BAA						14.11	176.5
5	TW2	m	14	181	173	175	16.5	180.5
	Auxology						15.8	180.5
	BoneXpert						16.35	184.6
	BAA						16.6	183.8
6	TW2	f	15.3	164	168	175	17.5	165
	Auxology						16	165
	BoneXpert						17.1	165.7
	BAA						15.6	165.4
7	TW2	m	15	178	165	170	15.8	174
	Auxology						17	175
	BoneXpert						17.3	179.5
	BAA						17.6	
8	TW2	m	16.7	175	168	180	17	180.5
	Auxology						16.20	180.5
	BoneXpert						17.44	176.5
	BAA						17	
9	TW2	m	17	172	165	170	17	174
	Auxology						16.4	175
	BoneXpert						16.54	174.8
	BAA						16.5	177
10	TW2	f	14	164	175	170	16	166
	Auxology						14.1	166
	BoneXpert						17	164.9
	BAA						14	164

Note: Table 1 and Figure 2 present the most representative data from 10 patients.

The percentile table (Fig. 2) presents the data of 10 patients including the number, the method for bone age assessment and expected height, the height of the patient and parents, gender and age. The table also shows the data obtained to allow analysis and comparison of assessment methods. Predictably, this is the most difficult question. The use of the growth formula has a large error of 5 cm, which is of key importance in the choice of surgical treatment strategy. A height percentile chart can be helpful, but as the child grows, expected height may also change to the lower side.

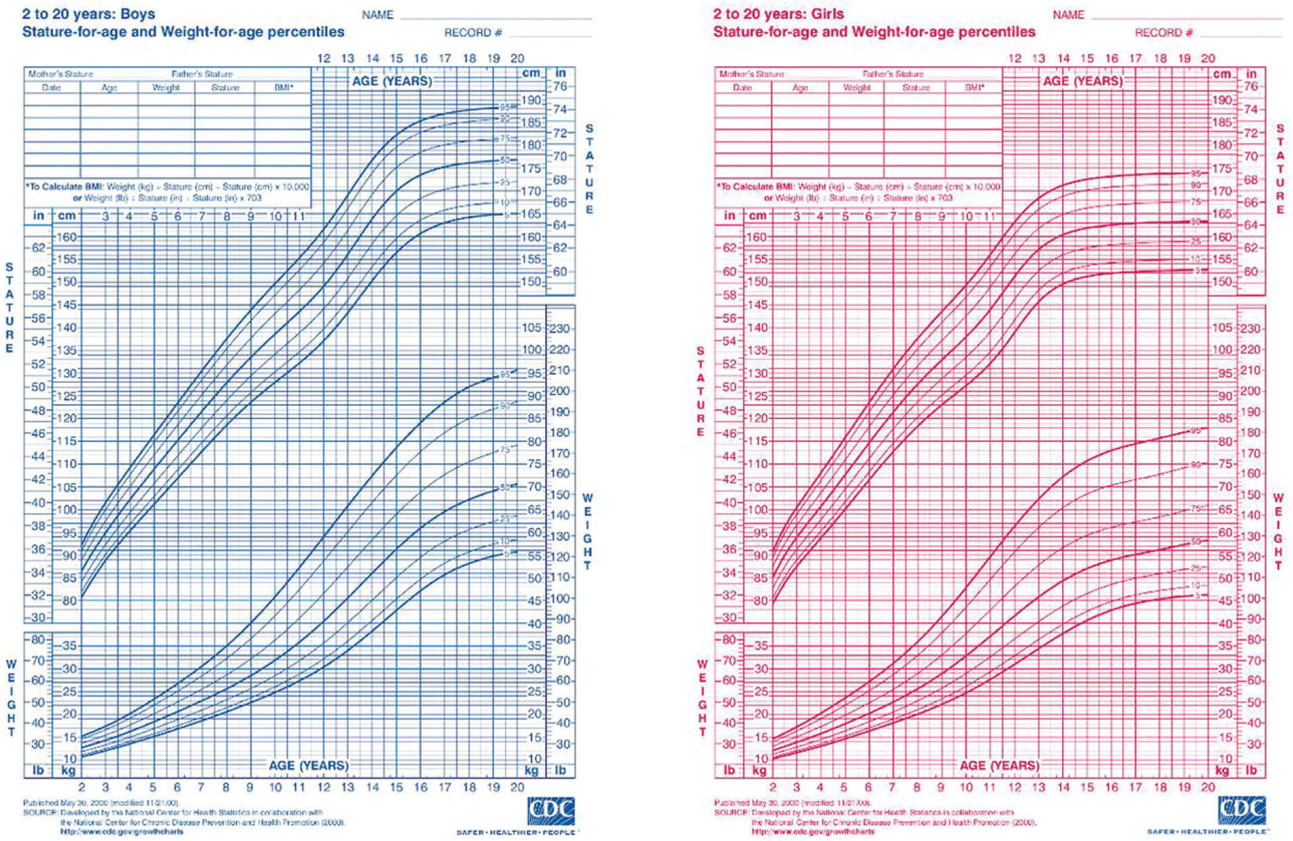

Fig. 2 Percentile table for height and weight for pediatric males and females aged 2 to 20 years

The results of the study in a group of 20 people showed an average difference of 21 months (80 %) in patients with bone age ahead of the passport age, and an average difference of 18 months (20 %) and in patients with delayed bone age.

Clinical instance

The patient's chronological age was 13.5 years at the time of admission, height was 168 cm. The mean KOOS subscale scores were: pain 69; symptoms 68; activities of daily living (ADL) 65; sport 54 [13, 14]. Pedi-IKDC [15] scored 68. The patient was diagnosed with rupture of the anterior cruciate ligament (Fig. 3), anteromedial instability of the knee joint. The initial knee injury was caused by a fall from a bicycle. The patient sustained another injury during boxing training and developed knee instability. Bone age assessment was produced for the patient to minimize the risk and choose the optimal ACL reconstruction technique. Estimation of skeletal maturity indicated bone age of 14.5 years with the Greulich-Pyle and Tanner-Whitehouse method, 14.2 years with Auxology© (Pfizer) reconstruction, 14.3 years with BoneXpert© (Fig. 4), 14.9 years with Bone Age Analyzer. The patient's predicted height based on hand and wrist radiograph was 175 cm. The patient's target height predicted by parental heights was 170.5 cm. The patient's peak active growth was 12.5 years. Based on the findings, surgical treatment included arthroscopic revision, debridement and ACL plastic surgery using the all-inside partial transphyseal technique. Postoperative period

was uneventful. During a after surgery, The range of motion in the knee joint was 180-100 degrees at a 6-month follow-up. No pain, no swelling observed. KOOS-Child questionnaire scores: pain 78; symptom 93; ADL 91; sport 82. Pedi-IKDC scored 74.

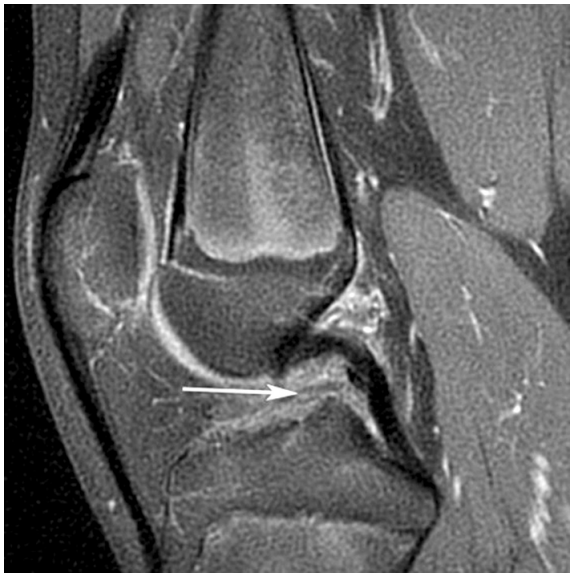

Fig. 3 MRI scan of the knee joint in the sagittal plane. The white arrow shows the anterior cruciate ligament rupture

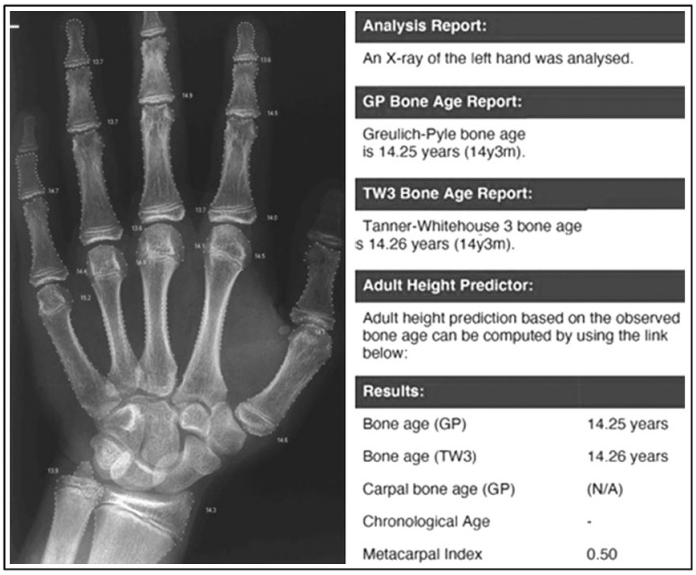

Fig. 4 Bone age calculated from an X-ray of the patient's hand using BoneXpert software

Bone age and predicted height of the patient were measured in the clinical case. Bone age was 1 year ahead of chronological (passport) age. The patient's height was 168 cm (with a target height of 175 cm), and stage IV of the Tanner Sexual Maturity Rating indicated sexual maturation. Position of bone canals in the tibia and femur, physeal injury, presence/absence of angular deformities (Fig. 5) and graft integrity (Fig. 6) were examined with radiographs and MRI scans of the knee joint at 12 months.

Bone age and expected height were calculated again using the BoneXpert software (Fig. 7). The calculations showed 11/2 year difference with the passport age (passport age 14 years, bone age 15.5 years). The height was 172 cm, and the expected height decreased to 174 cm suggesting completed growth.

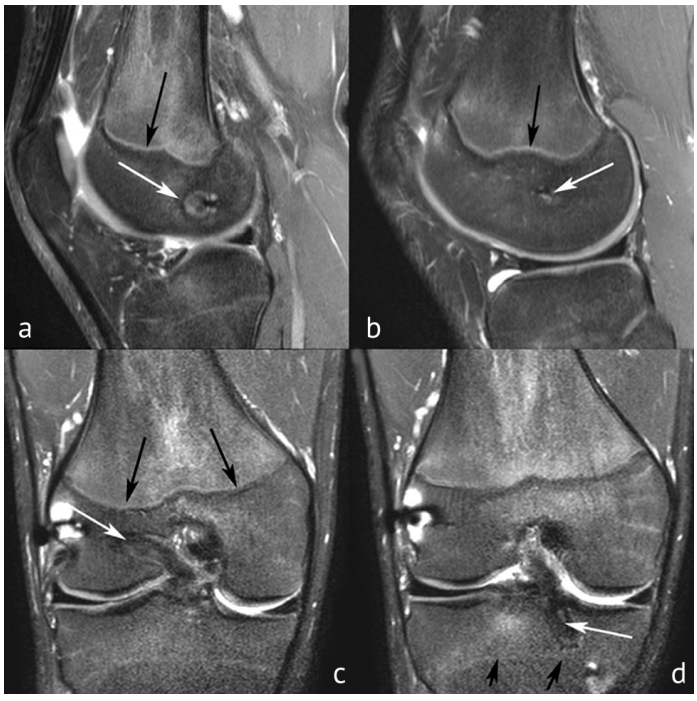

Fig. 5 MRI sagittal view of the knee joint (*a* and *b*) at 12-month follow-up showing the location of the canal in the lateral condyle of the femur (white arrows) relative to the growth plate (black arrows). MRI coronal view (*c* and *d*) shows the location of the canals in the femur and tibia (white arrows) relative to the growth plates (black arrows)

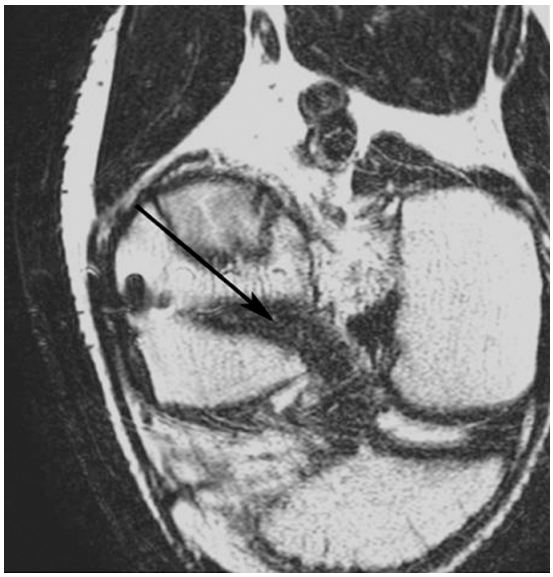

Fig. 6 MRI view of the knee at 12 months of surgery. The black arrow shows the integrity of the graft

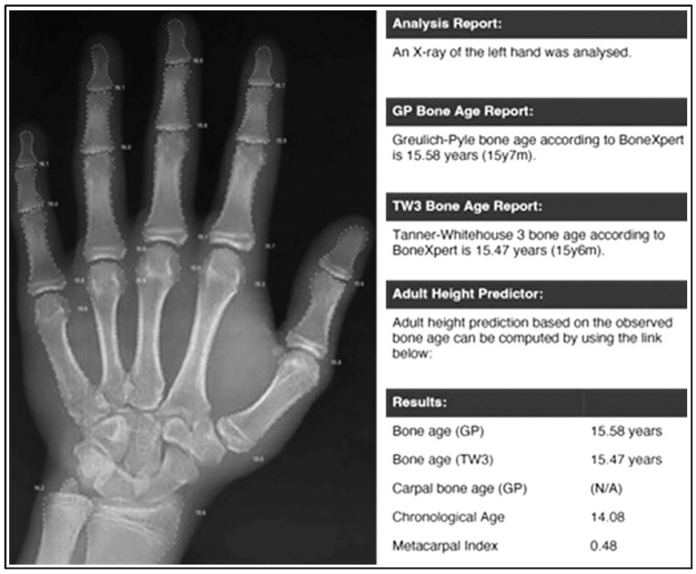

Fig. 7 Bone age calculated from a radiograph of the patient's hand using the BoneXpert software at 12 months of surgery

DISCUSSION

The findings showed a difference between chronological and bone age. These studies are normally reported in journals of endocrinology and pediatrics, and there are no reported on the use of these methods in the journals of traumatology and orthopaedics. There is a predictable sequence of development and progression of ossification centers in healthy children. An age is characterized by specific radiological findings indicating a stage of maturation. Skeletal maturity assessment is a more accurate indicator of human body maturation than chronological age. Final height can be predicted with more reliability using bone age [6]. Two methods were used in the series to determine bone age of patients: bone-specific scoring system of Tanner and Whitehouse (TW2.1975) [7] and the Atlas of Greulich and Pyle (Greulich W.W. and Pyle S.I., 1959) [8]. The TW2 method is based on accurate measurements of each bone and on the assessment of numerical scores with the sum of the scores facilitating the assessment of overall skeletal maturity. In the Greulich and Pyle method, BA is evaluated by comparing the radiograph of the patient with the nearest standard radiograph in the atlas; thus, this method reflects the maturity level of all bones in the hand and wrist.

Bone age can be estimated using machine learning methods [9, 10] as a promising trend in the field. The Bone Age Analyzer program, developed by specialists from Belarus [10, 11], is a combined algorithm for bone age assessment based on the use of neural network models to improve the accuracy. The data obtained from the neural network analysis are in line with the data obtained using the BoneXpert© [12], Auxology© (Pfizer) programs and manual calculations using the Greulich-Pyle Atlas and the Tanner-Whitehouse method. It is important to note that opinions of a radiologist, trauma surgeon and pediatric endocrinologist may differ, since the assessment methods may be somewhat subjective and be associated with specific specialty [16, 17]. However, the use of combined algorithms for bone age assessment based on neural networks helps reduce the subjectivity and improve the accuracy of measurements. When using the there were no difficulties with the use of Auxology© software (Pfizer) [18, 19].

There are many methods for bone age assessment, and advanced techniques are based on the use of neural networks and machine learning. This simplifies the calculation process reducing the role of the human factor. The availability of such methods is currently limited. For example, the well-known BoneXpert© program [12] may not be available to the Russian doctors due to its high

cost. However, there are hopes that developments from allied countries and Russian innovations will become more accessible in the future and will positively effect the use of the methods [20-30]. We evaluated stages of patients' sexual maturation using the Tanner Sexual Maturity Rating, which helped to track development during puberty assessing the bone age of children to determine growth patterns. In our series, we used data that required no specific statistical processing. We used mandatory questionnaires including KOOS-Child and Pedi-IKDC, which are widely used in pediatric trauma and orthopaedic practice worldwide. The questionnaires have been validated and culturally adapted in Russian for use in children with various knee pathologies.

CONCLUSION

Age characteristics and bone age assessment are essential for predicted and target growth of patients with open growth plates undergoing surgical treatment. Bone age assessments help determine the maturity of bones and growth plates, which play a crucial role in bone growth and function. In our series, the patient had not yet completed his growth, so passing channels through the growth plates could affect the integrity and the function. The *all inside partial transphyseal* technique was practical in the case. The *all inside all epiphyseal* technique should be used for large expected growth rates (> 5 cm < 10 cm) to minimize the risk of injury to growth plates. If the expected height is greater than 10 cm of the actual height, then surgical treatment may be further delayed by the need for a more beneficial effect. Introduction of implants can lead to uneven load distribution and cause curvature of the skeleton and functional impairment.

The patient's bone age assessment and projected height are essential for preoperative planning. A variety of methods can be used for assessing bone maturation, and will help the doctor to choose an adequate surgical treatment which can be further delayed for a more favorable outcome. The main bone age assessment methods are the Greulich-Pyle and Tanner-Whitehouse based on the level of maturity for 20 selected regions of interest in specific bones of the wrist and hand. The Auxology© software and the analogues can facilitate the choice of the most effective surgical treatment and help to avoid possible complications associated with injury to growth plates.

Conflict of interest *The authors declared no potential conflicts of interest with respect to the authorship and/or publication of this article.*

Funding *The authors received no financial support for the research and/or authorship of this article.*

Ethical review *The study was carried out in accordance with the principles of the Declaration of Helsinki of the World Medical Association (as amended in 2013). The study was approved by the ethics committee. (04.02.2021, No. 1-2021).*

Informed consent *Patients or their legal representatives and volunteers who participated in the clinical study gave written consent.*

REFERENCES

1. Ivanov YaA, Eltsin AG, Mininkov DS. Modern concepts of treatment of complicated diaphyseal forearm fractures (literature review). *N.N. Priorov Journal of Traumatology and Orthopedics*. 2021;28(1):89-107. doi: 10.17816/vto51034
2. Tyurin KA, Zaharchenko AE. Safety rules in the process of physical exercises. Injury prevention and first aid. *Trends in the development of science and education*. 2020;(67-3):145-150. (In Russ.) doi: 10.18411/lj-11-2020-123
3. Kolunin ET, Prokop'ev Nya, Baranhin OV. Prevention of child injuries in physical education and sports. *Modern problems of physical culture and sports: materials of the XXIV All-Russian scientific and practical conference*. Ed. E.A. Vetoshkina. Khabarovsk: Far Eastern State Academy of Physical Culture; 2020:140-145. (In Russ.)
4. Milewski MD, Beck NA, Lawrence JT, Ganley TJ. Anterior cruciate ligament reconstruction in the young athlete: a treatment algorithm for the skeletally immature. *Clin Sports Med*. 2011;30(4):801-10. doi: 10.1016/j.csm.2011.08.001

5. Yoo WJ, Kocher MS, Micheli LJ. Growth plate disturbance after transphyseal reconstruction of the anterior cruciate ligament in skeletally immature adolescent patients: an MR imaging study. *J Pediatr Orthop*. 2011;31(6):691-6. doi: 10.1097/BPO.0b013e3182210952
6. Dedov II, Peterkova VA, Semicheva TV, et al. *Pediatric endocrinology. Guide to pediatric endocrinology*. Moscow: Universum Publishing; 2006:600. (In Russ.)
7. Tanner JM, Whitehouse RH. A note on the bone age at which patients with true isolated growth hormone deficiency enter puberty. *J Clin Endocrinol Metab*. 1975;41(4):788-790. doi: 10.1210/jcem-41-4-788
8. Iannaccone, G. (1959). W. W. Greulich and S. I. Pyle: Radiographic atlas of skeletal development of the hand and wrist. 2nd edition. I volume-atlante di 256 pagine. Stanford University Press, Stanford, California, 1959. *Acta Geneticae Medicae Et Gemellologiae: Twin Research*. 8(4):513-513. doi: 10.1017/S1120962300018680
9. Thodberg HH, Kreiborg S, Juul A, Pedersen KD. The BoneXpert method for automated determination of skeletal maturity. *IEEE Trans Med Imaging*. 2009;28(1):52-66. doi: 10.1109/TMI.2008.926067
10. Kosik II, Kabak SL, Karapetyan GM, et al. Determination of bone age using artificial intelligence. *Belarusian State Medical University at the forefront of medical science and practice: peer-reviewed annual collection of scientific papers*. Minsk: Belarusian State Medical University; 2020:154-165. (In Russ.)
11. Kosik II, Nedzved AM, Karapetyan GM. Combined algorithm for determining bone age based on the analysis of hand radiographs. *Journal of the Belarusian State University. Mathematics and Informatics*. 2020;(2):105114. (In Russ.) doi: 10.33581/2520-6508-2020-2-105-114
12. Thodberg HH. Automatic determination of skeletal maturity using appearance models Proc. ESPE/LWPES 7th Joint Meeting. *Hormone Res*. 2005;64(Suppl. 1). doi: 10.1159/000088318
13. Ivanov YaA, Yeltsin AG, Mininkov DS. Validation and cultural adaptation of Russian version of KOOS-child questionnaire. *N.N. Priorov Journal of Traumatology and Orthopedics*. 2021;28(1):53-64. (In Russ.) doi: 10.17816/vto60489
14. Örtqvist M, Roos EM, Broström EW, et al. Development of the Knee Injury and Osteoarthritis Outcome Score for children (KOOS-Child): comprehensibility and content validity. *Acta Orthop*. 2012;83(6):666-73. doi: 10.3109/17453674.2012.747921
15. Kocher MS, Smith JT, Iversen MD, et al D. Reliability, validity, and responsiveness of a modified International Knee Documentation Committee Subjective Knee Form (Pedi-IKDC) in children with knee disorders. *Am J Sports Med*. 2011;39(5):933-9. doi: 10.1177/0363546510383002
16. De Sanctis V, Soliman AT, Di Maio S, Bedair S. Are the new automated methods for bone age estimation advantageous over the manual approaches? *Pediatr Endocrinol Rev*. 2014;12(2):200-205.
17. Manzoor Mughal A, Hassan N, Ahmed A. Bone age assessment methods: a critical review. *Pak J Med Sci*. 2014;30(1):211-215. doi: 10.12669/pjms.301.4295
18. Kim JR, Shim WH, Yoon HM, et al. Computerized Bone Age Estimation Using Deep Learning Based Program: Evaluation of the Accuracy and Efficiency. *AJR Am J Roentgenol*. 2017;209(6):1374-1380. doi: 10.2214/AJR.17.18224
19. Yildiz M, Guvenis A, Guven E, Talat D, Haktan M. Implementation and statistical evaluation of a web-based software for bone age assessment. *J Med Syst*. 2011;35(6):1485-9. doi: 10.1007/s10916-009-9425-z
20. Halabi SS, Prevedello LM, Kalpathy-Cramer J, et al. The RSNA Pediatric Bone Age Machine Learning Challenge. *Radiology*. 2019;290(2):498-503. doi: 10.1148/radiol.2018180736
21. Booz C, Yel I, Wichmann JL, Boettger S, et al. Artificial intelligence in bone age assessment: accuracy and efficiency of a novel fully automated algorithm compared to the Greulich-Pyle method. *Eur Radiol Exp*. 2020;4(1):6. doi: 10.1186/s41747-019-0139-9
22. Lee H, Tajmir S, Lee J, et al. Fully Automated Deep Learning System for Bone Age Assessment. *J Digit Imaging*. 2017;30(4):427-441. doi: 10.1007/s10278-017-9955-8
23. Nadeem MW, Goh HG, Ali A, et al. Bone Age Assessment Empowered with Deep Learning: A Survey, Open Research Challenges and Future Directions. *Diagnostics* (Basel). 2020;10(10):781. doi: 10.3390/diagnostics10100781
24. Iglovikov VI, Rakhlin A, Kalinin AA, Shvets AA. Paediatric Bone Age Assessment Using Deep Convolutional Neural Networks. In: *Deep Learning in Medical Image Analysis and Multimodal Learning for Clinical Decision Support. DLMIA ML-CDS 2018. Lecture Notes in Computer Science*. Springer, Cham.; 2018;11045. doi: 10.1007/978-3-030-00889-5_34
25. Nguyen QH, Nguyen BP, Nguyen MT, et al. Bone age assessment and sex determination using transfer learning. *Expert Systems with Applications*. 2022;200:116926. doi: 10.1016/j.eswa.2022.116926
26. Lea WW, Hong SJ, Nam HK, et al. External validation of deep learning-based bone-age software: a preliminary study with real world data. *Sci Rep*. 2022;12(1):1232. doi: 10.1038/s41598-022-05282-z

27. Wang X, Zhou B, Gong P, et al. Artificial Intelligence-Assisted Bone Age Assessment to Improve the Accuracy and Consistency of Physicians With Different Levels of Experience. *Front Pediatr*. 2022;10:818061. doi: 10.3389/fped.2022.818061
28. Guo L, Wang J, Teng J, Chen Y. Bone age assessment based on deep convolutional features and fast extreme learning machine algorithm. *Front Energy Res*. 2022;9: 813650. doi: 10.3389/fenrg.2021.813650
29. Son S.J., Song Y., Kim N., et al. TW3-based fully automated bone age assessment system using deep neural networks. *IEEE Access*. 2019;7:33346-33358. doi: 10.1109/ACCESS.2019.2903131
30. Li Y, Huang Z, Dong X, et al. Forensic age estimation for pelvic X-ray images using deep learning. *Eur Radiol*. 2019;29(5):2322-2329. doi: 10.1007/s00330-018-5791-6

The article was submitted 09.03.2023; approved after reviewing 16.05.2023; accepted for publication 01.12.2023.

Information about the authors:

Iaroslav A. Ivanov – Candidate of Medical Sciences, surgeon, docyaroslav@gmail.com, https://orcid.org/0000-0002-6352-2784;

Dmitry S. Mininkov – Candidate of Medical Sciences, Senior Researcher, 45040311@mail.ru, https://orcid.org/0000-0002-9490-6932;

Daria A. Gushchina – graduate student, Gushchina-DA@yandex.ru, https://orcid.org/0000-0003-1877-3557;

Alexander G. Yeltsin – Candidate of Medical Sciences, surgeon, traumatologist-orthopedist, agyeltsin@gmail.com, https://orcid.org/0000-0002-7736-9493.

Contribution of the authors:

Ivanov Ia.A. – concept, research design, data collection, processing, text writing.

Mininkov D.S. – data collection

Gushchina D.A. – data collection.

Yeltsin A.G. – data collection, text editing.

Original article
https://doi.org/10.18019/1028-4427-2024-30-1-76-89

Synthetic biomaterials based on hydroxyapatite and tricalcium phosphate: analysis of current clinical trials

U.F. Mukhametov[1], D.S. Ivliev[2,3], I.F. Gareev[4]✉, S.V. Lyulin[5], D.Yu. Borzunov[6,7]

[1] Republican Clinical Hospital named after. G.G. Kuvatova, Ufa, Russian Federation
[2] Federal Centers of Traumatology, Orthopedics and Endoprosthetics, Smolensk, Russian Federation
[3] Smolensk State Medical University, Smolensk, Russian Federation
[4] Bashkir State Medical University, Ufa, Russian Federation
[5] Carmel Medical Center, Chelyabinsk, Russian Federation
[6] Ural State Medical University, Ekaterinburg, Russian Federation
[7] Central City Clinical Hospital No. 23, Ekaterinburg, Russian Federation

Corresponding author: Ilgiz F. Gareev, ilgiz_gareev@mail.ru

Abstract

Introduction To date, a wide variety of synthetic materials, including metals, polymers and ceramics, have been proposed and used as a substitute for bone grafts in the field of traumatology/orthopedics, neurosurgery and oral and maxillofacial surgery (OMFS). However, the most studied materials are calcium phosphate ceramics (CPC), in particular hydroxyapatite and tricalcium phosphate, as well as their mixtures, called byphasic calcium phosphates. This interest stems from the fact that the main component of bone is the apatite mineral calcium phosphate. Hydroxyapatite and tricalcium phosphate are among the most commonly used and effective synthetic substitutes for bone grafts. They have not only osteoconductive properties, but also osteoinductive. These properties, combined with cell-mediated resorption, ensure complete regeneration of bone defects. This study will analyze existing clinical trials, registered on the clinicaltirals.gov website, on the use of hydroxyapatite and tricalcium phosphate in the field of traumatology and orthopedics, neurosurgery and OMFS.

Aim To identify the potential for clinical use, as well as possible side effects, of CPC as a replacement for bone grafts.

Materials and methods The search strategy was to use material from the clinicaltrials.gov website, which focused on key terms such as "hydroxyapatite", "tricalcium phosphate", "hydroxyapatite and tricalcium phosphate", "traumatology and orthopedics", "maxillofacial surgery", "dentistry", "neurosurgery", "bone", and "diseases of the musculoskeletal system", and the criteria for inclusion and exclusion of the data from clinical trials were divided into two stages.

Results and discussion As of November 2022, there were approximately 85 clinical trials with hydroxyapatite application, approximately 49 clinical trials with tricalcium phosphate, and approximately 16 clinical trials with the hydroxyapatite/tricalcium phosphate combination. Most of the studies were Phase 1-2, Phase 2, or Phase 4. Most focused on tibial trauma therapy, osteoporosis/osteopenia, alveolar bone resorption, and spinal surgery. It was found that full results were published only in 3, 7 and 2 clinical trials on the use of hydroxyapatite, tricalcium phosphate and their combination, respectfully. All clinical trials had similar preparation methods and all of those clinical trials produced positive results without serious side effects.

Conclusion There is a wide potential for clinical use of CPC as synthetic bone graft substitutes without reports of serious side effects. Many preclinical and clinical studies are currently underway on the use of hydroxyapatite and tricalcium phosphate, and their future results will further explore their clinical potential.

Keywords: hydroxyapatite, tricalcium phosphate, diseases of the musculoskeletal system, therapy, analysis, clinical trials

For citation: Mukhametov UF, Ivliev DS, Gareev IF, Lyulin SV, Borzunov DYu. Synthetic biomaterials based on hydroxyapatite and tricalcium phosphate: analysis of current clinical trials. *Genij Ortopedii*. 2024;30(1):76-89. doi: 10.18019/1028-4427-2024-30-1-76-89

INTRODUCTION

Bone tissue has a remarkable ability to regenerate and repair through physiological remodeling or in response to injury. In a number of situations, bone tissue repair does not occur spontaneously due to certain (unfavorable) local causes (vascular damage, infection, etc.), bone defect of a critical size, systemic causes, or a combination thereof [1, 2]. A number of surgical interventions to stimulate bone regeneration involve the use of biological support including a bone graft or a substitute, natural or synthetic [3-6]. Autogenous bone (autograft) remains to be the "gold standard" of bone grafting. Only an autologous graft provides the most desirable properties of a biomaterial, including osteoconduction, osteoinduction and osteogenesis [7-9]. However, additional surgical interventions are required to obtain autologous bone grafts, which can lead to complications, and, importantly, the volume of autologous bone tissue is always limited. The use of allografts may solve a number of problems associated with the use of autografts, but it also raises some concerns, such as the risk of infection transmission, immunological reactions of the recipient, loss of biological and mechanical properties due to their processing, increased cost and lack of availability [10, 11]. High biological safety is a desirable characteristic of synthetic bone grafts. Approximately 60 % of current synthetic bone substitutes available are ceramic biomaterials [12]. One of the most common is calcium phosphate ceramics (CPC), characterized by a chemical composition close to the mineral phase of calcified tissue, namely calcium hydroxyapatite [13]. In addition, the composition of the raw product can be controlled by adjusting the calcium to phosphate (Ca/P) ratio [13]. Hydroxyapatite and tricalcium phosphate are the most widely used CPCs, mainly in the combination in so-called biphasic calcium phosphate ceramics [14, 15]. Hydroxyapatite and tricalcium phosphate are among the most common bioactive materials currently used in neurosurgery, orthopedic and dental surgery [16–18]. This class of materials can be synthesized according to several protocols such as solid state reactions, sol-gel, precipitation methods, emulsion methods, hydrothermal reactions, mechanochemical methods, hydrolysis of other calcium phosphates and chemical vapor deposition [19, 20].

Numerous studies have demonstrated the ability of hydroxyapatite to stimulate new bone formation in vivo. Therefore, this material is generally considered osteoinductive [21]. New bone formation without the addition of bone morphogenetic proteins or osteogenic cells at extraskeletal sites has also been observed with the use of tricalcium phosphate [22]. However, it should be emphasized that at present some of the mechanisms underlying osteoinduction are not fully understood. This property is indeed related in a non-trivial way to the chemical composition and crystallinity of the material, its stoichiometry, dissolution/precipitation behavior, surface chemistry and charge, as well as microporosity and roughness. Both hydroxyapatite and tricalcium phosphate have been widely used as bone fillers in the form of powders, cements, solids, porous solids, discs and granules in many clinical trials since the early 1980s [23]. Hydroxyapatite has also been used to create bioactive coatings on metal implants to enhance the biomimetic response of such implants [24]. To date, the only commercially acceptable method for applying such coatings is plasma spraying.

Tricalcium phosphate has three recognized polymorphs: 1) β-tricalcium phosphate, which is stable below 1125 °C; 2) α-tricalcium phosphate, which is stable between 1125 °C and 1400 °C, and 3) α'-tricalcium phosphate, which can be stable at temperatures above 1430 °C [14, 15]. α-Tricalcium phosphate and β-tricalcium phosphate have different dissolution rates in the body and can be used together in appropriate combinations [25]. α-Tricalcium phosphate and α′-tricalcium phosphate have a lower theoretical density than hydroxyapatite, but β-tricalcium phosphate is more preferred for biomedical applications due to its mechanical characteristics, chemical stability and resorption rate [26].

Another important area of research into CaP-based biomaterials has focused on biphasic calcium phosphates (BCP). By definition, BCP consists of two distinct CaP phases: most often the more stable hydroxyapatite phase and the more soluble β-tricalcium phosphate phase in varying proportions [27]. This combination has significant advantages over other types of CaP bioceramics, allowing better

control of biological activity and biodegradation, which guarantees the stability of the biomaterial and promotes osseointegration of newly formed bone tissue into the implant. The combination of hydroxyapatite/tricalcium phosphate has osteoconductive properties and the possibility of acquiring osteoinductive properties [28, 29].

As of November 2022, the site *clinicaltrials.gov* lists approximately 85 registered clinical trials using hydroxyapatite alone or in combination with other biomaterials in traumatology and orthopedics, maxillofacial surgery (MFS) and neurosurgery. There have been 49 clinical trials reported on the use of tricalcium phosphate in the same areas of medicine. However, of these clinical trials, only five trials published full results using hydroxyapatite and seven using tricalcium phosphate, respectively. In addition, there are 16 clinical trials using a combination of hydroxyapatite/tricalcium phosphate, with a predominance of one or another synthetic biomaterial, two clinical trials with results were among them.

In this study, we analyzed various applications of synthetic biomaterials (hydroxyapatite and tricalcium phosphate composites) in traumatology and orthopedics, maxillofacial surgery and neurosurgery; we paid special attention to the corresponding methods of synthesis and processing of hydroxyapatite and tricalcium phosphate composites, as well as their storage conditions.

Purpose: to identify the potential for clinical use of calcium phosphate ceramics as a substitute of bone grafts, as well as possible side effects of their use.

MATERIALS AND METHODS

Search strategy

We conducted a comprehensive search for clinical trials demonstrating the use of hydroxyapatite and tricalcium phosphate composites, alone or in combination, as effective synthetic bone substitutes for various musculoskeletal conditions. Databases including *clinicaltirals.gov* were used to obtain all relevant clinical trials. Search words were: hydroxyapatite, tricalcium phosphate, hydroxyapatite and tricalcium phosphate, traumatology and orthopaedics, maxillofacial surgery, dentistry, neurosurgery, bone and diseases of the musculoskeletal system. To select studies, we used the following inclusion and exclusion criteria, which were divided into two stages.

Stage 1:

1) clinical trials on humans with the use of hydroxyapatite and tricalcium phosphate
2) clinical trials in phases 1 to 4:
   a) location;
   b) area of application;
   c) phase;
   d) study status.

Stage 2:

1) clinical trials which results were published;
2) phases of clinical trials with selected study criteria for statistical analysis:
   a) field of application;
   b) treatment;
   c) intervention model'
   d) source;
   e) selection and processing methods;
   f) results.

Selection of clinical trials

After applying the inclusion and exclusion criteria in the first stage, a total of 67 clinical trials with hydroxyapatite, 29 clinical trials with tricalcium phosphate and 12 clinical trials with the hydroxyapatite/tricalcium phosphate combination were excluded, respectively, as there were studies that were either in the early phase 1, or the phase was not specified or had an inapplicable phase (note: excluding those with results). We analyzed the remaining clinical trials (18, 20, and 4, respectively) by area of application, phase, status, and location. Only 12 clinical trials using hydroxyapatite and tricalcium phosphate alone or in combination (3, 7 and 2, respectively) were selected for the second stage because they met the stated criteria of this study (Fig. 1).

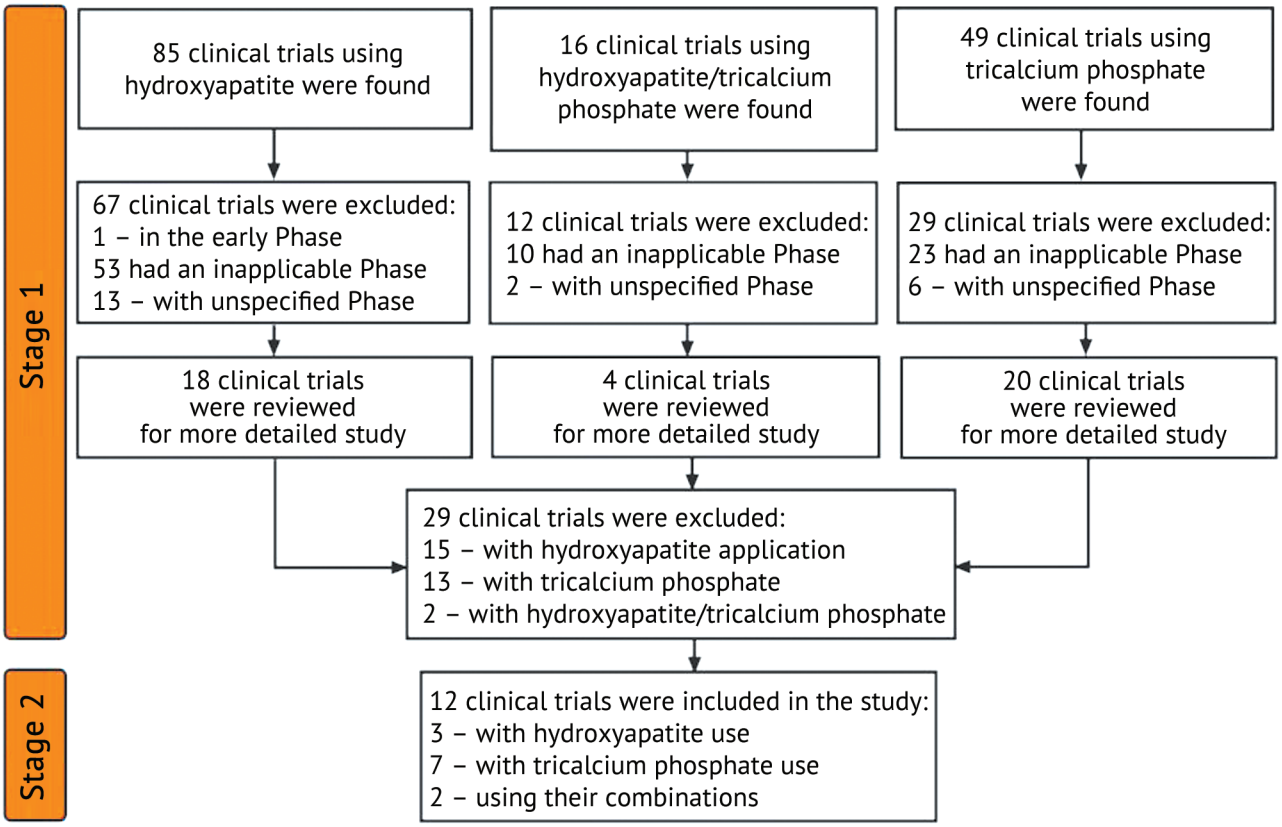

Fig. 1 Study design

Commercial products

About twenty-three major commercial bone graft products (scaffolds) have been identified from clinicaltirals.gov data: OsteoGen™, NanoBone®, Kyphos FS™, KYPHON ActivOs®, Ossix™, Bio-Oss®, CERAMENT® G, Siloss®, i-FactorTM, ReproBone®, AllogenixTM, Straumann BoneCeramic®, CustomBone, OsteoGen® Plug, CERVIOS chronOS™, AttraX® Putty, chronOS®, Easy-graft® CLASSIC, NovoMax™, Guidor®, Guidor easy-graft® CRYSTAL, PD VitalOs cement®, Neofuse®, which may differ in composition from each other, i.e. contain hydroxyapatite or tricalcium phosphate, or these synthetic biomaterials were used additionally. Moreover, four growth factor-enhanced bone grafts and two peptide-enhanced xenohybrid bone grafts were identified, respectively.

Statistical analysis

The statistical methods applied were t-test, ANOVA, chi-square analysis or Mann–Whitney test. A probability p value < 0.05 (*), < 0.01 (**), or < 0.001 (***) was considered statistically significant. Statistical analysis was performed using IBM SPSS 22.0 software and graphs were generated using Graphpad Prism 7.0.

RESULTS

Statistics from registered clinical trials on the use of hydroxyapatite and tricalcium phosphate

The use of synthetic biomaterials is a relatively new area that has great potential for solving many serious problems in neurosurgery, traumatology, orthopedics and maxillofacial surgery (Fig. 2). Additional research may be required to fully exploit this potential, but it is now confident that significant progress has been made in studying the effectiveness of the use of hydroxyapatite and tricalcium phosphate in these areas of medicine (Fig. 3).

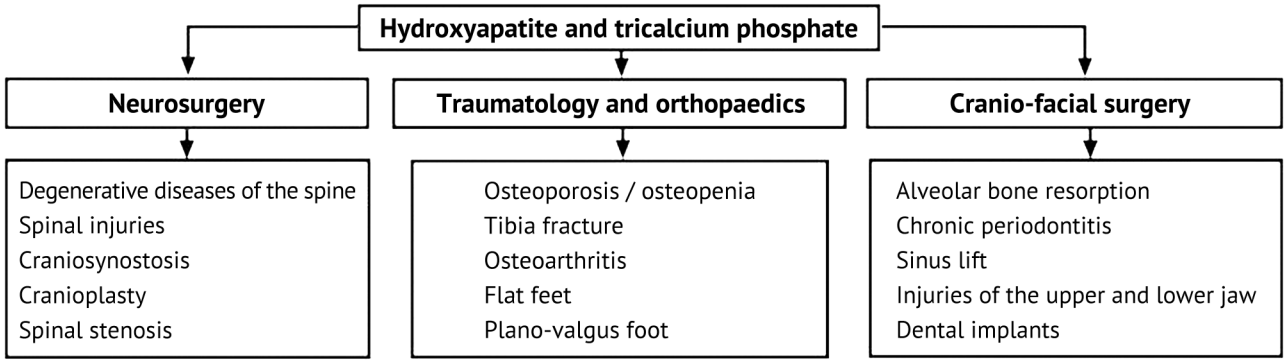

Fig. 2 Most common pathologies that can be treated with hydroxyapatite and tricalcium phosphate as bone substitutes

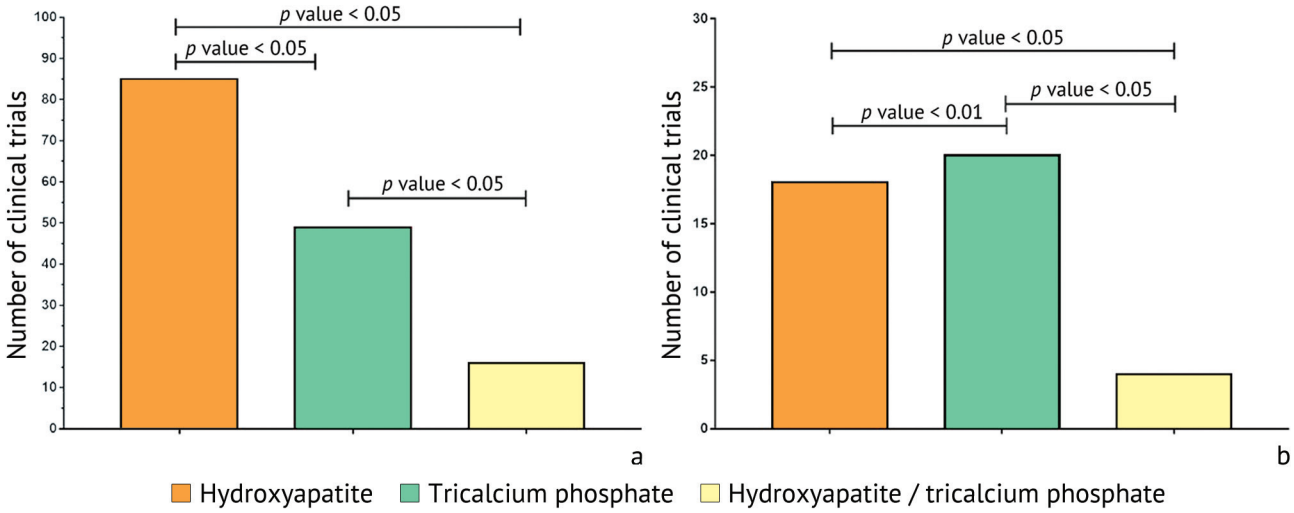

Fig. 3 Comparative analysis of clinical trials on the use of hydroxyapatite, tricalcium phosphate and their combination: *a* hydroxyapatite vs tricalcium phosphate vs hydroxyapatite/tricalcium phosphate in the first phase of this study; 85, 49 and 16 clinical trials (*p value* < 0.05 and *p value* < 0.01); *b* hydroxyapatite vs tricalcium phosphate vs hydroxyapatite/tricalcium phosphate after applying inclusion and exclusion criteria for the first stage of this study; 18, 20 and 4 clinical trials (*p value* < 0.05 and *p value* < 0.01)

At the time of the study (November 2022), 85 clinical trials using hydroxyapatite and 49 using tricalcium phosphate were registered worldwide. Also, 16 clinical trials were conducted with the combination of hydroxyapatite/tricalcium phosphate to study their clinical use in diseases of the musculoskeletal system. The number of registered clinical trials has increased significantly since their first official use that was reported on November 15, 2005, and registration on *clinicaltrials.gov* on September 11, 2006 (Figure 4).

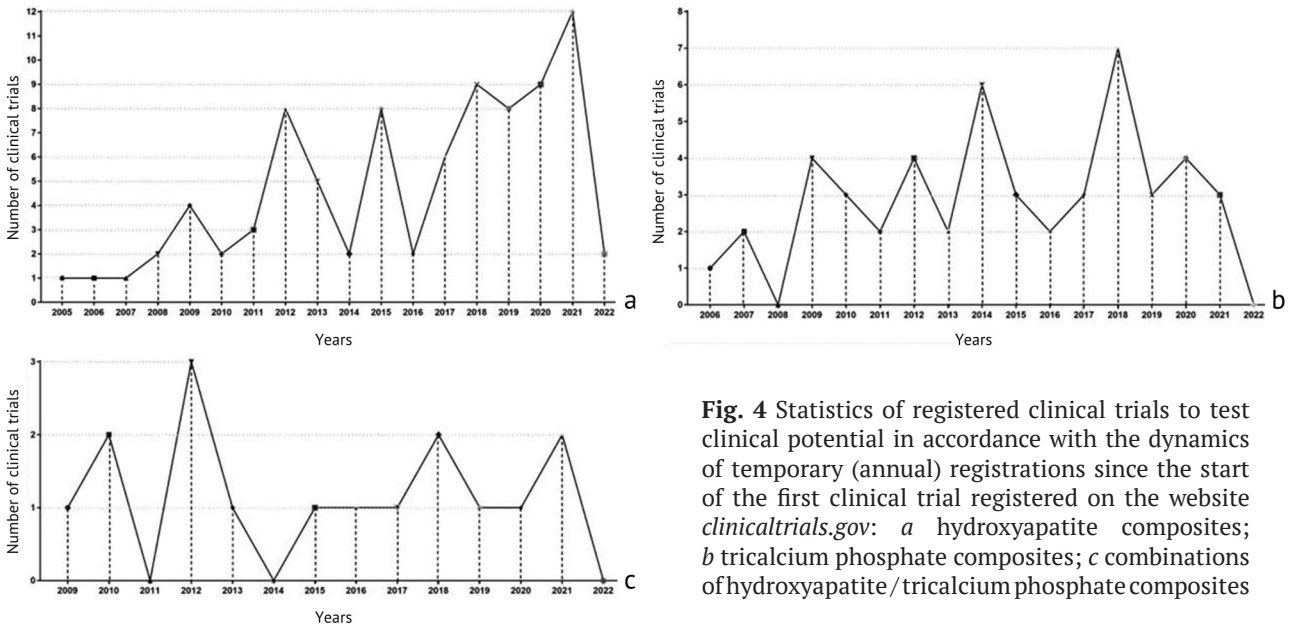

Fig. 4 Statistics of registered clinical trials to test clinical potential in accordance with the dynamics of temporary (annual) registrations since the start of the first clinical trial registered on the website *clinicaltrials.gov*: *a* hydroxyapatite composites; *b* tricalcium phosphate composites; *c* combinations of hydroxyapatite / tricalcium phosphate composites

Features of clinical trials

Based on the inclusion and exclusion criteria, 42 clinical trials that used hydroxyapatite, tricalcium phosphate and their combination were analyzed (18, 20 and 4, respectively). The reasons for exclusion in the first phase of the clinical trial study (Fig. 5) were as follows: 53 (79.1 %), 23 (79.1 %) and 10 (83.3 %) clinical trials had an inapplicable phase; 13 (19.4 %), 6 (20.9 %) and 2 (16.7 %) clinical trials did not specify the phase. There was one clinical trial that used hydroxyapatite in the early phase.

Clinical trials with hydroxyapatite are presented in 6 phases (Fig. 6 a), with tricalcium phosphate in 5 phases (Fig. 6 b), with a combination of hydroxyapatite / tricalcium phosphate – in 2 phases (Fig. 6 c).

However, of this small number of clinical trials, only 12 published full results (3, 7 and 2, respectively).

Reported clinical trial statuses were: have not started enrolling patients; are enrolling patients; active but not yet enrolling patients; discontinued; completed; withdrawn, and unknown status (Fig. 7).

Regarding the status of the 42 clinical trials analyzed, clinical trials with hydroxyapatite were mainly completed (50 % of 18 clinical trials); those using tricalcium phosphate were mostly completed (40 % of 20) and have an unknown status (40 % of 20); those using the hydroxyapatite/tricalcium phosphate combination were mainly completed (75 % of 4 clinical trials) (Fig. 8).

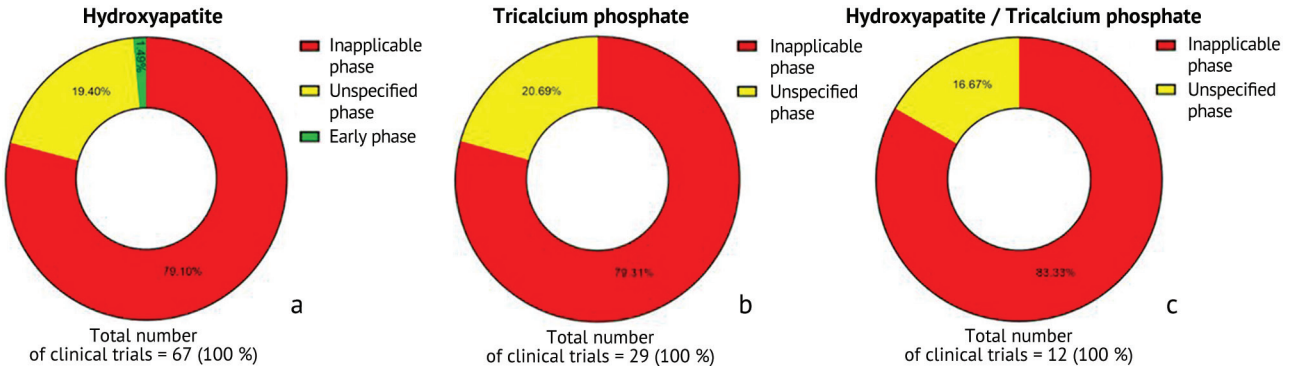

Fig. 5 Reasons for exclusion of clinical trials at the first stage of the study on the use of: *a* hydroxyapatite, *b* tricalcium phosphate; *c* combinations of hydroxyapatite /tricalcium phosphate

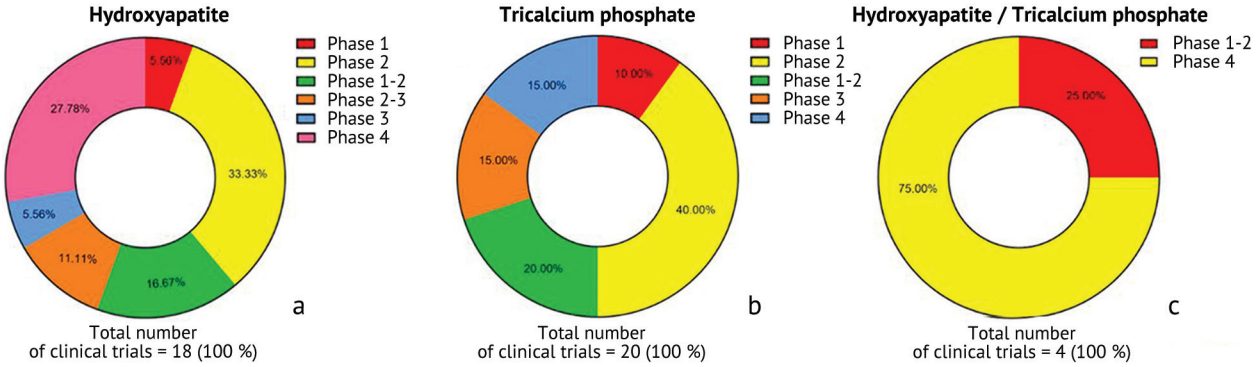

Fig. 6 Distribution by phase of registered clinical trials on application of: *a* hydroxyapatite, *b* tricalcium phosphate; *c* combinations of hydroxyapatite /tricalcium phosphate

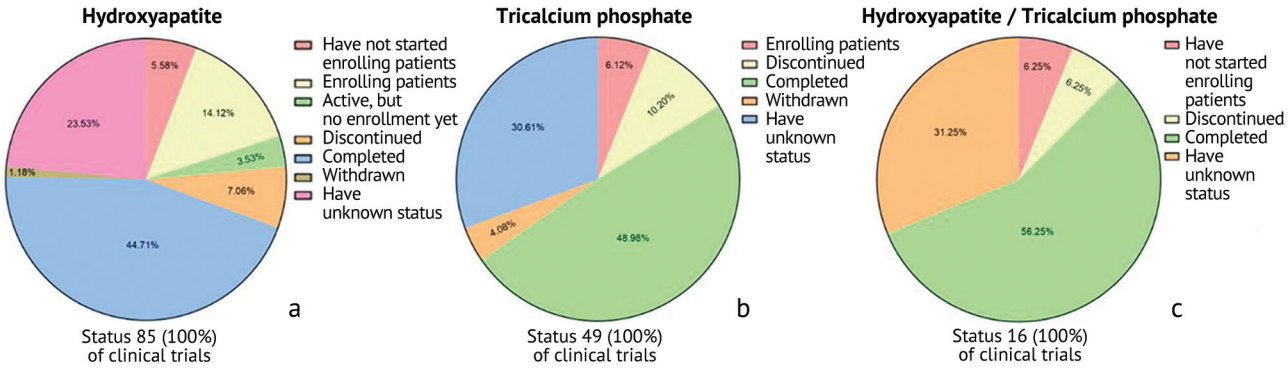

Fig. 7 Distribution based on progress of clinical trials registered in the clinicaltrials.gov database on application of: *a* hydroxyapatite, *b* tricalcium phosphate; *c* combinations of hydroxyapatite /tricalcium phosphate

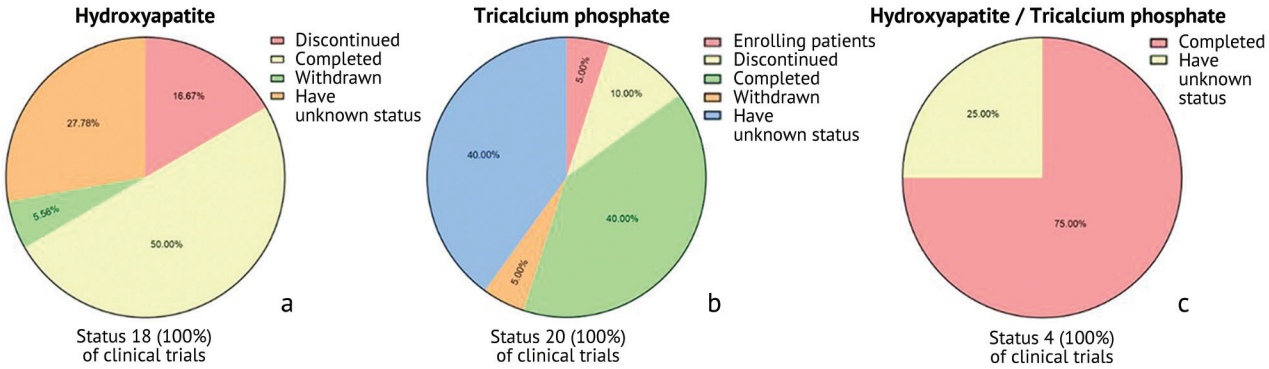

Fig. 8 Distribution depending on the progress of the analyzed clinical trials on application of: *a* hydroxyapatite, *b* tricalcium phosphate; *c* combination of hydroxyapatite / tricalcium phosphate

Geographical distribution

The analyzed 42 clinical trials with hydroxyapatite and tricalcium phosphate have been currently conducted in 19 countries. The USA, Switzerland, Iran and India lead in the number of clinical trials with hydroxyapatite; Spain, USA and Russia lead in the number of trials with tricalcium phosphate. The distribution of the number of clinical trials with the hydroxyapatite/tricalcium phosphate combination is uniform (Table 1).

Table 1

Distribution of clinical trials by regions

Country	Number of trials									
	Total	Hydroxyapatite			Tricalcium phospate			Combination of hydroxyapatite/tricalcium phosphate		
		abs.	%	Phases	abs.	%	Phases	abs.	%	Phases
USA	5	2	11.0	4	3	15.0	1. 3 и 1-2			
Spain	4	1	5.6	1-2	3	15.0	1 и 2			
Austria	3	1	5.6	1-2	1	5.0	1-2	1	25.0	1-2
Egypt	3	1	5.6	2	1	5.0	2	1	25.0	4
Brazil	2	1	5.6	2-3				1	25.0	4
Germany	2	1	5.6	3	1	5.0	2			
India	2	2	11.0	2						
Iran	2	2	11.0	2						
Russia	2				2	10.0	2 и 1-2			
Switzerland	3	2	11.0	2 и 4	1	5.0	4			
South Korea	2	1	5.6	4				1	25.0	4
Belgium	1				1	5.0	4			
Hungary	1				1	5.0	2			
Indonesia	1	1	5.6	1						
Mexico	1				1	5.0	3			
Singapore	1				1	5.0	2			
France	1	1	5.6	1-2						
Sweden	1	1	5.6	2-3						
USA+ Austria + Canada + England	2	1	5.6	4	1	5.0	3			
Unknown	3				3	15.0	2. 1-2. 4			
Total	42	18	100		20	100		4	100	

Conclusions from the techniques/protocols used for clinical application of hydroxyapatite and tricalcium phosphate

The results revealed that hydroxyapatite and tricalcium phosphate are used in a variety of different compositional and structural forms, including stoichiometric, calcium-deficient and ion-substituted, dense and porous, nanocrystalline and microcrystalline, colloidal, granular and monolithic. Each of the forms has specific properties and causes unique biological reactions. Nanostructured and nanocrystalline CaP are traditional materials used in bone tissue bioengineering. Among a dozen different CaP phases, synthetic hydroxyapatite and tricalcium phosphate have been the most commonly used as bone substitutes due to their high similarity to natural bone. Therefore, compared to other CaP materials, the number of clinical studies on the use of hydroxyapatite and tricalcium phosphate is the greatest.

There are protocols for incorporating hydroxyapatite into silk polymers. This type of composite material exhibited a higher cell adhesion and osteogenic differentiation capacity compared to its components used separately. In addition, to facilitate the bond between the scaffold and the host tissue, hydroxyapatite was used not only as a bulk component of the scaffold, but also as a surface coating. This form of hydroxyapatite can inhibit the release of certain compounds or elements limited by the bulk structure of the material. A thin layer of hydroxyapatite coating has shown to be effective in inhibiting the release of inorganic polyphosphate from the surface of osteochondral constructs

composed of calcium polyphosphate, yielding a new form of biphasic constructs. Ion-doped hydroxyapatite particles were also frequently encountered in the protocols. Some clinical trials have involved embedding bone morphogenetic proteins or other growth factors, such as recombinant basic human fibroblast growth factor-β (rhFGF-β), onto hydroxyapatite and tricalcium phosphate scaffolds to induce cell differentiation or other specific effects. CaP cements are a special form of hydroxyapatite or tricalcium phosphate materials because their main ingredients are amorphous CaP or mono-, di-, tri- or tetra-CaP, which can set and harden into hydroxyapatite or tricalcium phosphate only after they are placed in bone cavity.

There is currently no consensus on the ideal phase ratio of BCP for clinical use. Various ratios of hydroxyapatite and tricalcium phosphate in combination have been evaluated in the literature to determine the optimal ratio for bone regeneration, but only hydroxyapatite/tricalcium phosphate ratios of 65/35, 60/40, and 50/50 have been used and have been successfully tested in human clinical trials. Interestingly, two hydroxyapatite/tricalcium phosphate ratios (30/70 and 20/80) also exhibited some osteoinductive properties.

All of the clinical trials were in phase 1-2, phase 2 or phase 4. The clinical trials showed positive results without serious side effects (Table 2).

Table 2

Distribution of the most effective clinical trials (with results) registered on clinicaltrial.gov on the use of hydroxyapatite, tricalcium phosphate and their combination in traumatology and orthopedics, neurosurgery and maxillofacial surgery

Indications	Number of persons in the trial	Intervention	NCT number	Phase	Short description
Hydroxyapatite					
Spinal canal stenosis and spondylolithsesis	69	Transforaminal lumbar interbody fusion	NCT02485574	–	Evaluation of a bone bridge in patients undergoing transforaminal interbody lumbar spine fusion. The option of using autologous bone with hydroxyapatite was not inferior to the option of using only autologous bone.
Hip joint arthropathy	167	BoneMaster Coated Acetabular Sheath and Plasma Coated Acetabular Sheath	NCT00859976	–	Randomized controlled trial of patients requiring total hip replacement. A method of fixing the hip joint to the bone is by applying a coating to the implant to stimulate bone growth in the femur. It was investigated whether Bonemaster (a thin electrochemically applied coating of hydroxyapatite) stimulates bone growth on the cup, compared with plasma spraying
Cleft lip and palate	5	Use of maxillary alveolar graft	NCT01932164	–	Alveolar bone defect reconstruction in patients with cleft lip and palate using mesenchymal stem cells from primary tooth pulp associated with collagen and hydroxyapatite biomaterial (Geistlich Bio-Oss®)
Tricalcium phosphate					
Preservation of the alveolar process. Dental implants	9	Easy-graft CLASSIC (β-tricalcium phosphate)	NCT03215667	–	Clinical and histological evaluation of in situ alloplastic compaction formed by β-tricalcium phosphate and polylactide membrane bone graft in preserving the alveolar bone after extraction of non-molar teeth with unretained extraction sockets
Alveolar bone resorption and periodontal disease	88	β-tricalcium phosphate alone	NCT01728844	–	GUIDOR® growth factor-enhanced bone graft substitute (recombinant basic human fibroblast growth factor-β (rhFGF-β)) in periodontal surgery demonstrated greater gingival and bone regeneration compared to bone graft substitute alone
Periodontal diseases	8	Easy-graft CLASSIC (β-tricalcium phosphate)	NCT02221557	–	Case series to compare the effectiveness of two different treatment approaches: a new alloplastic bone graft material while preserving the alveolar process and existing methods of using allograft

Continuation of Table 2

Distribution of the most effective clinical trials (with results) registered on clinicaltrial.gov on the use of hydroxyapatite, tricalcium phosphate and their combination in traumatology and orthopedics, neurosurgery and maxillofacial surgery

Indications	Number of persons in the trial	Intervention	NCT number	Phase	Short description
Degenerative disease of the lumbar spine	104	Instrumented posterolateral fusion with interbody support	NCT00943384	–	chronOS Strip is a synthetic bone void/defect filler made from β-tricalcium phosphate granules and absorbable polymer [poly(lactide-co-ε-caprolactone)]. chronOS Strip in combination with autologous bone and/or bone marrow or autograft is intended for posterolateral spinal fusion. A prospective multicenter case series to evaluate the rates of posterolateral fusion in a prospective series of patients with degenerative disc disease. chronOS Strip in combination with bone marrow aspirate and local bone was applied to the posterolateral gutters
Dental implants	26	Sinus lift and dental implantation. Aastrom (BRCs)	NCT00980278	Phase 1-2	Determine the ability of your own bone marrow tissue to promote bone regeneration (growth) in the jaw area where the implant was installed. Process Name: Aastrom Bone Repair Cell (BRC) Therapy
Peri-implantitis	5	Easy-graft CLASSIC (β-tricalcium phospate)	NCT03213210	–	Single-arm study to evaluate the effectiveness of a treatment approach using a novel β-tricalcium phosphate and polylactide membrane moldable bone graft for peri-implantitis
Preservation of the alveolar process. Dental implants	45	Easy-graft CLASSIC (β-tricalcium phosphate). Lyophilized FDBA Bone Allograft with Collagen Plug	NCT02702609	–	A randomized controlled trial to compare the effectiveness of two different treatment approaches using a novel β -tricalcium phosphate molded bone graft for alveolar process preservation in an atraumatic extraction socket versus a collagen plug allograft
Hydroxyapatit / tricalcium phosphate					
Periodontal disease	41	Enamel matrix derivative, hydroxyapatite / β-tricalcium phosphate, flap approach operation	NCT02474498	Phase 4	Clinical evaluation of the treatment of class II mandibular furcation defects using enamel matrix derivative (EMD) and/or hydroxyapatite/tricalcium phosphate bone substitute
Intervertebral disc degeneration, intervertebral disc displacement and ossification of the posterior longitudinal ligament	85	CERVIOS chronOS™ and Bonion™	NCT01615328	Phase 4	Cervios ChronOs™ is a polyetheretherketone (PEEK) cage with β-tricalcium phosphate. Bonion™ is a PEEK frame filled with hydroxyapatite/demineralized bone matrix (DBM). However, comparative studies have not been performed between PEEK cage with β-tricalcium phosphate and PEEK cage with hydroxyapatite/DBM. The rate of bone fusion between these cervical spine cages was assessed using postoperative computed tomography (CT)

Note: type of study – interventional

DISCUSSION

Research into the use of CPC-based synthetic biomaterials has made significant progress over the past four decades since they were first used in clinical settings. This study focused on the analysis of the most widely used synthetic ceramic-based biomaterials in clinical practice, namely hydroxyapatite and tricalcium phosphate. The main areas of their clinical application are traumatology and orthopaedics, neurosurgery and maxillofacial surgery. Among the most common pathologies where they are used are injuries/fractures of long bones, osteoprosis/osteopenia, degenerative diseases of the spine and alveolar bone resorption; but there are also a significant number of clinical trials on osteoarthritis, craniopasticity and periodontal defects. The clinical trials break new ground on novel synthetic biomaterial transplantation techniques that offer potential benefits for the future of global public health as they target the field of regenerative medicine and tissue engineering of musculoskeletal diseases.

The growing number of clinical trials with application of hydroxyapatite and tricalcium phosphate represents a transition from preclinical to clinical medicine. Current clinical trials registered on *clinicaltrials.gov* site are primarily in phase 1-2, phase 2 or phase 4 and demonstrate safety and effectiveness. Given the promising results of clinical trials with the use of composite biomaterials based on hydroxyapatite, tricalcium phosphate, or a combination of both, it can be stated that they have great potential to be applied as bone graft substitutes.

Hydroxyapatite is a chemical analogue of biogenic apatite, the main component of all hard tissues of the mammalian body, with the exception of calcium carbonate otoconia of the inner ear. It attracted attention in the early days of biomaterials science due to its expected biocompatibility based on its high level of chemical and crystallographic similarity to the inorganic component of bones and teeth [30]. Bioactivity and biocompatibility of hydroxyapatite give it an advantage over bioinert ceramics such as titanium dioxide, alumina and silica and helps it interact more closely with the cells and tissues of the biological environment [31]. Moreover, many relatively simple synthesis protocols have been established for hydroxyapatite, allowing researchers to produce particles of precisely defined sizes and shapes [32]. Functionalization and surface modification of hydroxyapatite can be accomplished through equally simple non-covalent interactions, taking advantage of the strong physical sorption capacity of the polyvalent ions that make up the surface of the hydroxyapatite particles itself [33, 34]. Currently, hydroxyapatite is also widely known as a drug delivery agent (antibiotics, growth factors, nucleic acids or ligands that facilitate targeted delivery and a specially controlled rate of drug release). In addition to loading with therapeutic agents, hydroxyapatite can also be converted into a bioimaging agent using various functionalization strategies [35]. Being relatively resistant to biodegradation, but with the ability to degrade quickly in certain environments, such as near cancer cells, hydroxyapatite also has the potential to act as a smart biomaterial that responds to environmental stimuli [36]. This ability to achieve multiple functional characteristics allows it to be used for multiple drug delivery, while its location is tracked and controlled by various diagnostic methods (computed tomography), which is one of the prerequisites for theranostics applications.

The main property of tricalcium phosphate is its osteoconductivity, which is one of the main reasons for its use as a biomaterial for bone defect repair. However, only the property of osteoconductivity deprives tricalcium phosphate composite materials of a sufficient degree of bone regeneration and remodeling [37]. Today it is known that the following factors are necessary for new bone growth: bioactive materials with scaffold function; various growth factors that induce cell differentiation; stem cells with the potential to differentiate into bone tissue. Therefore, the bone-restorative effect of tricalcium phosphate can be maximized if we provide it with stem cells and/or growth factors to stimulate osteoblast differentiation. In clinical applications, degradation and mechanical properties are important physical parameters of tricalcium phosphate, which are mainly related to porosity and surface size. Continuous degradation of tricalcium phosphate provides sufficient space for cell growth, while excellent mechanical properties can maintain the space structure for long-term cell growth [38]. However, they limit each other because higher porosity leads to higher degradation and poorer mechanical properties [38]. Therefore, to improve the physical bone repair properties of tricalcium phosphate, it is necessary to combine it with other materials. Thus, the combination of hydroxyapatite and tricalcium phosphate has many advantages [27]. Tricalcium phosphate provides calcium and phosphorus ions, which are useful in differentiating osteoblast maturation.

In fact, hydroxyapatite provides a favorable microporous scaffold environment that promotes osteoblast proliferation and differentiation. Both tricalcium phosphate and hydroxyapatite can promote new bone formation [28, 29]. However, compared to the use of hydroxyapatite or tricalcium phosphate alone, their combination can produce more new bone in a shorter period of time [39]. By adjusting the hydroxyapatite/tricalcium phosphate ratio, a balance can be maintained between ceramic material absorption and new bone formation. In particular, the so-called ReproBone® is a porous resorbable ceramic bone graft substitute (composed of 60 % hydroxyapatite and 40 % β-tricalcium phosphate), similar to the mineral component of the human bone, which has already been clinically tested to create synthetic bone grafts with promising results [40, 41].

CONCLUSION

The results of clinical trials reveal that the combination of hydroxyapatite and tricalcium phosphate has many advantages. Hydroxyapatite and tricalcium phosphate used alone or in combination do not have any serious side effects.

We expect that the number of clinical studies devoted to the use of synthetic biomaterials based on hydroxyapatite and tricalcium phosphate in traumatology and orthopaedics, neurosurgery and maxillofacial surgery would help to more clearly define the potential for their therapeutic use, which can promote bone tissue regeneration and potentially improve the quality of life of patients with bone defects.

Conflicting Interests *The authors declare no conflict of interest.*

Financing *The work was carried out with the funds from the Strategic Academic Leadership Program of the Bashkir State Medical University (PRIORITY-2030).*

REFERENCES

1. Salhotra A, Shah HN, Levi B, Longaker MT. Mechanisms of bone development and repair. *Nat Rev Mol Cell Biol*. 2020;21(11):696-711. doi: 10.1038/s41580-020-00279-w
2. Lyulin SV, Ivliev DS, Balaev PI, et al. Surgical treatment results of metastatic spine disease with using minimally invasive technologies, including 3D video endoscopic technologies. *Zhurnal Voprosy Neirokhirurgii Imeni N.N. Burdenko*. 2021;85(4):49-57. doi: 10.17116/neiro20218504149
3. Zhu Y, Goh C, Shrestha A. Biomaterial Properties Modulating Bone Regeneration. *Macromol Biosci*. 2021;21(4):e2000365. doi: 10.1002/mabi.202000365
4. Qi J, Yu T, Hu B, et al. Current Biomaterial-Based Bone Tissue Engineering and Translational Medicine. *Int J Mol Sci*. 2021;22(19):10233. doi: 10.3390/ijms221910233
5. Wubneh A, Tsekoura EK, Ayranci C, Uludağ H. Current state of fabrication technologies and materials for bone tissue engineering. *Acta Biomater*. 2018;80:1-30. doi: 10.1016/j.actbio.2018.09.031
6. Liu M, Nakasaki M, Shih YV, Varghese S. Effect of age on biomaterial-mediated in situ bone tissue regeneration. *Acta Biomater*. 2018;78:329-340. doi: 10.1016/j.actbio.2018.06.035
7. Schmidt AH. Autologous bone graft: Is it still the gold standard? *Injury*. 2021;52 Suppl 2:S18-S22. doi: 10.1016/j.injury.2021.01.043
8. Lyulin S, Balaev P, Subramanyam KN, et al. Three-Dimensional Endoscopy-Assisted Excision and Reconstruction for Metastatic Disease of the Dorsal and Lumbar Spine: Early Results. *Clin Orthop Surg*. 2022;14(1):148-154. doi: 10.4055/cios21006
9. Valtanen RS, Yang YP, Gurtner GC, et al. Synthetic and Bone tissue engineering graft substitutes: What is the future? *Injury*. 2021;52 Suppl 2:S72-S77. doi: 10.1016/j.injury.2020.07.040
10. Zeiter S, Koschitzki K, Alini M, et al. Evaluation of Preclinical Models for the Testing of Bone Tissue-Engineered Constructs. *Tissue Eng Part C Methods*. 2020;26(2):107-117. doi: 10.1089/ten.TEC.2019.0213
11. Confalonieri D, Schwab A, Walles H, Ehlicke F. Advanced Therapy Medicinal Products: A Guide for Bone Marrow-derived MSC Application in Bone and Cartilage Tissue Engineering. *Tissue Eng Part B Rev*. 2018;24(2):155-169. doi: 10.1089/ten.TEB.2017.0305

12. Mukhametov UF, Lyulin SV, Borzunov DY, et al. Alloplastic and Implant Materials for Bone Grafting: a Literature Review. *Creative surgery and oncology*. 2021;11(4):343-353. (In Russ.) doi: 10.24060/2076-3093-2021-11-4-343-353
13. Hou X, Zhang L, Zhou Z, et al. Calcium Phosphate-Based Biomaterials for Bone Repair. *J Funct Biomater*. 2022;13(4):187. doi: 10.3390/jfb13040187
14. Ielo I, Calabrese G, De Luca G, Conoci S. Recent Advances in Hydroxyapatite-Based Biocomposites for Bone Tissue Regeneration in Orthopedics. *Int J Mol Sci*. 2022;23(17):9721. doi: 10.3390/ijms23179721
15. Safronova TV, Selezneva II, Tikhonova SA, et al. Biocompatibility of biphasic α,β-tricalcium phosphate ceramics in vitro. *Bioact Mater*. 2020;5(2):423-427. doi: 10.1016/j.bioactmat.2020.03.007
16. Pazarçeviren AE, Tezcaner A, Keskin D, et al. Boron-doped Biphasic Hydroxyapatite/β-Tricalcium Phosphate for Bone Tissue Engineering. *Biol Trace Elem Res*. 2021;199(3):968-980. doi: 10.1007/s12011-020-02230-8
17. Bai Y, Sha J, Kanno T, et al. Comparison of the Bone Regenerative Capacity of Three-Dimensional Uncalcined and Unsintered Hydroxyapatite/Poly-d/l-Lactide and Beta-Tricalcium Phosphate Used as Bone Graft Substitutes. *J Invest Surg*. 2021;34(3):243-256. doi: 10.1080/08941939.2019
18. Rh Owen G, Dard M, Larjava H. Hydoxyapatite/beta-tricalcium phosphate biphasic ceramics as regenerative material for the repair of complex bone defects. *J Biomed Mater Res B Appl Biomater*. 2018;106(6):2493-2512. doi: 10.1002/jbm.b.34049
19. Ding X, Li A, Yang F, et al. β-tricalcium phosphate and octacalcium phosphate composite bioceramic material for bone tissue engineering. *J Biomater Appl*. 2020;34(9):1294-1299. doi: 10.1177/0885328220903989
20. Madhumathi K, Rubaiya Y, Doble M, et al. Antibacterial, anti-inflammatory, and bone-regenerative dual-drug-loaded calcium phosphate nanocarriers-in vitro and in vivo studies. *Drug Deliv Transl Res*. 2018;8(5):1066-1077. doi: 10.1007/s13346-018-0532-6
21. Wierichs RJ, Wolf TG, Campus G, Carvalho TS. Efficacy of nano-hydroxyapatite on caries prevention-a systematic review and meta-analysis. *Clin Oral Investig*. 2022;26(4):3373-3381. doi: 10.1007/s00784-022-04390-4
22. Alenezi A, Chrcanovic B, Wennerberg A. Effects of Local Drug and Chemical Compound Delivery on Bone Regeneration Around Dental Implants in Animal Models: A Systematic Review and Meta-Analysis. *Int J Oral Maxillofac Implants*. 2018;33(1):e1-e18. doi: 10.11607/jomi.6333
23. Shimazaki K, Mooney V. Comparative study of porous hydroxyapatite and tricalcium phosphate as bone substitute. *J Orthop Res*. 1985;3(3):301-10. doi: 10.1002/jor.1100030306
24. Pan J, Prabakaran S, Rajan M. In-vivo assessment of minerals substituted hydroxyapatite / poly sorbitol sebacate glutamate (PSSG) composite coating on titanium metal implant for orthopedic implantation. *Biomed Pharmacother*. 2019;119:109404. doi: 10.1016/j.biopha.2019.109404
25. Tripathi G, Sugiura Y, Kareiva A, et al. Feasibility evaluation of low-crystallinity β-tricalcium phosphate blocks as a bone substitute fabricated by a dissolution-precipitation reaction from α-tricalcium phosphate blocks. *J Biomater Appl*. 2018;33(2):259-270. doi: 10.1177/0885328218788255
26. Correa D, Almirall A, Carrodeguas RG, et al. α-Tricalcium phosphate cements modified with β-dicalcium silicate and tricalcium aluminate: physicochemical characterization, in vitro bioactivity and cytotoxicity. *J Biomed Mater Res B Appl Biomater*. 2015;103(1):72-83. doi: 10.1002/jbm.b.33176
27. Ebrahimi M, Botelho MG, Dorozhkin SV. Biphasic calcium phosphates bioceramics (HA/TCP): Concept, physicochemical properties and the impact of standardization of study protocols in biomaterials research. *Mater Sci Eng C Mater Biol Appl*. 2017;71:1293-1312. doi: 10.1016/j.msec.2016.11.039
28. Ebrahimi M, Botelho M. Biphasic calcium phosphates (BCP) of hydroxyapatite (HA) and tricalcium phosphate (TCP) as bone substitutes: Importance of physicochemical characterizations in biomaterials studies. *Data Brief*. 2016;10:93-97. doi: 10.1016/j.dib.2016.11.080
29. Kim SE, Park K. Recent Advances of Biphasic Calcium Phosphate Bioceramics for Bone Tissue Regeneration. *Adv Exp Med Biol*. 2020;1250:177-188. doi: 10.1007/978-981-15-3262-7_12
30. DileepKumar VG, Sridhar MS, Aramwit P, et al. A review on the synthesis and properties of hydroxyapatite for biomedical applications. *J Biomater Sci Polym Ed*. 2022;33(2):229-261. doi: 10.1080/09205063.2021.1980985
31. Ramesh N, Moratti SC, Dias GJ. Hydroxyapatite-polymer biocomposites for bone regeneration: A review of current trends. *J Biomed Mater Res B Appl Biomater*. 2018;106(5):2046-2057. doi: 10.1002/jbm.b.33950
32. Ghiasi B, Sefidbakht Y, Mozaffari-Jovin S, et al. Hydroxyapatite as a biomaterial - a gift that keeps on giving. *Drug Dev Ind Pharm*. 2020;46(7):1035-1062. doi: 10.1080/03639045.2020.1776321
33. Lytkina D, Gutsalova A, Fedorishin D, et al. Synthesis and Properties of Zinc-Modified Hydroxyapatite. *J Funct Biomater*. 2020;11(1):10. doi: 10.3390/jfb11010010
34. Coutinho TC, Tardioli PW, Farinas CS. Hydroxyapatite nanoparticles modified with metal ions for xylanase immobilization. *Int J Biol Macromol*. 2020;150:344-353. doi: 10.1016/j.ijbiomac.2020.02.058

35. Huang SM, Liu SM, Ko CL, Chen WC. Advances of Hydroxyapatite Hybrid Organic Composite Used as Drug or Protein Carriers for Biomedical Applications: A Review. *Polymers* (Basel). 2022;14(5):976. doi: 10.3390/polym14050976
36. Higino T, França R. Drug-delivery nanoparticles for bone-tissue and dental applications. *Biomed Phys Eng Express*. 2022;8(4). doi: 10.1088/2057-1976/ac682c
37. Trabelsi M, AlShahrani I, Algarni H, et al. Mechanical and tribological properties of the tricalcium phosphate - magnesium oxide composites. *Mater Sci Eng C Mater Biol Appl*. 2019;96:716-729. doi: 10.1016/j.msec.2018.11.070
38. Vahabzadeh S, Robertson S, Bose S. Beta-phase Stabilization and Increased Osteogenic Differentiation of Stem Cells by Solid-State Synthesized Magnesium Tricalcium Phosphate. *J Mater Res*. 2021;36(15):3041-3049. doi: 10.1557/s43578-021-00311-5
39. Jinno T, Davy DT, Goldberg VM. Comparison of hydroxyapatite and hydroxyapatite tricalcium-phosphate coatings. *J Arthroplasty*. 2002;17(7):902-9. doi: 10.1054/arth.2002.34821
40. Ji W, Kerckhofs G, Geeroms C, et al. Deciphering the combined effect of bone morphogenetic protein 6 and calcium phosphate on bone formation capacity of periosteum derived cells-based tissue engineering constructs. *Acta Biomater*. 2018;80:97-107. doi: 10.1016/j.actbio.2018.09.046
41. Kerckhofs G, Chai YC, Luyten FP, Geris L. Combining microCT-based characterization with empirical modelling as a robust screening approach for the design of optimized CaP-containing scaffolds for progenitor cell-mediated bone formation. *Acta Biomater*. 2016;35:330-40. doi: 10.1016/j.actbio.2016.02.037

The article was submitted 07.03.2023; approved after reviewing 05.06.2023; accepted for publication 01.12.2023.

Information about the authors:

Ural F. Mukhametov – Candidate of Medical Sciences, Head of Department, ufa.rkbkuv@doctorrb.ru, https://orcid.org/0000-0003-3694-3302;

Denis S. Ivliev – neurosurgeon, ivlievdenis95@gmail.com, https://orcid.org/0000-0002-6106-7693;

Ilgiz F. Gareev – Ph.D., Senior Researcher, ilgiz _gareev@mail.ru, https://orcid.org/0000-0002-4965-0835;

Sergey V. Lyulin – Doctor of Medical Sciences, Head of Department, carmel74@yandex.ru, https://orcid.org/0000-0002-2549-1059;

Dmitry Yu. Borzunov – Doctor of Medical Sciences, Professor, Professor of Department, borzunov@bk.ru, https://orcid.org/0000-0003-3720-5467.

Original article
https://doi.org/10.18019/1028-4427-2024-30-1-90-98

Pathomorphologic evaluation of intra-articular injections of soluble platelet-rich plasma for treatment of experimental osteoarthritis

A.A. Tretyakov[1]✉, D.A. Zinovkin[1], F.N. Karpenko[2], M.P. Potapnev[2], V.I. Nikolaev[1], Z.I. Pranjol[3]

[1] Gomel State Medical University, Gomel, Republic of Belarus
[2] Republic Research and Production Center for Transfusiology and Medical Biotechnologies, Minsk, Republic of Belarus
[3] School of Life Science, University of Sussex, Brighton, UK

Corresponding author: Alexander A. Tretyakov, alextret73@gmail.com

Abstract

Introduction Non-surgical treatment of osteoarthritis is aimed at managing joint degeneration and inflammation to prolong the life of the original joint and delay total joint replacement. The objective was to pathomorphologically substantiate preclinical effectiveness of PRP in OA using comparative analysis of depleted plasma and serum.

Material and methods The experiment was performed in 120 Wistar rats, divided into 4 groups. Osteoarthritis was simulated using an original method. Knee joint injection given to the animals after skin dissection under inhalation anesthesia and visual control two weeks later contained 0.05 ml PRP in group 1, 0.05 ml plasma in groups 2 and 0.05 ml blood serum in groups 3. The same volume of physiological saline solution was used for the injections produced for control animals. Injections were administered three times at 2-week intervals. Animals were sacrificed in groups of 10 at 2 weeks of each injection.

Results The median MANKIN value scored 2.0 (1.0; 2.0) in group 1, 6.0 (5.0; 7.0) in group 2 and 7.0 (6.0; 7.0) in group 3 at 6 weeks. The median MANKIN value scored 7.5 (7.0, 8.0) in the control group. Statistically significant differences were determined between the groups at $p < 0.001$.

Discussion Literature data on preclinical evaluation of the effectiveness of PRP therapy in biological models of OA are controversial. An original, low-traumatic functional method was used for simulating knee OA to reproduce major pathogenetic mechanisms in rats.

Conclusion The findings suggested a pronounced therapeutic effect with improved morphofunctional features of the hyaline cartilage and MANKIN score of 2 at 6 days of intra-articular administration of modified PRP as compared with plasma and serum.

Keywords: osteoarthritis, experimental model, laboratory rat, articular cartilage, joint capsule, subchondral bone, treatment of osteoarthritis, platelet-rich plasma, PRP, blood serum

For **citation**: Tretyakov AA, Zinovkin DA, Karpenko FN, Potapnev MP, Nikolaev VI, Pranjol ZI. Pathomorphologic evaluation of intra-articular injections of soluble platelet-rich plasma for treatment of experimental osteoarthritis. *Genij Ortopedii*. 2024;30(1):90-98. doi: 10.18019/1028-4427-2024-30-1-90-98

INTRODUCTION

In recent decades, the orthobiological approach, as one of the principles of regenerative medicine, has been used for the local treatment of OA among specialists developing technology for new or optimized biological materials and among orthopaedic and trauma surgeons for stabilization of degenerative changes in articular cartilage [1-3]. Blood derivatives, including autologous conditioned blood serum (SC) or platelet-rich plasma (PRP) can be used for the treatment of OA [4-12]. Literature data on preclinical evaluation of the PRP therapy in biological models of OA are controversial due to different methods of simulating OA, technologies for obtaining experimental PRP products, the frequency of their intra-articular administration and the intervals between injections [13, 14, 15]. Experimental OA is normally inducted by intra-articular administration of monoiodoacetate or a talc suspension. In our opinion, the effect of chemicals on the hyaline cartilage can cause a chemical injury and affect evaluation of the results of therapy [15, 16]. Therefore, an original, low-traumatic functional method was used in our series for simulating knee OA in rats to reproduce major pathogenetic mechanisms of the condition [14, 17]. The frequency of administration of experimental PRP products varies from one to three intra-articular injections among different authors. Pathomorphological and immunological assessment of the effectiveness of PRP therapy includes increased thickness of the articular cartilage, improved tinctorial properties of the articular cartilage matrix, appearance of fibro-hyaline cartilage and an analgesic anti-inflammatory effect [18-24]. Non-surgical treatment of OA is aimed at managing joint degeneration and inflammation to prolong the life of the original joint and delay total joint replacement. Original technologies for obtaining biologically standardized autologous and donor PRP has been developed at the Republican Scientific and Practical Center for Transfusiology and Medical Biotechnology (Republic of Belarus, Minsk). The effectiveness of the products was evaluated with OA simulated in experimental animals optimizing minimally invasive intra-articular administration of blood derivatives.

The **objective** was to pathomorphologically substantiate preclinical effectiveness of PRP in OA using comparative analysis of depleted plasma and serum.

MATERIAL AND METHODS

Laboratory animals

The experiment involved 120 Wistar rats (60 females and 60 males). The animals were kept in the vivarium of the Gomel State Medical University in cages of 3 individuals, with humidity and temperature controlled. Water and food were provided ad libidum. The day/night cycle was 12 hours. Prior to experiments, the animals got acclimatized for 14 days. Animals were kept and cared for in accordance with the recommendations of Good Laboratory Practice of the Ministry of Health of the Republic of Belarus (TPK 125-2008 (02040)). Animals were sacrificed following the bioethical principles of the Declaration of Helsinki for the Humane Treatment of Laboratory Animals as amended in 2013 [18]. Experimental studies with animals were approved by the ethics committee of Gomel State Medical University (minutes of meeting of the committee No. 4 dated December 23, 2020). Animals were randomized using envelopes/random number generator and divided into 4 equal groups (30 animals each). The first group (study group) included rats that received allogeneic plasma enriched with soluble platelet factors (PRP), the second group (comparison group 1) included rats that were injected with rat plasma, and the third (comparison group 2) received injections with serum blood of rats, the fourth group included controls.

Preparation of plasma, serum, PRP

The protocol for obtaining PRP included several strictly defined stages. Blood sampling was carried out in rats cardially with a syringe under general anesthesia with 2.5 % sodium thiopental administered intraperitoneally at a dose of 45 mg/kg body weight. The method allows you to take approximately 10 ml of blood. The contents of the syringe were transferred into tubes with 3.8 % sodium citrate (9:1 ratio) and centrifuged at room temperature at 1000 rpm within 20 minutes. Plasma and buffy platelets were collected using a Pasteur pipette and centrifuged at 1500 rpm. within 20 minutes. The resulting upper layer was selected and used as plasma with blood components removed, depleted plasma. The platelet content in the depleted and enriched layers was monitored using a Sysmex XP-300 hematology analyzer (Sysmex Europe GmbH, Germany). The lower platelet-rich layer was adjusted with depleted plasma to a platelet concentration of 2.0×10^{12}/ml. To assess the purity of PRP, white blood cells were counted with the count being less than 0.1×10^{3}/μl. The resulting plasma fractions were frozen at -70 °C. The enriched plasma was thawed and centrifuged at 3000 rpm. within 15 minutes after 1 to 3 days. The supernatant was collected, filtered using sterile filters with a pore diameter of 0.2 μm, packaged in 0.25 ml Eppendorf tubes and stored at -70 °C prior to the use [19]. Serum was obtained according to standard methods. The resulting blood in a volume of 5 to 10 ml was left at 4 °C for an hour. The clotted blood was centrifuged for 20 minutes at 2000 rpm. The supernatant, serum without evidence of hemolysis, was transferred into Eppendorf tubes and stored at -70 °C prior to the use.

Surgical simulation of osteoarthritis and dosing protocol

Osteoarthritis of the knee joint was simulated in rats using the original method [25]. The technique included several stages. The skin and fascia of the rodent knee was dissected under inhalation anesthesia in aseptic conditions. A sterile needle was injected into the joint cavity and a mechanical trauma to the cartilaginous structures of the lateral condyles of the femur and tibia was produced with the cutting part of the bevel of needle. The diameter of the needle matched with the overall thickness of the cartilaginous layer of the articular surfaces, and sutures were applied to the dissected tissues. Two days later, rats were subjected to use walking wheel system to create static and dynamic loading on injured joints reproducing major pathogenetic mechanisms of osteoarthritis. Two weeks after simulation of OA under inhalation anesthesia, after skin dissection under visual control, 0.05 ml of PRP was injected into the knee joints of animals in group 1, 0.05 ml of plasma injected in group 2, and 0.05 ml of blood serum administered in group 3. The same volume of saline was injected in control rats. Injections were produced three times at intervals of 2 weeks. Animals were sacrificed two weeks after each injection in groups of 10. Major stages of the experiment are presented in Figure 1.

Preparation of histological preparations

The joint was exposed and placed in the decalcifying liquid Histodecalc (Sigma, Italy) for 48-72 hours immediately after the animal was sacrificed. The joint was sagittally cut and the pieces of tissue fixed in 10 % neutral Lilly-buffered formalin for 24-48 hours. Histological processing was produced using the STP-120 histoprocessor (ThermoScientific, Germany) with the tissues embedded in paraffin blocks. A series of sections 4 μm thick were produced from paraffin blocks using a ThermoScientificMicrom HM 450 microtome (ThermoScientific, Germany). Staining with safranin O was produced after dewaxing as reported by R. Asjid et al. [21].

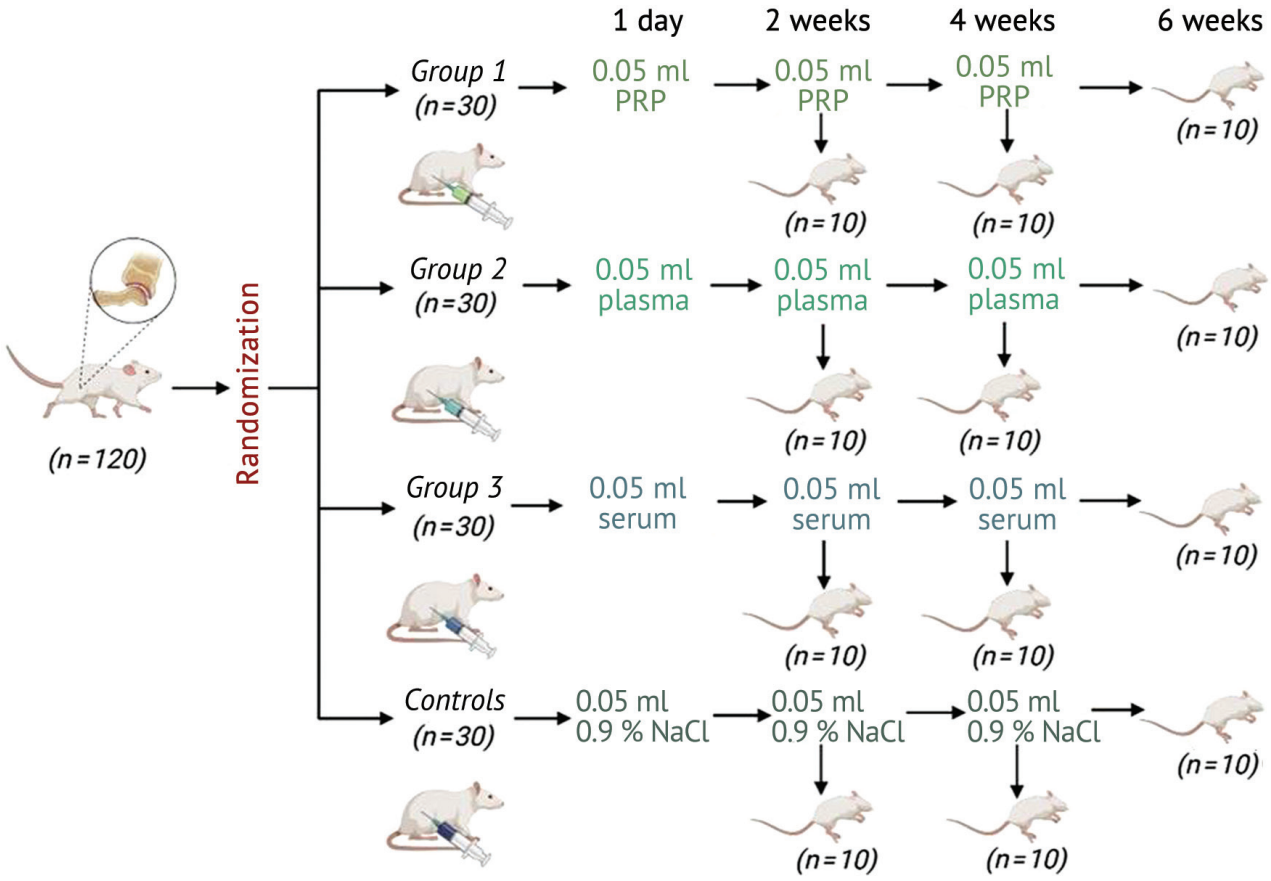

Fig. 1 Diagram of the experiment with therapy of the knee osteoarthritis induced in rats

Morphometric analysis

Microscopic and morphometric analyses were produced using a NikonEclipse 50i light microscope (Nikon, Japan). Morphometric assessment of hyaline cartilage was produced at the site of injury with 3 non-overlapping fields of view. A MANKIN scoring scale modified by F.M.D. Henson et al. was used to evaluate pathological changes in articular cartilage [21] (Table 1).

Table 1

Modified MANKIN score

Structure	Cellularity	Matrix integrity	Integrity of the border line	Score
Smooth surface / normal	Normal location	Normal staining	Normal, not impaired	0
Rough surface/single crack or area of cartilage separation	Clusters of cells in the superficial layer or loss of 10 % of cells	Slight loss of staining	Impaired	1
Multiple cracks/moderate cartilage separation	Disarrangement or loss of 25 % cells	Moderate loss of staining		2
Fragmentation or severe separation of cartilage	Rows of cells are missing or cell loss is up to 50 %	Severe loss of staining		3
Loss of cartilage fragments	Single cells	No staining		4
Erosion does not reach the boundary line				5
Erosion deeper than the boundary line				6

Statistical analysis

The Shapiro – Wilk test did not reveal a normal distribution, and the parameters in our series were presented as the median, 25th and 75th percentiles. Between-the-group comparisons were performed using the Kruskal – Wallis test. Dunn's test was used for post-hoc testing. Results were considered statistically significant at $p < 0.05$. The GraphPadPrism v. 7.04 software package (GraphPadSoftware inc., USA) was used for statistical analysis and graphical presentation of the findings.

RESULTS

All animals tolerated surgical knee manipulations performed under anesthesia and remained alive on to sacrifice. Histological signs of severe osteoarthritis were identified in animals of all groups 2 weeks after the first injection. Destruction of hyaline cartilage with loss of the fragments was observed with areas of cell loss and staining identified, and the border line had areas of discontinuity. The median Mankin score was 10.50 (9.0; 11.0) in group 1, 11.0 (9.0; 12.3) in group 2, 10.5 (9.8; 11.6) in group 3 and 12.0 (10.8; 13.0) in controls. No statistically significant differences were detected between the groups ($p = 0.326$) (Fig. 2a).

Microscopic examination of histological preparations of hyaline cartilage of the rodent joints performed at 4 weeks of the first injection of blood derivatives showed cracks and fragmentation of the cartilage, greater clonality of chondrocytes, areas of lost staining and discontinuity of the border line in group 1. Areas of destruction and loss of cartilage fragments, loss of the cellularity and staining in isolated areas were observed in group 2. Areas of lost cartilage fragments replaced by immature connective tissue, discontinuity of the border line were detected in group 3. Immature connective tissue at the site of the cartilage defect, loss of cellularity and discontinuity of the border line were noted in control animals. The median Mankin score was 3.00 (3.0; 4.3) in group 1, 4.0 (3.0; 5.3) in group 2, 7.0 (6.8; 8.0) in group 3 and 8.0 (7.0; 9.0) in controls at 4 weeks of the experiment. Statistically significant differences were identified between the groups ($p < 0.001$). Between-the-group differences are presented in Figure 2b.

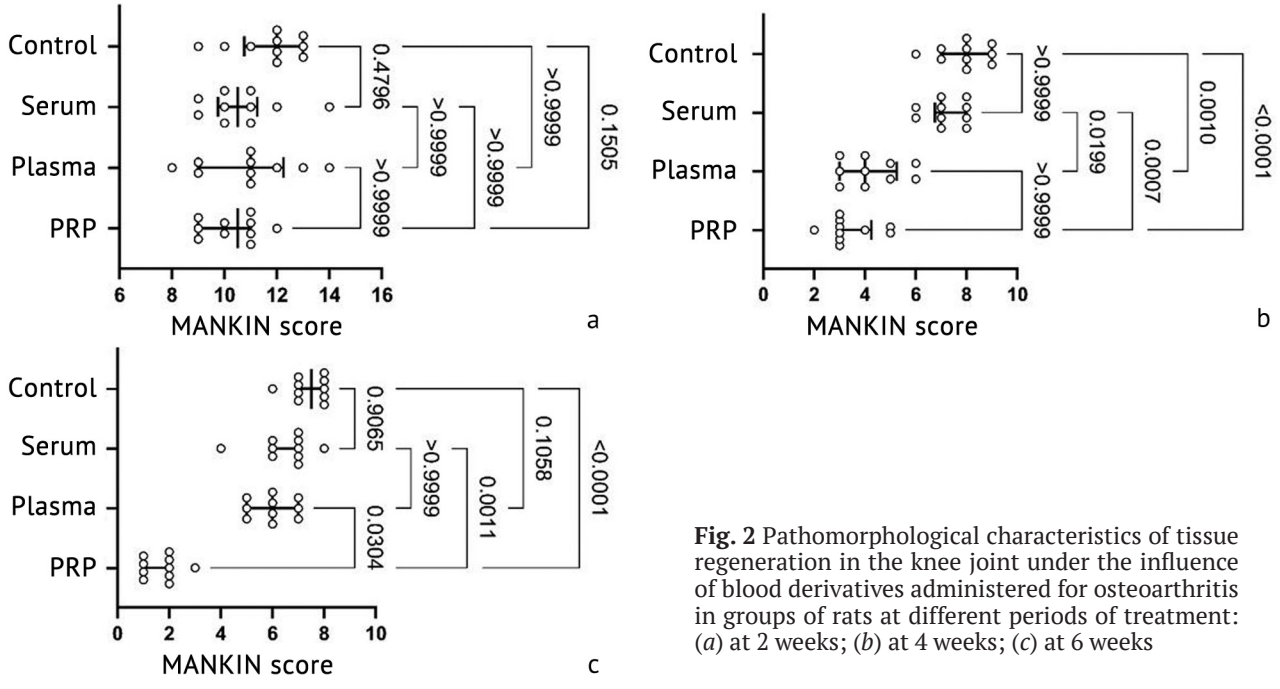

Fig. 2 Pathomorphological characteristics of tissue regeneration in the knee joint under the influence of blood derivatives administered for osteoarthritis in groups of rats at different periods of treatment: (*a*) at 2 weeks; (*b*) at 4 weeks; (*c*) at 6 weeks

Animals in group 1 showed sporadic rugosity of the surface of the hyaline cartilage and small areas of lost staining in the matrix at 6 weeks of the experiment. Sporadic rugosity of the surface of the hyaline cartilage and small areas of cartilage replaced with connective tissue were seen in group 2. Areas of hyaline cartilage replaced with connective tissue and decrease in the cellularity and matrix staining were observed in group 3. Control rats showed areas of cartilage completely replaced with connective tissue to the full depth and a significant decrease in cellularity in these areas. Most representative microphotographs are presented in Figure 3.

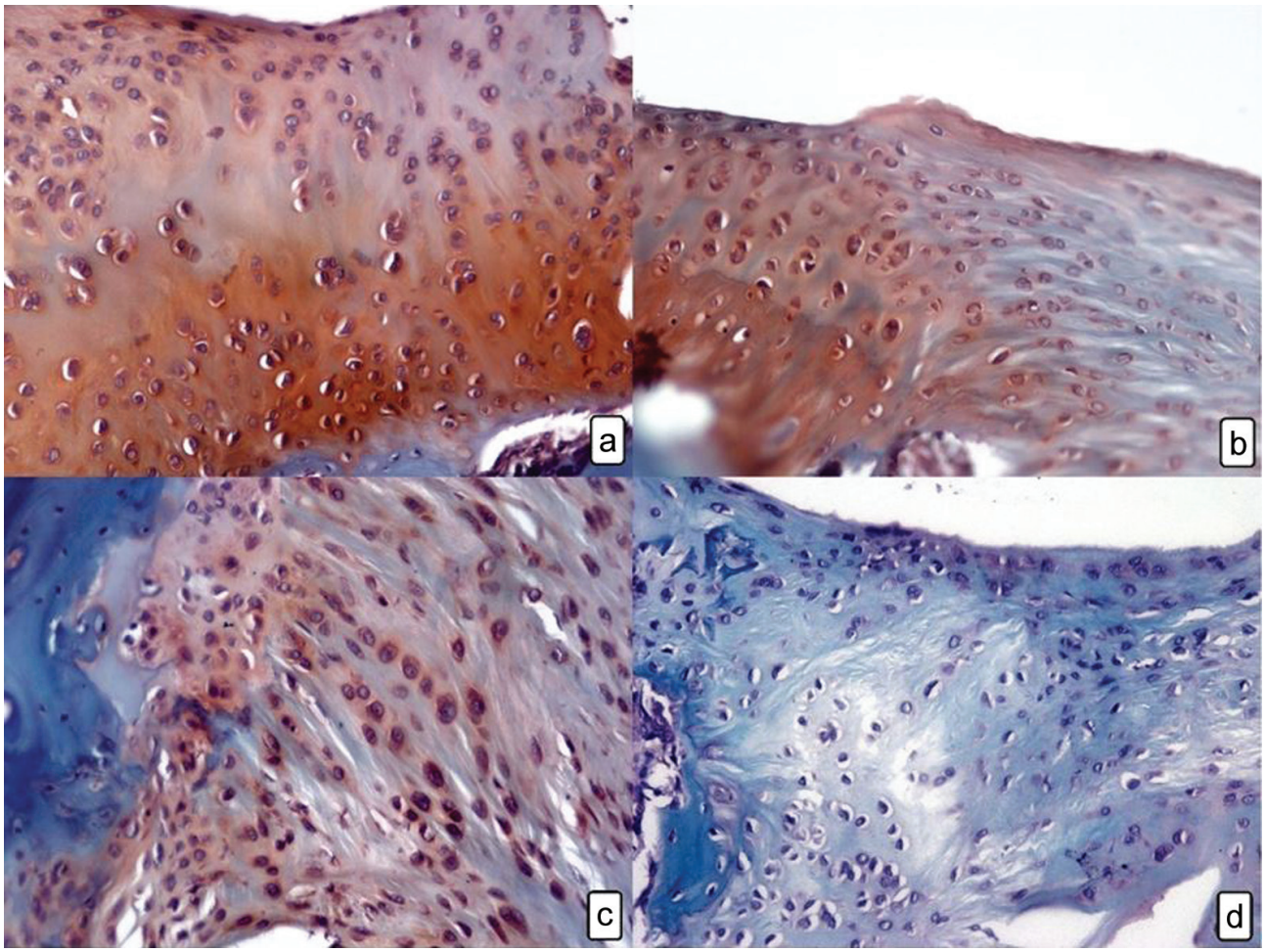

Fig. 3 Pathomorphological picture of the knee cartilage in rats treated for 6 weeks using: (*a*) PRP; (*b*) plasma; (*c*) serum; (*d*) saline solution. Stained with safranin O. Magnification ×200

The median Mankin score was 2.0 (1.0; 2.0) in group 1, 6.0 (5.0; 7.0) in group 2, 7.0 (6.0 ; 7.0) in group 3 and 7.5 (7.0, 8.0) in controls. Statistically significant differences were identified between the groups ($p < 0.001$). Between-the-group differences are presented in Figure 2c.

DISCUSSION

Pathological findings obtained in our series indicated increased cellularity, decreased surface rugosity and accumulation of proteoglycans in the intact hyaline cartilage with a deep cartilage defect being filled with connective tissue [26]. The findings are consistent with those by A. Boffa et al. in a systematic review (2021), showing similar changes in small laboratory animals reported in 28 studies. A group of animals receiving PRP therapy was compared with controls receiving a saline solution in the studies

presented in the systematic review [20]. Our study showed a statistically significant effect of PRP in comparison with control and serum groups [27-28] that can be associated with the pronounced regenerative potential of PRP compared to blood plasma containing no platelets and soluble platelet factors, and the blood serum containing a natural (3-5 times lower) level of soluble platelet factors. Similar data were reported in experimental studies of other authors [26, 29].

CONCLUSION

The findings suggested a pronounced therapeutic effect with improved morphofunctional features of the hyaline cartilage and Mankin score of 2 at 6 days of intra-articular administration of modified PRP as compared with plasma and serum.

Conflict of interest *The authors declare that there are no obvious or potential conflicts of interest related to the publication of this article.*

Financing *The work was produced as part of the project of the Ministry of Health of the Republic of Belarus "Development of a method for obtaining and using autologous plasma-containing soluble platelet factors in the treatment of patients with osteoarthritis" of the subprogram "Transplantation of cells, tissues and organs" of the state scientific and technical program "New methods of providing medical care", state registration No.: 20192357 dated 02.09.2019.*

Ethical review *The studies were approved by the ethical committee of the State Medical University, minutes of meeting No. 4 of December 23, 2020, and were conducted in accordance with the ethical principles of the Declaration of Helsinki.*

Informed consent *Not applicable.*

REFERENCES

1. Wu PI, Diaz R, Borg-Stein J. Platelet-Rich Plasma. *Phys Med Rehabil Clin N Am*. 2016;27(4):825-853. doi: 10.1016/j.pmr.2016.06.002
2. Cole BJ, Karas V, Hussey K, et al. Hyaluronic Acid Versus Platelet-Rich Plasma: A Prospective, Double-Blind Randomized Controlled Trial Comparing Clinical Outcomes and Effects on Intra-articular Biology for the Treatment of Knee Osteoarthritis. *Am J Sports Med*. 2017;45(2):339-346. doi: 10.1177/0363546516665809
3. Eismont OL. Orthobiologics in osteoarthritis treatment. *Medicinskie Novosti*. 2020;8(311):45-48. (In Russ.)
4. Laver L, Marom N, Dnyanesh L, et al. PRP for Degenerative Cartilage Disease: A Systematic Review of Clinical Studies. *Cartilage*. 2017;8(4):341-364. doi: 10.1177/1947603516670709
5. Joshi Jubert N, Rodríguez L, Reverté-Vinaixa MM, Navarro A. Platelet-Rich Plasma Injections for Advanced Knee Osteoarthritis: A Prospective, Randomized, Double-Blinded Clinical Trial. *Orthop J Sports Med*. 2017;5(2):2325967116689386. doi: 10.1177/2325967116689386
6. Fox BA, Stephens MM. Treatment of knee osteoarthritis with Orthokine-derived autologous conditioned serum. *Expert Rev Clin Immunol*. 2010;6(3):335-345. doi: 10.1586/eci.10.17
7. Frisbie DD, Kawcak CE, Werpy NM, et al. Clinical, biochemical, and histologic effects of intra-articular administration of autologous conditioned serum in horses with experimentally induced osteoarthritis. *Am J Vet Res*. 2007;68(3):290-296. doi: 10.2460/ajvr.68.3.290
8. Österdahl J. Evaluation of autologous conditioned serum. *Swed Uni Agricultural Sci*. 2008;(3):1-5.
9. Marx RE, Carlson ER, Eichstaedt RM, et al. Platelet-rich plasma: Growth factor enhancement for bone grafts. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 1998;85(6):638-646. doi: 10.1016/s1079-2104(98)90029-4
10. Kotlubaeva EYu, Belashov NV, Lapinin AI. On the history of the use and effectiveness of PRP-therapy. *Scientific almanac*. 2020;(1-2(63)):69-72. Available from: https://ukonf.com/doc/na.2020.01.02.pdf. Accessed Oct 25, 2024. (In Russ.)
11. Potapnev MP, Zagorodny GM, Krivenko SI, et al. Modern aspects of the use of plasma enriched in soluble platelet factors in the treatment of injuries and diseases of the musculoskeletal system. *Sports medicine: research and practice*. 2019;9(4):33-45. (In Russ.) doi: 10.17238/ISSN2223-2524.2019.4.33

12. Yamaguchi R, Terashima H, Yoneyama S, et al. Effects of platelet-rich plasma on intestinal anastomotic healing in rats: PRP concentration is a key factor. *J Surg Res*. 2012;173(2):258-66. doi: 10.1016/j.jss.2010.10.001
13. Nikolaev VI, Petkevich OV, Tretyakov AA, et al. *Method of experimental modeling of osteoarthritis of the knee joint in rats*. Patent of the Republic of Belarus, no. 23186, 2010. Available at: https://elib.gsmu.by/handle/GomSMU/3486. Accessed 25 Okt, 2023. (In Russ.)
14. Park YG, Han SB, Song SJ, et fl. Platelet-rich plasma therapy for knee joint problems: review of the literature, current practice and legal perspectives in Korea. *Knee Surg Relat Res*. 2012;24(2):70-8. doi: 10.5792/ksrr.2012.24.2.70
15. Troyanov AA, Potapnev MP, Kondratenko GG, et al. Biological effects and healing action of plasma enriched with soluble factors, platelets, in conditions of experimental hyperglycemia. *Medicinskyi zhurnal*. 2018;(2):107-112. (In Russ.)
16. Hanafy AS, El-Ganainy SO. Thermoresponsive Hyalomer intra-articular hydrogels improve monoiodoacetate-induced osteoarthritis in rats. *Int J Pharm*. 2020;573:118859. doi: 10.1016/j.ijpharm.2019.118859
17. Bansal H, Leon J, Pont JL, et al. Platelet-rich plasma (PRP) in osteoarthritis (OA) knee: Correct dose critical for long term clinical efficacy. *Sci Rep*. 2021;11(1):3971. doi: 10.1038/s41598-021-83025-2
18. Magalon J, Chateau AL, Bertrand B, et al. DEPA classification: a proposal for standardising PRP use and a retrospective application of available devices. *BMJ Open Sport Exerc Med*. 2016;2(1):e000060. doi: 10.1136/bmjsem-2015-000060
19. Potapnev MP, Krivenko SI, Bogdan VG, et al. Platelet-rich derived plasma: manufacture and medical application. *Healthcare*. 2018;10(859): 38-44. (In Russ.)
20. Boffa A, Salerno M, Merli G, et al. Platelet-rich plasma injections induce disease-modifying effects in the treatment of osteoarthritis in animal models. *Knee Surg Sports Traumatol Arthrosc*. 2021;29(12):4100-4121. doi: 10.1007/s00167-021-06659-9
21. Asjid R, Faisal T, Qamar K, et al. Effect of Platelet-rich Plasma on Mankin Scoring in Chemically-induced Animal Model of Osteoarthritis. *J Coll Physicians Surg Pak*. 2019;29(11):1067-1071. doi: 10.29271/jcpsp.2019.11.1067
22. Papalia R, Diaz Balzani L, Torre G, et al. Intraoperative application Platelet rich fibrin, postoperative injections OF PRP or microfracture only for osteochondral lesions of the knee: a five-year retrospective evaluation. *J Biol Regul Homeost Agents*. 2016;30(4 Suppl 1):41-49.
23. Malanin DA, Tregubov AS, Demeshchenko MV, Cherezov LL. *PRP-therapy for osteoarthritis of large joints*. Volgograd: VolgSMU Publ.; 2018:49. (In Russ). Available from: http://www.prplab.ru/docs/PRP-terapiya-pri-osteoartrite-krupnyh-sustavov.pdf. Accessed 25 Okt, 2023. (In Russ.)
24. Glynn LG, Mustafa A, Casey M, et al. Platelet-rich plasma (PRP) therapy for knee arthritis: a feasibility study in primary care. *Pilot Feasibility Stud*. 2018;4:93. doi: 10.1186/s40814-018-0288-2
25. Tretsyakov AA, Nikolaev VI, Zinovkin DA, Serdiuchenko NS. Experimental model of knee osteoarthritis in rats. *News of biomedical sciences*. 2020;20(4):90-97. (In Russ.)
26. Huang GS, Peng YJ, Hwang DW, et al. Assessment of the efficacy of intra-articular platelet rich plasma treatment in an ACLT experimental model by dynamic contrast enhancement MRI of knee subchondral bone marrow and MRI T2* measurement of articular cartilage. *Osteoarthritis Cartilage*. 2021;29(5):718-727. doi: 10.1016/j.joca.2021.02.001
27. Azizi S, Kheirandish R, Farsinejad A, Rasouli N. The effect of intraarticular serum rich in growth factors (SRGF) on knee osteoarthritis in the rat model. *Transfus Apher Sci*. 2017;56(3):371-375. doi: 10.1016/j.transci.2017.02.006
28. Araya N, Miyatake K, Tsuji K, et al. Intra-articular Injection of Pure Platelet-Rich Plasma Is the Most Effective Treatment for Joint Pain by Modulating Synovial Inflammation and Calcitonin Gene-Related Peptide Expression in a Rat Arthritis Model. *Am J Sports Med*. 2020;48(8):2004-2012. doi: 10.1177/0363546520924011
29. Subbot AM, Trufanov SV, Shakhbazyan NP. Comparative analysis of the regeneratory potential of blood derivatives on a cell model of corneal epithelium damage. *Genes and cells*. 2021;16(1):64-68. (In Russ.) doi: 10.23868/202104010

The article was submitted 13.06.2023; approved after reviewing 23.10.2023; accepted for publication 01.12.2023.

Information about the authors:

Alexander A. Tretyakov – Senior lecturer, alextret73@gmail.com, https://orcid.org/0000-0001-9902-1829;

Dimitry A. Zinovkin – Candidate of Biological Sciences, Associate Professor, zinovkin_da@gsmu.by, https://orcid.org/0000-0002-3808-8832;

Fedor N. Karpenko – Candidate of Medical Sciences, Director, director@blood.by, https://orcid.org/0000-0003-1648-8330;

Mikhail P. Potapnev– Doctor of Medical Sciences, Professor, potapnev@blood.by, https://orcid.org/0000-0001-7705-9383;

Vladimir I. Nikolaev – Candidate of Medical Sciences, Associate Professor, nikolaev.5252@mail.ru, https://orcid.org/0000-0001-9886-7216;

Midi Zahidul I. Pranjol – MD, Associate Professor, Senior lecturer, z.pranjol@sussex.ac.uk, https://orcid.org/0000-0002-6164-6281.

Contribution of the authors:

Tretyakov A.A. – conceptualization, project management, research, collection and analysis of literature sources, preparation and writing of the manuscript of the article, preparation of the work for publication.

Zinovkin D.A. – analysis of literature sources, methodology, data processing, analysis, preparation of work for publication.

Karpenko F.N., Potapnev M.P. – ideological concept of the work, making adjustments to the original version.

Nikolaev V.I. – conceptualization, project management, control and management of research work; analysis of literature sources, editing of the article.

Pranjol M.Z.I. – data processing, statistical analysis, work with graphic images.

Original article
https://doi.org/10.18019/1028-4427-2024-30-1-99-106

Comparative experimental study of biomechanical features of suture materials in tendon repair

V.M. Malishevsky[1]✉, R.V. Paskov[2], K.S. Sergeev[2]

[1] Regional Clinical Hospital No. 2, Tyumen, Russian Federation
[2] Tyumen State Medical University, Tyumen, Russian Federation

Corresponding author: Vladimir M. Malishevsky, mvm9233@yandex.ru

Abstract

Introduction Many different suture configurations and pathomorphology of tendon repair have been described for tendon repair over the past 20 years. However, the biomechanical properties of suture material at primary flexor tendon repair have not been sufficiently explored. A cyclic loading test is performed to evaluate the performance of the different sutures under repeated loading conditions simulating dynamic conditions in postoperative rehabilitation procedures.

The objective was to compare the strength of suture materials under cyclic loading on a biological model of a tendon.

Material and methods Eighty porcine digital flexor tendons were examined in a pilot study. The sutured tendons were tested with a universal testing machine. Tendon repair was produced using polypropylene in group I, braided polyamide suture in group II, complex polytetrafluoroethylene thread in group III and a thread of superelastic titanium nickelide in group IV. The standard Chang protocol was used for cyclic loading.

Results The percentage of intact sutures was 25 % in group I and in group II, 80 % in group III and 85 % in group IV after completing the entire load cycle. A pairwise comparison showed suture disruption being more common for group I and group II as compared to group III and group IV. Irreversible gap was more common for group 1 as compared to group IV. Neither knot ruptures nor tissue cutting were seen in the groups.

Discussion The topic of biomechanical properties of suture material remains poorly understood. Although static load testing is commonly used in current experimental studies and cyclic testing is suitable for simulating postoperative conditions. The search continues for the “ideal” suture material for flexor tendon repair to prevent tears and retain tensile properties until the repair reaches strength.

Conclusion The threads of polytetrafluoroethylene and nickelide-titanium showed the best biomechanical properties for tendon repair in the form of linear strength, good elasticity and low plasticity of the suture material. There were no significant differences between polypropylene and braided polyamide threads.

Keywords: tendon, cyclic load, titanium nickelide, tendon suture

For citation: Malishevsky VM, Paskov RV, Sergeev KS. Comparative experimental study of biomechanical features of suture materials in tendon repair. *Genij Ortopedii*. 2024;30(1):99-106. doi: 10.18019/1028-4427-2024-30-1-99-106

INTRODUCTION

Hand wounds with tendon damage account for 18.8 % of all injuries to the upper limbs [1, 2]. Injuries to flexor tendons are characterized by significant periods of temporary disability and a high level of disability ranging between 21 % and 28 % of all those examined by the Physical Disability Board of Review for the consequences of traumatic injuries [3, 4].

With more than a century of experience in the study and application of flexor tendon suturing techniques, poor outcomes are reported in 7 to 30 % of cases due to insufficient tensile strength of the tendon suture. Mechanical resistance to tendon sliding consists of external and internal sources of resistance [5, 6]. After tendon suture, internal resistance increases by 27.4 % for low-friction repair techniques and 59.9 % for high-friction repair techniques. External resistance can also increase dramatically after injury and surgery due to soft tissue swelling, joint swelling, and pain-induced contraction of antagonist muscles [7, 8, 9]. It is essential to explore ways of increasing the strength of the hand tendon repair.

The strength of the tendon suture depends on such parameters as the type of suture material; its caliber; the number of threads passing through the diameter of the tendon; loop configuration; a distance from the end of the tendon; additional tension at the tendon contact site and the location of the node [10, 11, 12]. Over the past 20 years researchers focused on the types of tendon sutures and the pathomorphology of tendon repair, but the biomechanical properties of the suture material during primary repair of flexor tendons have not been sufficiently explored. It is not the strength of the thread that matters with the strength of the knot being essential with the loss of strength in the knot ranging between 10 and 50 % of the original for most threads [13, 14]. The strength of the knot is associated with the superficial properties of the threads, which determine sliding. The use of synthetic non-absorbable suture materials for tendon sutures is one of the modern global trends in surgery. New types of materials with improved characteristics are being developed and introduced into surgical practice.

The phenomenon of hysteresis delay of biological tissues discovered by V.E. Gunter facilitated a new class of biocompatible materials including superelastic shape memory alloys being used in Russia [15, 16, 17, 18]. A method of manufacturing a superelastic thread from titanium nickelide was patented in 2006 [17, 18]. At a baseline, wire samples and threads are a composite consisting of a core – monolithic titanium nickelide – and a surface layer with a microstructured surface. The diameter of titanium nickelide threads ranges between 60 and 120 microns. The threads have a microstructured surface that increases the area of their contact with the tissues being connected. They are also able to function reliably in the body under alternating effects due to their elasticity and resilience, and can be used for tendon sutures [19, 20]. The strength of this material in tendon repair has not been sufficiently studied and its biomechanical properties can be compared with more common suture materials.

The objective was to compare the strength of suture materials under cyclic loading on a biological model of a tendon.

MATERIAL AND METHODS

Eighty flexor tendons of the second digit of the forelimbs taken from five-month-old piglets weighing 90-110 kg were explored. The mean diameter and length of each porcine tendon were 5 ± 1 mm and 60 ± 10 mm, respectively, which correlated with the parameters of human flexor digitorum profundus tendons. A transverse incision was made through each porcine tendon using a scalpel. The incision area corresponded to the base of the mechanical finger designed as

described below, to simulate a complete tendon injury in a “difficult anatomical area.” The ends of the tendons were repaired by one surgeon using four types of suture material with a 6-strand M-Tang suture [21, 22] (Fig. 1).

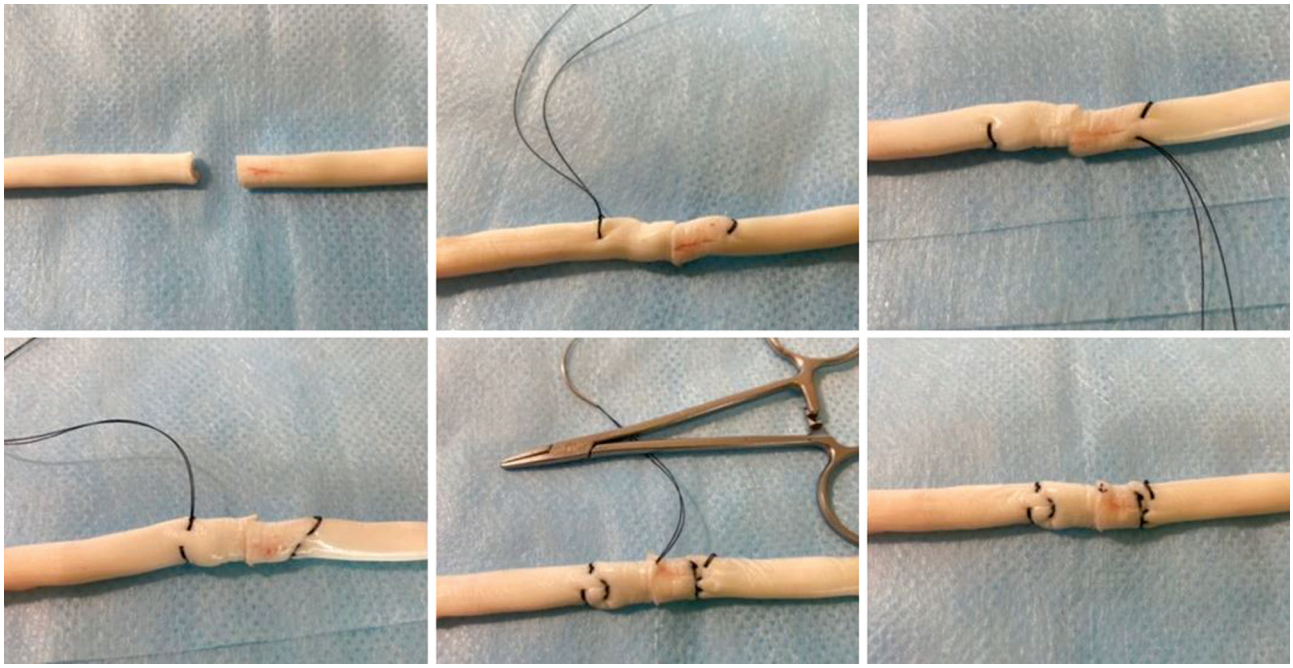

Fig. 1 6-thread M-Tang suturing

The caliber of the suture material was 4/0 (0.15 mm) with 10 mm distance from the ends of the tendons and 2 mm loop length. No additional epitendinous suture was applied for a more objective examination of the strength of the suture material. Institutional ethics committee approval was not required for this type of study. Four types of suture material used to restore the tendon included:

(1) Polypropylene (monofilament) synthetic thread;

(2) Non-absorbable polyamide braided thread;

(3) Complex polytetrafluoroethylene thread;

(4) Super-elastic titanium nickelide thread.

Depending on the suture material used, all tendons were randomly distributed into 4 groups, 20 samples each. The cross-linked tendons were kept at 5°C and hydrated prior to strength and cyclic testing [23]. At the final stage, all repaired tendons were examined using the original device (Fig. 2).

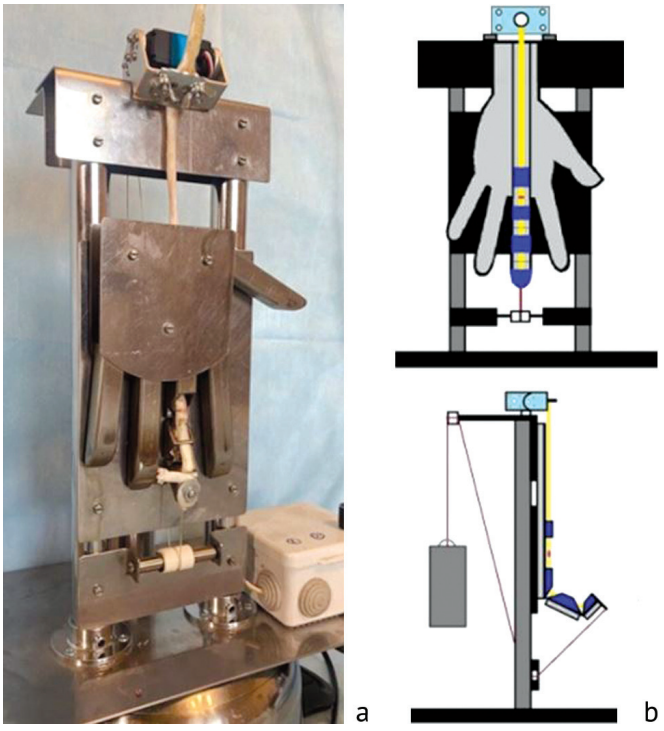

Fig. 2 A device for practicing the skills of applying a tendon suture and testing its strength (*a*). Diagram of cyclic strength testing (*b*)

A device (RF patent application No. 2023119917 dated July 28, 2023) was previously developed for applying cyclic testing protocols to examine a biological model of a tendon suture. The distal end of the tendon was secured to the mechanical finger using a clamping screw, and the proximal end of the tendon was secured to the servo drive. A weight of 1 kg was used for static loading to achieve full extension of the finger at the beginning of each cycle and provide a pre-start load.

The standard protocol of Chang et al. was used to determine the fatigue strength of the suture material which was the sum of the number of cycles and the load used in cyclic test protocols for tendon sutures [24, 25, 26]. It was a cyclic tensile strength test using 2 N for preload, then a cyclic load of 15 N to simulate passive mobilization, and 2000 cycles at 0.3 Hz or until the suture breaks. The cyclic tensile strength test was produced as reported in previous publication. Visual confirmation of each parameter was obtained for each cycle using video recording.

Statistical analysis was performed using IBM SPSS 28.0.1. Quantitative data were presented as the arithmetic mean with standard deviation (M ± SD) in the normal distribution and as the median with the interquartile range Me [27, 28] in the non-normal distribution using the Kolmogorov – Smirnov test with Lilliefors correction. Analysis of qualitative variables was produced in groups using the Pearson χ^2 test. A significance level of $p < 0.05$ was accepted for significant differences comparing four groups, taking into account the Bonferroni correction, $p < 0.0085$.

RESULTS

The average size of the gap between the ends of the tendons repaired in the absence of thread rupture was 3.47 ± 2.07 mm in the first group, 1.6 ± 0.7 mm in the second group, 1 .32 ± 0.75 mm in the third group, 1.16 ± 0.5 mm in the fourth group with a cyclic loading protocol of 2000 cycles performed. No node ruptures or tissue eruption were detected in any group.

A comparison of different types of suture material showed a reversible gap (up to 1 mm) between the ends of the repaired tendons being common (Table 1) in the group of complex polytetrafluoroethylene thread (group 3) and superelastic titanium nickelide thread (group 4) in comparison with polypropylene (monofilament) synthetic thread (group 1) and non-absorbable polyamide braided thread (group 2). No significant differences were found between groups 1 and 2, and between groups 3 and 4. An irreversible gap was more common for a polypropylene thread as compared to a titanium nickelide thread. Thread rupture was more common for complex polytetrafluoroethylene thread in comparison with groups 3 and 4 (Table 1).

Table 1

Analysis of a gap or thread breakage occurred with different types of suture material

	Group 1 (*n* = 20)	Group 2 (*n* = 20)	Group 3 (*n* = 20)	Group 4 (*n* = 20)	*p* (1-2)	p (1-3)	*p* (1-4)	*p* (2-3)	*p* (2-4)	*p* (3-4)
Reversible gap 1 mm	5 (25 %)	5 (25 %)	16 (80 %)	17 (85 %)	–	**0.003**	**0.001**	**0.001**	< **0.001**	–
Irreversible gap ⩾ 2 mm	12 (60 %)	5 (25 %)	3 (15 %)	2 (10 %)	–	–	**0.006**	–	–	–
Thread rupture	3 (15 %)	10 (50 %)	1 (5 %)	1 (5 %)	–	–	–	**0.006**	**0.006**	–

Dynamic changes in the tendon suture were analyzed depending on the number of load cycles (Fig. 3).

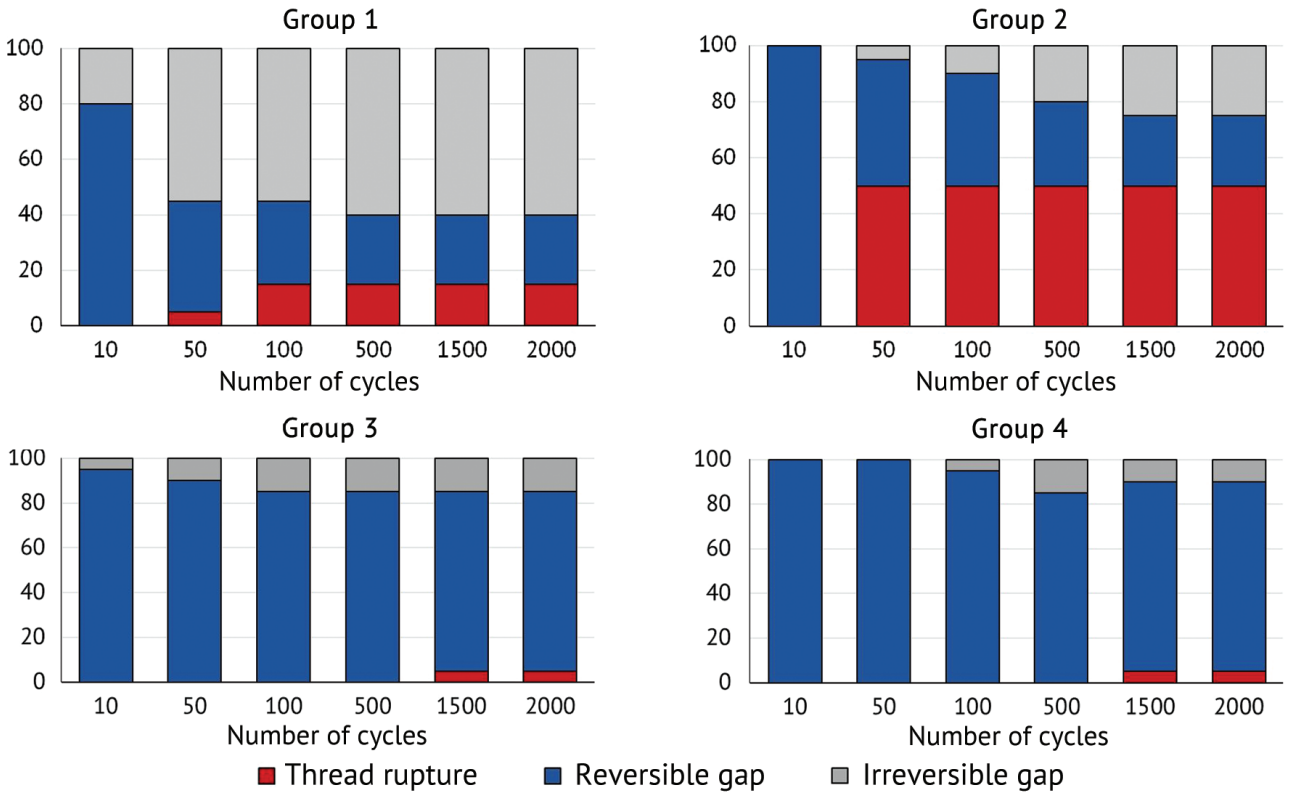

Fig. 3 Correlation between the gap between the ends of tendons (mm) and the number of load cycles in the study groups

An irreversible gap seen in the first group (polypropylene monofilament thread) was recorded in 20 % of cases after the first 10 cycles and in 55 % of cases after 50 cycles. The thread broke in 15 % of cases after 100 cycles of repetitions with an irreversible gap detected in 60 % of cases. The ratio remained until the end of the 2000 cycle. The largest average gap between the ends of the tendons with no thread rupture was recorded after 2000 repeated cycles (3.47 mm) in the first group. The results obtained confirm the excessive elasticity and plasticity of polypropylene, which can lead to weakening and stretching of tendon sutures after 50 repeated loading cycles.

The thread broke in half of the cases (50 %) of the second group (polyamide braided thread) with 50 repeated cycles. An irreversible gap of more than 2 mm detected after 50 cycles in 45 % of cases, decreased to 30 % after 1000 cycles. The high probability of thread breakage with 50 repeated cycles was associated with the low elasticity and low linear strength of the braided polyamide thread compared to other materials. An irreversible gap was recorded in 10 % of cases of the third group (polytetrafluoroethylene thread) with 50 repeated cycles. This number increased to 15 % and remained unchanged after 100 repetition cycles throughout the test. A single case of thread breakage was recorded after 100 repeated cycles with the only case of thread rupture registered after 1500 cycles. A single case of irreversible gap was detected after 100 repeated cycles, and a single case of thread rupture occurred after 1500 cycles in the fourth group (superelastic nickel-titanium thread).

DISCUSSION

Over the past 20 years, there has been a marked increase in the number of clinical and experimental publications on primary flexor tendon repair. Researchers sought to compare different tendon sutures and explore the pathomorphology of tendon repair, while biomechanical properties

of suture material remained poorly studied, although early postoperative rehabilitation and the final functional result would be dependent on the strength of the suture material.

Four suture materials were examined in our experimental study using an original device for cyclic testing of a biological model of a tendon suture. Static load-to-failure testing was produced in the experimental studies of suture material strength using Instron 3343 Single Column System (Instron Corp, Canton, Massachusetts) [29, 30, 31, 32, 33]. Cyclic testing is indicated for simulating postoperative conditions compared to static testing, which uses a constant speed of movement with increasing force. Cyclic testing has also been shown to induce tear formation in repaired flexor tendons at lower loads compared to static testing. This suggests that cyclic testing is a more rigorous and realistic measure of the effectiveness of flexor tendon repair than linear stretch testing.

Twenty-five percent of the tendon sutures remained intact for the polypropylene and braided polyamide sutures after completing the entire cyclic loading protocol of 2000 repetitions. When using, an irreversible gap was recorded in half of the cases with a polypropylene (monofilament) synthetic thread after 50 cycles of load repetitions, and suture rupture was more common after 2,000 cycles in comparison with complex polytetrafluoroethylene thread and nickel-titanium thread. This indicates that polypropylene thread has excessive elasticity and plasticity, unlike other types of suture material, which leads to weakening and stretching of the tendon sutures with early mobilization rehabilitation protocol.

There were no significant differences between polypropylene and braided polyamide threads. With the latter, a thread break was recorded in half the cases after 50 repeated cycles. A rupture in the group was more common after 2000 cycles as compared to the use of complex polytetrafluoroethylene thread and nickelide-titanium thread. This indicated low elasticity and linear strength with the braided polyamide suture as compared to other groups, which explained the likelihood of suture rupture during the first two weeks after surgery with the connected tendon ends being the weakest during this period. Polytetrafluoroethylene and nickel-titanium threads demonstrated the best biomechanical properties in the form of linear strength, good elasticity and low flexibility.

There were no significant differences between the threads after 2000 cycles, however, an irreversible gap was seen later being less common with use of a titanium nickelide thread.The average gap size in the absence of a thread breakage after 2000 repetition cycles was also minimum for the titanium nickelide thread.

CONCLUSION

The results of an experimental study of the fatigue strength of the tendon suture were demonstrated in four groups of biological models.

The demonstrated results of comparing the strength of different types of suture material on a biological model of a tendon under cyclic loading will allow in clinical practice to select the optimal suture material for suturing the flexor tendons and will ensure an improvement in the functional result, since the strength of the tendon suture guarantees the success of early active postoperative rehabilitation.

Conflict of interest *The authors declare that there are no obvious or potential conflicts of interest related to the publication of this article.*

Financing *The authors declare that there was no external funding for the study.*

Ethical review *Not applicable.*

Informed consent *Not applicable*.

REFERENCES

1. Minaev TR, Yuldashev AA, Nizov ON, et al. Analysis of recovery operations at injuries of flexor tendons of hand fingers. *Bulletin of emergency medicine*. 2014;(3):20-25. (In Russ.)
2. Manninen M, Karjalainen T, Määttä J, Flinkkilä T. Epidemiology of Flexor Tendon Injuries of the Hand in a Northern Finnish Population. *Scand J Surg*. 2017;106(3):278-282. doi: 10.1177/1457496916665544
3. Zenchenko A.V., Chernyakova Yu.M. Biology of healing, biomechanics changes and rehabilitation after flexor tendons repair. *Medical news*. 2020;(10):13-19. (In Russ.)
4. Kazantaev KE, Nabiev EN, Mukhamedkerim KB. et al. Pathomorphological aspects of research in long-term consequences of injuries to the flexor tendons of the fingers. *Bulletin KazNMU*. 2022;(1):279-285. (In Russ.)
5. Battiston B, Triolo PF, Bernardi A, Artiaco S, Tos P. Secondary repair of flexor tendon injuries. *Injury*. 2013;44(3):340-345. doi: 10.1016/j.injury.2013.01.023
6. Tang JB, Amadio PC, Boyer MI, et al. Current practice of primary flexor tendon repair: a global view. *Hand Clin*. 2013;29(2):179-189. doi: 10.1016/j.hcl.2013.02.003
7. Chang JH, Shieh SJ, Kuo LC, Lee YL. The initial anatomical severity in patients with hand injuries predicts future health-related quality of life. *J Trauma*. 2011;71(5):1352-1358. doi: 10.1097/TA.0b013e318216a56e
8. Kiseleva A.N., Nakonechny D.G., Weber E.V. and others. Results of treatment of patients with injuries of the flexor tendons of the fingers. *Modern achievements of traumatology and orthopedics*. St. Petersburg: RNIITO Publ.;2018:118-120.
9. Venkatramani H, Varadharajan V, Bhardwaj P, et al. Flexor tendon injuries. *J Clin Orthop Trauma*. 2019;10(5):853-861. doi: 10.1016/j.jcot.2019.08.005
10. Chang MK, Tay SC. Flexor Tendon Injuries and Repairs: A Single Centre Experience. *J Hand Surg Asian Pac Vol*. 2018;23(4):487-495. doi: 10.1142/S2424835518500479
11. Thangavelu M, Veerasamy N, Kanthan A. Study on evaluation and management of hand injuries. *J Evol Med Dent Sci*. 2016;(5):4703-4706. doi: 10.14260/jemds/2016/1072
12. Hurley CM, Reilly F, Callaghan S, Baig MN. Negative Predictors of Outcomes of Flexor Tendon Repairs. *Cureus*. 2019;11(3):e4303. doi: 10.7759/cureus.4303
13. Kadar A, Fainzack A, Vigler M. Dynamic Tendon Grip (DTG™) novel knot array compared to traditional sutures for zone two flexor tendon injury - a biomechanical feasibility study. *BMC Musculoskelet Disord*. 2022;23(1):320. doi: 10.1186/s12891-022-05279-9
14. Zafonte B, Rendulic D, Szabo RM. Flexor pulley system: anatomy, injury, and management. *J Hand Surg Am*. 2014;39(12):2525-32; quiz 2533. doi: 10.1016/j.jhsa.2014.06.005
15. Mirzoev MSh, Shakirov MN, Porokhova ED, DzhoNibekova RN. Experimental study of integration features of porous permeable and mesh titanium nickelide in vivo. *Avicenna Bulletin*. 2020;22(3):434-439. (In Russ.) doi: 10.25005/2074-0581-2020-22-3-434-439
16. Kokorev OV, Gyunter SV, Khodorenko VN, Dambaev GTs. Effect of modified surface and architectonics of porous-permeable TiNi-based alloy scaffold on cellular biocompatibility. *Acta biomedical scientifica*. 2018;3(3):188-194. (In Russ.) doi 10.29413/ABS.2018-3.3.29
17. Fedorov PG, Arshakyan VA, Gyunter VE. Modern sutural materials (review of literature). *Acta Biomedica Scientifica*. 2017;2(6):157-162. doi: 10.12737/article_5a0a8e626adf33.46655939
18. Nadezhdin SV, Kovaleva MG, Kolpakov AY, et al. Evaluation of biocompatibility and bioresistance of the workpieces of the nickel-titanium implants with modified nanosized surface layers in the in vivo experiments. *Journal Biomed*. 2016;(1):95-101. (In Russ.)
19. Kornilov DN, Popov IV, Rayevskaya LY, et al. Superelastic nickel titanium implant for tendon injury in experiment – outcomes of treatment and morphological background. *Siberian Medical Journal* (Irkutsk). 2014;126(3):21-25. (In Russ.)
20. Wu YF, Cao Y, Zhou YL, Tang JB. Biomechanical comparisons of four-strand tendon repairs with double-stranded sutures: effects of different locks and suture geometry. *J Hand Surg Eur Vol*. 2011;36(1):34-39. doi: 10.1177/1753193410379554
21. Tang JB. Tendon injuries across the world: treatment. *Injury*. 2006;37(11):1036-42. doi: 10.1016/j.injury.2006.07.027
22. Tang JB, Zhang Y, Cao Y, Xie RG. Core suture purchase affects strength of tendon repairs. *J Hand Surg Am*. 2005;30(6):1262-1266. doi: 10.1016/j.jhsa.2005.05.011
23. Bao R, Cheng S, Zhu J, et al. A Simplified Murine Model to Imitate Flexor Tendon Adhesion Formation without Suture. *Biomimetics* (Basel). 2022;7(3):92. doi: 10.3390/biomimetics7030092
24. Chang MK, Lim ZY, Wong YR, Tay SC. A review of cyclic testing protocols for flexor tendon repairs. *Clin Biomech* (Bristol, Avon). 2019;62:42-49. doi: 10.1016/j.clinbiomech.2018.12.007
25. de Wit T, Walbeehm ET, Hovius SE, McGrouther DA. The mechanical interaction between three geometric types of nylon core suture and a running epitenon suture in repair of porcine flexor tendons. *J Hand Surg Eur Vol*. 2013;38(7):788-94. doi: 10.1177/1753193413484876

26. Peltz TS, Haddad R, Walsh WR. The change in three-dimensional geometry of the Kessler flexor tendon repair under tension: a qualitative assessment using radiographs. *J Hand Surg Eur Vol*. 2010;35(8):676-677. doi: 10.1177/1753193409356374
27. Bavrina AP, Saperkin NV. Observational epidemiological studies and features of the presentation of findings in a scientific report. *Medical almanac*. 2021;(2(67)):83-89. (In Russ.)
28. Orlov AI. Key stages of statistical methods development. *Scientific journal of KubSAU*. 2014;(97(03)):73-85. (In Russ.)
29. Weissman JP, Sasson DC, Chappell AG, et al. Practice Patterns in Operative Flexor Tendon Laceration Repair: A 15-Year Analysis of Continuous Certification Data from the American Board of Plastic Surgery. *Plast Reconstr Surg Glob Open*. 2022;10(10):e4558. doi: 10.1097/GOX.0000000000004558
30. Chinen S, Okubo H, Kusano N, et al. Effects of Different Core Suture Lengths on Tensile Strength of Multiple-Strand Sutures for Flexor Tendon Repair. *J Hand Surg Glob Online*. 2020;3(1):41-46. doi: 10.1016/j.jhsg.2020.10.006
31. Rawson SD, Margetts L, Wong JK, Cartmell SH. Sutured tendon repair; a multi-scale finite element model. *Biomech Model Mechanobiol*. 2015;14(1):123-33. doi: 10.1007/s10237-014-0593-5
32. Sull A, Inceoglu S, August A, et al. Comparison of Barbed Sutures in Porcine Flexor Tenorrhaphy. *Hand* (N Y). 2016;11(4):475-478. doi: 10.1177/1558944715626928
33. Wong YR, Tay SC. A Biomechanical Study of a Novel Asymmetric 6-Strand Flexor Tendon Repair Using Porcine Tendons. *Hand* (N Y). 2018;13(1):50-55. doi: 10.1177/1558944716685829

The article was submitted 19.10.2023; approved after reviewing 23.10.2023; accepted for publication 01.12.2023.

Information about the authors:

Vladimir M. Malishevsky – orthopedic traumatologist, Head of Service, mvm9233@yandex.ru, https://orcid.org/0000-0002-8725-4155;

Roman V. Paskov – Doctor of Medical Sciences, Professor of Department, paskovroman@mail.ru, https://orcid.org/0000-0001-9225-614X;

Konstantin S. Sergeev – Doctor of Medical Sciences, Professor, Head of Department, sergeev.trauma@inbox.ru, https://orcid.org/0000-0002-6621-9449.

Contribution of the authors:

Malishevsky V.M. – research, data processing, writing the initial draft.

Paskov R.V. – methodology, validation, formal analysis.

Sergeev K.S. – conceptualization, reviewing and editing, supervision, project management

All authors confirm that their authorship meets the international ICMJE criteria (all authors made a significant contribution to the development of the concept, conduct of the study and preparation of the article, read and approved the final version before publication).

Clinical case
https://doi.org/10.18019/1028-4427-2024-30-1-107-113

Bilateral reconstruction of palmar soft tissues defects of the hands after thermal injury

E.M. Biktasheva, B.Sh. Minasov, M.M. Valeev✉, R.R. Yakupov, T.B. Minasov, T.R. Mavlyutov

Bashkir State Medical University, Ufa, Russian Federation

Corresponding author: Marat M. Valeev, valeevmm@rambler.ru

Abstract

Introduction Thermal injury to the palmar surface of the hand is usually complicated by flexion desmogenic contracture of the finger joints. This condition is more complicated with significant wound areas and depths of soft tissue destruction. Conventional surgical methods and soft tissue reconstructions may fail to provide full restoration of the hand function.

The objective was to present the optimal treatment strategy for patients with scar flexion contractures of the fingers after thermal injury to the palmar surface of both hands using a pediatric case report.

Material and methods A child aged 2 years and 4 months underwent surgical treatment to include excision of scars, skin grafting of both hands with a vascularized fasciocutaneous flap raised with the radial artery.

Result The patient could regain all types of hand grip on both sides 12 years after surgical treatment. Both hands were aesthetically acceptable.

Discussion Treatment of patients with thermal injury and substantial soft tissue damage is a complex disease process. Conservative treatment and surgical procedures using non-vascularized skin flaps are normally used for the condition. These approaches are associated with cicatricial and arthrogenic flexion contracture of the finger joints. The radical treatment includes thorough wound debridement and early flap coverage and wound closure using a flap with an axial-pattern blood supply, free flaps and reverse-flow flaps. The surgical approach helps to avoid flexion contracture of the fingers initiating early restoration of professional, social stereotypes and stereotypes in everyday life.

Conclusion The clinical observation has shown the possibility of one-stage organ-preserving surgical treatment using flaps with an axial blood supply.

Keywords: hand injury, thermal burn, cicatricial deformity, plastic surgery, microsurgery

For citation: Biktasheva EM, Minasov BSh, Valeev MM, Yakupov RR, Minasov TB, Mavlyutov TR. Bilateral reconstruction of palmar soft tissues defects of the hands after thermal injury. *Genij Ortopedii*. 2024;30(1):107-113. doi: 10.18019/1028-4427-2024-30-1-107-113

INTRODUCTION

Thermal injury to the soft tissues of the palmar surface of the hand can be associated with flexion desmogenic contracture of the fingers. Treatment would be dependent on the severity and depth of soft tissue damage, resources available for mobilization of healthy tissues and specific skin architecture on the palmar surface of the hand [1-7]. The case becomes more complicated with combined injury to the covering tissues and other anatomical formations of the hand (bone fractures, injury to tendons, blood vessels and nerves), which is associated with impairment of fine motor skills, negative psychological effects in an individual, depression, psychological and emotional changes in a child [8-15]. Reconstruction of soft tissue defects in the hand is essential and can be performed with modern surgical technologies [16-20].

MATERIAL AND METHODS

A boy of 2 years and 4 months grew up and developed uneventfully. At the age of 2 years, during a picnic, the child fell into the embers of a bonfire receiving burns of both hands. Dressings were performed after radical necrectomy in the burn department. The wounds healed by secondary intention. Physical examination revealed a hypertrophic scar on the palmar surface extending to the fingers of the left hand and flexion desmogenic contracture of the fingers. There were no active movements in the fingers. Passive movements of the fingers could not be produced being severely painful. All types of hand grip were impaired (Fig. 1a). Flexion desmogenic contracture of the 3rd and 4th fingers was noted in the right hand. Active extension movements in the fingers amounted to 90 degrees. The main types of hand grip were limited (Fig. 1b).

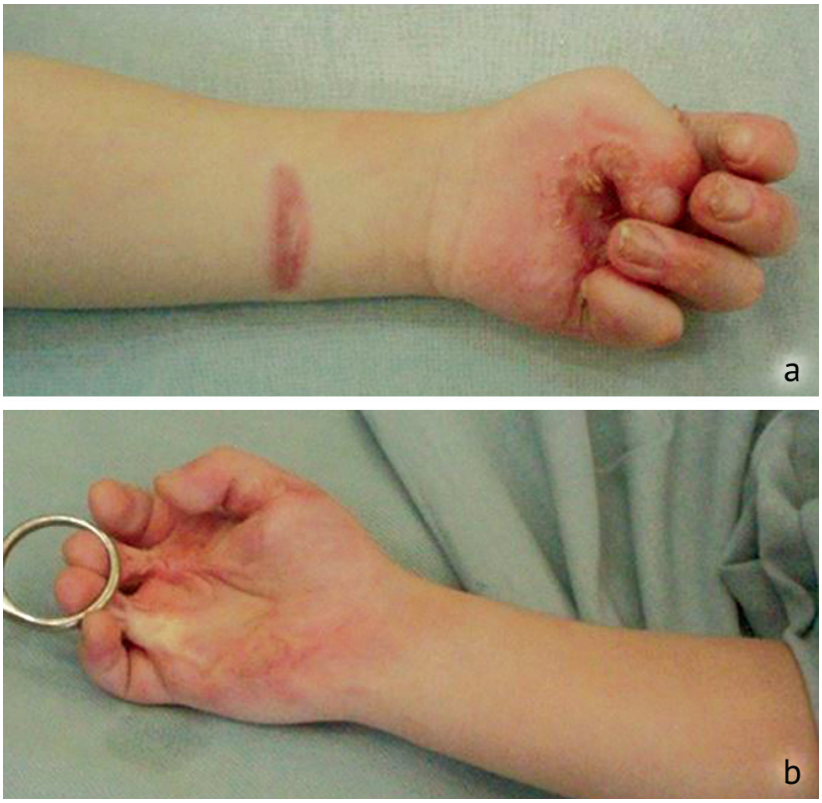

Fig. 1 Preoperative appearance of both hands: (a) left side; (b) right side

Stages of postoperative rehabilitation were discussed with the parents prior to surgery. Amputation of the 5th finger of the left hand was offered for functional reasons. Surgical intervention performed on December 12, 2007 under general anesthesia included excision of scars on the palmar surface,

amputation of the 5th finger, reconstructive surgery for the left hand using a vascularized fasciocutaneous flap.

Description of the operation: the patient was positioned supine with the left upper limb abducted. Scars on the palmar surface of the hand were excised after the limb was properly treated. A skin defect measuring 5.0 by 8.0 cm and covering the entire palmar surface, the main and middle phalanges was revealed. The fifth finger was amputated, and a skin flap from the dorsal surface of the finger was translocated to the palm defect (Fig. 2).

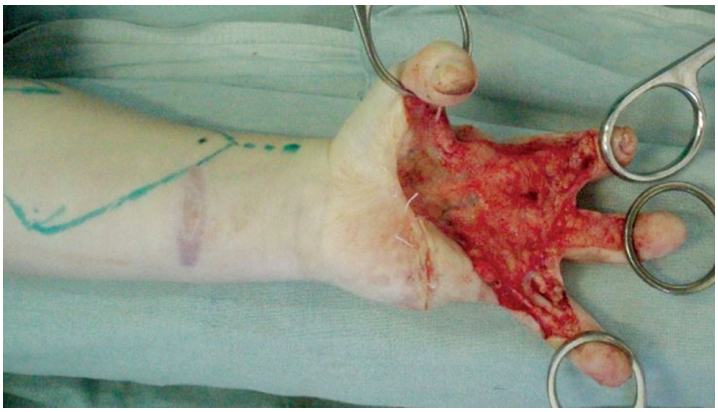

Fig. 2 Appearance of the left hand with scars excised and the fifth finger amputated

The radial artery and accompanying veins of the anatomical snuffbox were exposed in the proximal direction of the forearm and a fasciocutaneous flap of the appropriate size was provided to close the skin palmar defect (Fig. 3).

Hemostasis was provided during surgery. The flap was rotated on the vascular pedicle to the palmar defect and fixed with interrupted sutures. The donor wound was closed with a split skin flap. Aseptic dressings were applied. The operating time was 3 hours 20 minutes. Blood loss during surgery was 40 ml. The procedure and anesthesia were uneventful.

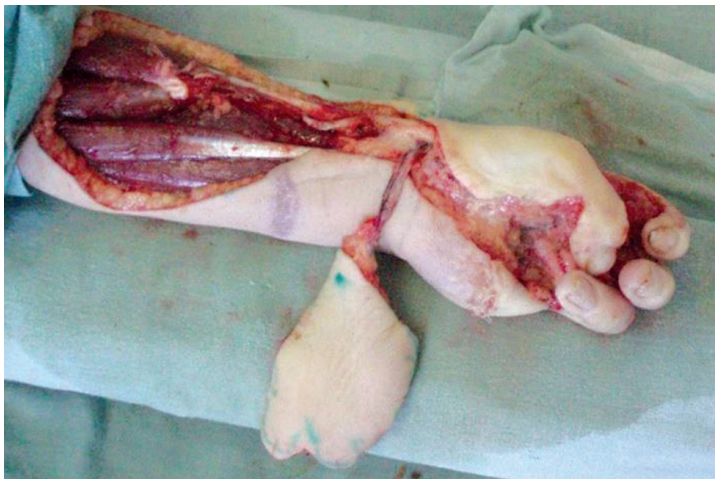

Fig. 3 The stage of isolating a fasciocutaneous flap on the distal vascular pedicle on the left forearm

Reconstructive surgery performed on the right hand four months later included anesthesia, treatment of the surgical field and the patient was positioned supine on the operating table. A skin defect formed on the palmar surface of the 3rd and 4th fingers after excision of scars on the right hand (Fig. 4).

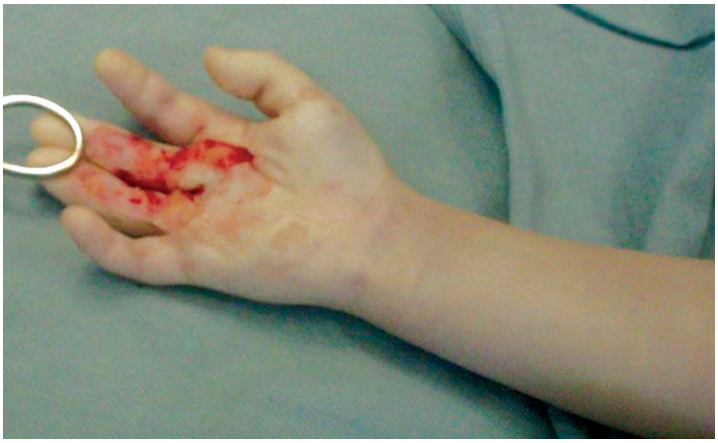

Fig. 4 Appearance of the right hand with scars excised

The distal part of the radial artery and accompanying veins were exposed on the right forearm and a simulated fasciocutaneous flap on a vascular pedicle of the appropriate size was isolated to close the skin defect on the palmar surface of the 3rd and 4th fingers (Fig. 5).

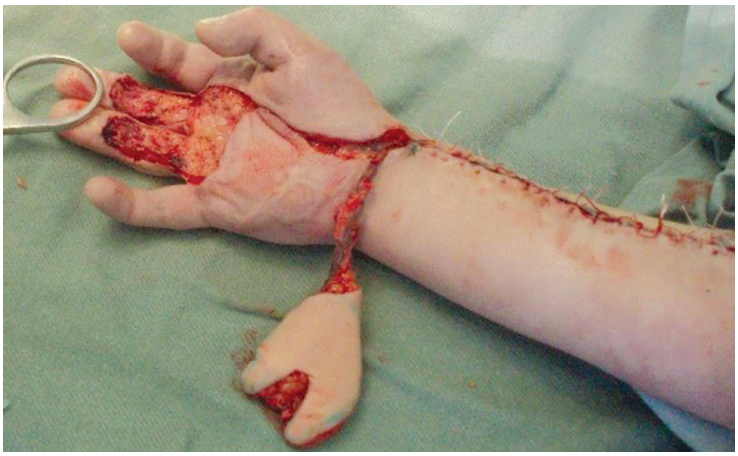

Fig. 5 The stage of isolating a fasciocutaneous flap on the distal vascular pedicle on the right forearm

Hemostasis was performed by electric coagulation and ligation of blood vessels during the operation. The autograft was moved on a vascular pedicle to the defect area on the palmar surface of the 3rd and 4th fingers and fixed with interrupted sutures. The donor wound was sutured with local tissues. Aseptic dressings applied. The operating time was 100 minutes. Blood loss was 30 ml. The operation and early postoperative period were uneventful.

RESULTS

The skin flaps have taken root. The wounds healed by primary intention. The patient completed a full course of rehabilitation. Two years later, local plastic surgery was required to form the interdigital space between the 3rd and 4th fingers. The boy is being followed up by the operating surgeon (Fig. 6).

Fig. 6 Long-term result of surgical treatment: (a, b) 3-year follow-up; (c, d) 12-year follow-up

DISCUSSION

Literature review showed that treatment strategy for patients with thermal trauma and significant soft tissue damage in hand still is controversial [13, 16]. Three treatment options are available for the patients. Conservative treatment is aimed at closure of the wound defect [2, 4, 5]. The patient was treated with dressings that resulted in the development of cicatricial flexion contracture of the fingers on both sides. Surgical treatment can be produced using non-vascularized skin autografts. These methods, already at the stage of preparation for plastic surgery, are associated with scars to be followed by arthrogenic flexion contracture of the joints of the fingers, apart from a long-term favorable functional outcome of such operations [6, 10, 18]. Other researchers support the radical treatment including thorough wound debridement and early flap coverage and wound closure using a flap with an axial-pattern blood supply, free flaps and reverse-flow flaps [7, 8, 9, 11, 12, 15, 16, 20]. The surgical approach we used in the case helps to avoid flexion contracture of the fingers initiating early restoration of professional, social stereotypes and stereotypes in everyday life.

CONCLUSION

Earlier surgical intervention is practical to include radical debridement with the demarcation line identified and closure of the resulting soft tissue defect using a flap with an axial-pattern blood supply to avoid the development of flexion desmogenic contracture of the joints of the fingers. The outcome of the case presented suggest that the treatment strategy can be optimal for patients with thermal injury and soft tissue injury to the palm of the hand. The reverse radial forearm fascial flap can be the method of choice for soft-tissue reconstruction of the hand with extensive scarry deformity of the palm and desmogenic flexion contracture of the fingers.

Conflict of interest *The authors declared no potential conflicts of interest with respect to the authorship and/or publication of this article.*

Financing *The authors received no financial support for the research and/or authorship of this article.*

Ethical review *TThe study was approved by the local ethics committee of the Bashkir State Medical University (Protocol No. 10 of October 23, 2022).*

Written ***informed consent*** *for the participation in the research project was obtained from the subject's parent/ legally acceptable representative.*

REFERENCES

1. Rodomanova LA, Medvedev GA. Plastic Replacement of Palmar Defects. *Traumatology and Orthopedics of Russia*. 2018;24(4):89-94. (In Russ.) doi: 10.21823/2311-2905-2018-24-4-89-94
2. Sidel'nikov VO, Fisun AYa, Cygan VN, et al. *Combat burn injuries*. Saint Petersburg: SpecLit; 2019:247. (In Russ.)
3. Bogdanov SB, Babichev RG. New approaches to the surgical treatment of burns of the dorsum of the hand. *Medical Bulletin of the South of Russia*. 2017;(2): 64-70. (In Russ.) doi: 10.21886/2219-8075-2017-8-2-64-70
4. Zhmajlik RR, Yakubovskij AP. Early necrectomy in the treatment of local burns. *Smolensk medical almanac*. 2016;(1):95-97. (In Russ.)
5. Perlovskaya VV, Stal'mahovich VN. Therapeutic tactics for cicatricial skin lesions in children. *Siberian Medical Journal* (Irkutsk). 2012;114(7):113-116. (In Russ.)
6. Rybchenok VV, Trusov AV, Tscherbakova MA, et al. Experience with a free full-sickness extended skin grafts in treatment of children witj skin extended defects. *Russian Journal of Pediatric Surgery, Anesthesia and Intensive Care*. 2017;7(4):58-63. (In Russ.) doi: 10.17816/psaic374
7. Minaev TR, Nizov ON, Hakimov AB, et al. Case from practice: secondary skin plastic after closing defects of the hand and fingers with a radial flap. *Bulletin of Emergency and Reconstructive Surgery*. (In Russ.) 2021;6(1):121-125.

8. Taraskin AF, Ostrovskij NV, Baranov NA, Egorova ES. The use of a reversed radiation flap to close a postoperative wound on the dorsum of the hand (clinical case). *Annals of Plastic, Reconstructive and Aesthetic Surgery*. (In Russ.) 2016;(1):119.
9. Sachkov A.V., Smirnov S.V., Migunov M.A. et al. Transposition of the pedicled radial forearm flap to reconstruct an electrical burn defect of the hand. *Transplantologiya. The Russian Journal of Transplantation*. (In Russ.) 2016;(3):37-40.
10. Aristov A.M., Bogdanov S.B., Kurinniy S.N., et al. Reconstructive surgical treatment of the total traumatic degloving of the hand and fingers (clinical case). *Issues of Reconstructive and Plastic Surgery*. 2020;23(4):66-74. (In Russ.) doi: 10.17223/1814147/75/08
11. Karim-Zade GD, Malikov MKh, Odinaev BA, et al. The outcomes of the forearm flap applications in the upper limb severe injuries reconstruction. *Avicenna Bulletin*. 2021;23(3):450-61. (In Russ.) doi: 10.25005/2074-0581-2021-23-3-450-461
12. Valeev MM, Minasov BSh, Zhukov AYu. *Social, home and professional reintegration of patients with soft tissue defects on the basis of functional and esthetic rehabilitation*. Ufa: Healthcare of Bashkortostan; 2005:401. (In Russ.)
13. Valeev MM. The use of autovital flaps for patients with soft tissue defects of the extremities. *Healthcare of Bashkortostan*. 2004;(6):67-80. (In Russ.)
14. Rodomanova L.A., Medvedev G.V. Plastic Replacement of Palmar Defects. *Traumatology and Orthopedics of Russia*. 2018;24(4):89-94. (In Russ.) doi: 10.21823/2311-2905-2018-24-4-89-94
15. Rodomanova LA, Medvedev GV, Cybul' ES, Afanas'ev AO, Zolotuhina IYu. Possibilities of using prelaminated tissue complexes in clinical practice in the treatment of patients with the consequences of thermal injuries of the upper limbs. *Annals of Plastic, Reconstructive and Aesthetic Surgery*. 2017;(1):126. (In Russ.)
16. Kutyanov DI, Rodomanova LA. Modern principles and trends of flap surgery on extremities. *Traumatology and Orthopedics of Russia*. 2015;(1):106-115. (In Russ.)
17. Çoban YK, Öcük Ö, Bekircan K. Wrapping degloved fingers with a distal-based radial forearm perforator flap: A repair method for multiple digital degloving injury. *Ulus Travma Acil Cerrahi Derg*. 2017;23(6):525-527. doi: 10.5505/tjtes.2017.57227
18. Kim MJ, Park BY. From mitten hand to five individual fingers: one-stage coverage using a deep inferior epigastric perforator free flap for an extensive degloving hand injury. *J Reconstr Microsurg*. 2018;3(1):e28-e31. doi: 10.1055/s-0038-1649490
19. Sen SK, Fitzgerald O'Connor E, Tare M. The free instep flap for palmar and digital resurfacing. *J Plast Reconstr Aesthet Surg*. 2015;68(9):1191-8. doi: 10.1016/j.bjps.2015.05.012
20. Valeev MM. *Medical rehabilitation of patients with consequences of injuries of the upper limbs based on surgical technologies*: Dokt. Dis. Ufa; 2006:279. Available at: https://www.dissercat.com/content/meditsinskaya-reabilitatsiya-bolnykh-s-posledstviyami-povrezhdenii-verkhnikh-konechnostei-na. Accessed 27 Jun, 2017.

The article was submitted 24.04.2023; approved after reviewing 05.06.2023; accepted for publication 01.12.2023.

Information about the authors:

Elina M. Biktasheva – Candidate of Medical Sciences, assistant, dr.elinabiktasheva@yandex.ru, https://orcid.org/0000-0001-6056-8819;

Bulat Sh. Minasov – Doctor of Medical Sciences, Professor, Head of the Department, B.minasov@ya.ru, https://orcid.org/0000-0002-1733-9823;

Marat M. Valeev – Doctor of Medical Sciences, Professor, Professor of the Department, valeevmm@rambler.ru, https://orcid.org/0000-0002-64-38-8820;

Rasul R. Yakupov – Doctor of Medical Sciences, Professor, Professor of the Department, rasulr@mail.ru, https://orcid.org/0000-0001-7650-1926;

Timur B. Minasov – Doctor of Medical Sciences, Professor, Professor of the Department, m004@yandex.ru, https://orcid.org/0000-0003-1915-3830;

Tagir R. Mavlyutov – Doctor of Medical Sciences, Assistant Professor, mavlutovtagir@mail.ru, https://orcid.org/0000-0002-5398-9356.

Contribution of the authors:

Biktasheva E.M., Minasov B.Sh., Valeev M.M. – conceptualization; methodology; validation; formal analysis; conducting research; data processing; preparation and writing of the initial version of the article; scientific editing; preparing work for publication; control; project management.

Yakupov R.R., Minasov T.B., Mavlyutov T.R. – formal analysis; conducting research; data processing; scientific editing; preparing work for publication.

Review article
https://doi.org/10.18019/1028-4427-2024-30-1-114-123

Current state and perspectives on the use of zirconium ceramic implants in traumatology and orthopaedics

E.A. Volokitina[1,2]✉, I.P. Antropova[1,2], K.A. Timofeev[1,2], R.A. Trufanenko[1,2]

[1] Ural Medical University, Ekaterinburg, Russian Federation
[2] Institute of High Temperature Electrochemistry of the Ural Branch of the Russian Academy of Sciences, Ekaterinburg, Russian Federation

Corresponding author: Elena A. Volokitina, volokitina_elena@rambler.ru

Abstract

Background Ceramic materials are currently in wide demand in various fields of medicine. Zirconium ceramics demonstrate exceptional mechanical properties and biocompatibility and do not cause cytotoxic effects or allergic reactions in surrounding tissues.

The objective was to present an analysis of current literature data on the use of zirconium ceramics as a bone replacement material in traumatology and orthopaedics.

Materials and methods The search for publications was conducted using the databases of Scopus, PubMed and the electronic scientific library eLIBRARY in the Russian and English languages using the keywords: bioceramics, bone, bone defect, zirconate, zirconium ceramics, bone tissue engineering, implant, scaffold, augment, biointegration, bioactivity. Depth of search for scientific papers was from 2000 to 2023.

Results and discussion Zirconium dioxide is the main ceramic bioinert material. The study presents the characteristics of ZrO_2 as a bone replacement material and its comparison with titanium implants. Data are presented on various strategies for improving zirconium bioceramics: improving the surface of the material by physical and chemical methods, obtaining volumetric porosity, including using additive technologies, creating composite materials, and developing bioactive coatings. New methods of creating zirconium ceramics compatible with living tissues containing bioactive ions that promote both osseointegration and bone tissue regeneration have been actively studied.

Conclusions Zirconium dioxide ceramics appear to be a promising alternative to titanium implants in terms of mechanical strength, biological functionality, chemical stability, osseointegration, and antibacterial properties. Future experimental and clinical studies will further improve zirconium ceramics.

Keywords: bioceramics, zirconate, bone defect, implant, biointegration

For citation: Volokitina EA, Antropova IP, Timofeev KA, Trufanenko RA. Current state and perspectives on the use of zirconium ceramic implants in traumatology and orthopaedics. *Genij Ortopedii*. 2024;30(1):114-123. doi: 10.18019/1028-4427-2024-30-1-114-123

INTRODUCTION

Annually, about 130 million fractures happen worldwide. A significant part of them develops bone defects that must be filled in [1]. Moreover, the problem of bone defect compensation exists in degenerative diseases of the musculoskeletal system, osteomyelitis, and oncological diseases that require surgical intervention using bone grafts [2]. Patients of older age groups, patients with complex comminuted fractures, patients with metabolic disorders are at risk for fracture nonunion due to impaired bone tissue repair [3]. Unfortunately, there are currently no complete solutions to this problem, since the ideal one would be to achieve a biocompatible scaffold similar to natural bone. One of the most important properties that a graft must have is osteoconduction, that is, the ability to function as a scaffold for mesenchymal stem cells (MSCs), osteoblasts and osteoclasts [4]. This property of the material is directly related to the quality of the surface, which should resemble the structure of cancellous bone [5]. Another required feature is osteoinduction or the ability of the graft to stimulate bone formation, ensure the recruitment, proliferation and subsequent differentiation of MSCs into chondro- and osteoblasts under the influence of growth factors, cytokines, and adhesion molecules. It is also worth noting that an important function of growth factors is induction of angiogenesis for the delivery of nutrient substrates to the developing bone tissue [6]. Osseointegration is a direct contact of the implant with the bone through newly formed bone tissue that should exclude the growth of fibrous tissue at the bone-implant interface. One of the determining factors for successful osseointegration is the geometry and size of pores on the surface and inside the structure of the material [7, 8]. Moreover, the osteosubstitution material must meet the mechanical characteristics of the bone, requirements of biocompatibility, strength, infectious safety and availability.

Autografting is considered the "gold standard" in the clinical practice due to a number of advantages: good osteoconduction, osteoinduction and stimulation of osteogenesis. However, we must not forget about possible complications both at the site of donor bone collection and at the site of bone defect [9, 10]. The use of allografts also has significant shortcomings: possible immune rejection, transmission of infection, and a high failure rate. The use of xenografts is limited by the presence of immunogenic interspecies barriers [11]. The shortage of natural sources due to growing demand for implants stimulated the search and development of artificial materials for osteoplasty.

The effectiveness of the interaction between the recipient bone bed and the implant depends not only on the regenerative potential of the bone tissue and the area of interaction between the implant and the bone in the defect area, but also on the compatibility of the osteosubstitution material with the body tissue in terms of physicochemical, biological and mechanical properties. Artificial materials that are developed specifically for medical purposes are biocompatible and are classified as biomaterials. Among such materials, a special place is occupied by bioceramics, which has a unique combination of properties versus metals or polymers. The biocompatibility of bioceramics ranges from oxides, which are inert in the body, to resorbable materials, which eventually decompose in the body. High internal strength, wear resistance, and low coefficient of friction allow the use of bioceramics under high loads. The compatibility of bioceramics with human tissue reduces the risk of adverse reactions or inflammation. Moreover, some types of bioceramics, in particular hydroxyapatite or bioactive glasses, exhibit properties that promote tissue regeneration and osseointegration. Bioceramics have the inherent versatility: the material can be molded into precise shapes and its composition can be tailored to improve specific properties. All these features make bioceramics an adequate material for solving a wide range of medical problems [12-15]. Research on ceramic biomaterials has been developing rapidly, finding new areas of application in medicine,

in particular in traumatology and orthopaedics. Moreover, the analysis of the contemporary market of bioceramics showed that there has been a steady tendency towards the change of other types of oxide ceramics by zirconium ceramics [16].

Purpose Based on literature data, determine the prospects for using zirconium ceramics as a bone substitution material in traumatology and orthopaedics

MATERIALS AND METHODS

The search for publications on the topic was carried out in the PubMed databases and the electronic scientific library eLIBRARY in two languages: Russian and English. Key words used were: bioceramics, bone, bone defect, zirconate, zirconium ceramics, bone tissue engineering, implant, scaffold, augment, biointegration, bioactivity. Depth of the search for scientific papers was from 2000 throughout 2023. The literature search using keywords and abstracts found 592 sources. Of these, 79 full-text articles were selected according to the specified criteria. The choice was determined by the fundamental nature, evidence, and relevance of the work on the use of zirconium ceramics in traumatology and orthopedics.

RESULTS AND DISCUSSION

The term "ceramics" comes from the Greek word κεραμικὸ (keramikò) which means "fired material". Ceramics include inorganic materials consisting of metallic and non-metallic components chemically bonded to each other. The properties of materials depend significantly on their microstructure [17]. The main characteristics of ceramic materials are high strength, resistance to corrosion and wear, and good compression resistance [12, 13]. However, fragility and relatively low tensile and bending strength are a serious problem for the use of ceramics as implants [18, 19]. For biomedical applications, such materials can be used as all-ceramic components, or they can contain particles of other materials [20]. Bioceramic scaffolds play a central role in the engineering of bone tissue substitutes as a support and modulator for cell attachment, proliferation and differentiation, and as a carrier of osteogenic substances. It is important to note that the morphology, microstructure, porosity, mechanical and physicochemical characteristics of the scaffold should be as close as possible to natural bone [21].

Depending on their activity in interacting with the human body, ceramic biomaterials can be divided into three groups: 1) inert; 2) having low or medium surface activity; 3) bioresorbable (adsorbable). The choice of the type of ceramic material (inert, bioactive or bioresorbable) in each specific case depends on what functions the implant performs.

Inert bioceramics do not promote connection with living tissues; connective tissue of varying thickness develops around the implant that holds the implant and, at the same time, isolates it from neighboring tissues. Possessing high biocompatibility and mechanical strength, such bioceramics are usually used for permanent implants. Materials with low and medium activity, in addition to their ability of binding to specific proteins, can also release ions, thereby facilitating the integration of implants into living tissues. Bioresorbable ceramics should remain in the target site until bone regeneration occurs [14, 22].

Inert bioceramics The first generation of biomaterials was developed in the 1960s. Those materials were bioinert, showed minimal interaction with surrounding tissues, and did not stimulate bone formation [23]. The most important bioceramic inert materials are zirconium dioxide (ZrO_2) and alumina (Al_2O_3). Their properties such as reduced wear rates and good long-term biocompatibility make these materials suitable for orthopaedic applications. The use of ceramic materials, compared to implants made of metal alloys, provides a lower rate of component wear and leads to a decrease in the release of metal ions. [24].

Al_2O_3 was the first oxide used in orthopaedics due to its biological safety, strength, and reduction in the rate of aseptic osteolysis in comparison with metal implants [25]. Polycrystalline aluminum oxide has a relatively low cost, due to which it is widely used in traumatology and orthopaedics as a component in friction pairs of endoprostheses [26].

Zirconium dioxide has more than double strength compared to aluminum oxide, due to which this material has been actively used in the production of implants [27]. Zirconium dioxide occurs in three main crystal phase structures: cubic, tetragonal and monoclinic. Microcracks in the crystalline-network structure of zirconium dioxide are self-limiting if the transition from tetragonal to monoclinic crystal structure is controlled [28]. To stabilize the structure of zirconium dioxide, various oxides are added to it, in particular, yttrium oxide [29]. Zirconium dioxide bioceramics, in particular yttria-stabilized tetragonal zirconia polycrystalline (Y-TZP) ceramics, exhibit exceptional mechanical properties and biocompatibility, and do not cause cytotoxic effects or allergic reactions in surrounding tissues. Although this biomaterial was claimed to be inert, the adsorption of blood proteins, platelets and the migration of osteogenic cells suggest biological interaction with zirconia dioxide-based surfaces [30, 31].

Ceramic implants appear to be a promising alternative to titanium implants in terms of mechanical strength, biological functionality, chemical stability and osseointegration. Scarano et al. examined bone response to zirconia implants in an experimental study in rabbits. It showed that newly formed bone was actively formed in close contact with the surfaces of zirconium ceramics, the bone-to-implant contact rate was 68.4 ± 2.4 %, mature bone and actively secreting osteoblasts were revealed in most parts of the implant, and no inflammation was detected [34]. Comparative studies *in vitro* and *in vivo* showed that zirconia implants have similar results with titanium-based implants in terms of osseointegration indices [32-35].

An advantage of zirconium dioxide, in comparison with titanium, was also found in terms of antibacterial properties. Scarano et al. showed that the percentage of the surface covered with bacteria on zirconium oxide disks was significantly lower than on similar titanium disks [36]. Roehling et al. compared experimental disks made of titanium and zirconium dioxide with three types of surface topography: after mechanical or sandblasting and acid etching. It was shown that zirconium dioxide has significantly lower bacterial adhesion compared to titanium [37].

The attractiveness of ZrO_2-based ceramics for medical use is due to its exceptional chemical inertness, high strength and good compatibility with the human body, but its inertness limits its use as a bone substitute material for filling bone tissue defects. Various strategies have been used to improve the integration of zirconia implants into bone tissue.

The ***surface properties of the implant*** are of great importance for the formation of peri-implant bone tissue. Various methods are used to improve the surface of zirconia. Airborne particle abrasion, or sandblasting of zirconia surfaces, significantly improves osteogenesis and osseointegration around implants compared to treated titanium surfaces [33, 38, 39]. To improve the surface properties of zirconium dioxide, chemical treatment (acid etching) is also used [40, 41]. However, the strength of zirconium dioxide can decrease in mechanical processing due to abrasion by particles and the formation of deep microcracks while thermal and acid treatments can reduce the bending strength of zirconium under the conditions of low-temperature degradation. Further research is expected to develop parameters for mechanical and chemical surface treatment of the material that do not affect its mechanical properties.

Ultraviolet radiation can induce electron excitation, increasing the surface energy of zirconium dioxide, which leads to a decrease in the contact angle of its surface with water from 51 to 9.4° and, accordingly, increases wettability [42]. This, in turn, makes the surface of the material biologically

more attractive for protein adsorption, osteoblast proliferation and osseointegration. Treatment of the zirconia surface with ultraviolet radiation promotes the attachment, proliferation and differentiation of osteoblasts without affecting the mechanical properties of the material [43].

Laser radiation may also be a promising way to improve osseointegration of zirconia. Laser modification improves the wettability of the material and increases the adhesion of osteoblasts compared to untreated samples [44].

The ***development of methods for obtaining porosity*** in ceramics enables to produce materials with improved osseointegration properties. Based on their structure, the following types of ceramics are distinguished: fine (less than 5 % of pores), coarse (from 5 to 30 % of pores), highly porous (more than 30 % of pores). The necessary porosity characteristics – the number of pores and their morphology – are achieved by special technological methods, including the introduction of special pore-forming additives. In this case, the geometry of pores in ceramics depends on the configuration of pore-forming particles [45]. Kalinina et al. developed highly porous bioceramics based on stabilized ZrO_2. A synthesized ceramic implant material with an open porosity of 55 % and a pore size of 40-800 nm was placed into the body of laboratory animals. Vascular ingrowth into the pore space of ceramics was demonstrated. The authors suggest that porous ceramics based on zirconium dioxide can be used in the production of implants for orthopaedics and traumatology [46]. Porous zirconium ceramics have been especially actively developed for the production of small-sized implants [45].

Work is underway to create domestic ceramic materials based on zirconium dioxide from nanostructured powders [47]. A highly dispersed powder (9-10 nm) was synthesized based on a tetragonal solid solution of partially stabilized zirconium dioxide (t-ZrO_2). Based on this powder, nanocrystalline ceramics (grain size 60-70 nm) with high physicochemical and mechanical characteristics were obtained. *In vivo* studies showed the absence of a toxic effect of the ceramic implant on the tissues surrounding the implant and on laboratory animals. The research results allow us to state that the resulting nano-sized bioceramics can be used for medical purposes [48]. Buyakova et al. presented the results of studies on the structure and mechanical behavior of porous ceramics produced from nanocrystalline powder of partially stabilized zirconium dioxide intended for use in joint replacement. Ceramics with porosity capable of providing a biomechanical connection at the bone tissue–implant interface were obtained; it opens up new possibilities in the use of highly porous ceramics for bone tissue substitution [49].

Additive technologies are being actively developed in relation to ceramic materials. Their use would provide personalized components from porous bioceramics to fill in large bone defects [50-52].

Zirconium dioxide-based materials have been used in orthopedics since the 1980s, mainly due to their excellent mechanical properties resulting from phase transformations. However, the material has been found to undergo hydrothermal aging (low temperature degradation), whereby its mechanical properties gradually deteriorate over time in a humid environment, what can lead to increased surface roughness and microcracking, with slow crack growth that ultimately causes catastrophic destruction [53, 54]. Material degradation is of particular importance for medical implants [55]. Fully stabilized zirconium dioxide is not subject to hydrothermal aging, but its mechanical properties are not high enough.

Creation of composite materials has largely solved the problem of low-temperature degradation of aluminum zirconium (ATZ). Ceramic composites made from hardened zirconium oxide are universal 56]. Compounds of alumina and zirconia have received considerable attention, particularly hardened materials known for their exceptional mechanical properties, including high strength, fracture viscosity, elasticity, hardness and wear resistance, and resistance to hydrothermal aging.

[57]. In this case, not only the composition of the material is important, but also the method of its synthesis. It has been shown, varying resistance of the resulting ceramic materials to degradation is observed by different temperatures [58]. ATZ ceramics hold significant promise for biomedical applications due to their biocompatibility and remarkable ability to withstand mechanical stress. Implants made from such ceramics have excellent wear resistance and strength, ensuring long survival in the human body and reducing the risk of adverse reactions, making them the preferred choice for the restoration and replacement of damaged bone tissue and joints, in particular in total hip and knee arthroplasty [31, 58-61], although Pluschev et al. indicated that if there is even minimal doubt about the stability of the head in the acetabulum, the use of ceramic components should be viewed critically [62].

Development of bioactive coatings on the surface of zirconia has been undertaken to improve the biocompatibility, antibacterial potential and biological activity of the material. Various coating materials with good biological properties have been described in the literature. Hydroxyapatite has mineral composition similar to bone, exhibits biologically active properties, enhancing osseointegration. Hydroxyapatite coatings enhance the osteogenesis capacity of porous zirconia scaffolds [63]. Moreover, an increase in the hydroxyapatite content led to a decrease in the mechanical and chemical stability of the material with a simultaneous increase in biological activity [64]. Research is being conducted to obtain and evaluate the quality of bioceramic coatings from a composite material based on the co-precipitation of hydroxyapatite and hydrated zirconium dioxide [65]. Calcium phosphate is also bioactive, but coatings made from this material exhibit low stability and provide weak adhesion to the substrate. To overcome these shortcomings, tricalcium phosphate-reinforced hydroxyapatite coatings have been studied [66]. A study conducted by Silva et al. showed that modification of the surface of scaffolds made of aluminum-zirconium porous ceramics with calcium phosphate and strontium included in its structure might yield scaffolds with high porosity, three-dimensional structure and preferential adhesion and maturation of osteoblastic cells, which are necessary to stimulate bone tissue regeneration in vivo [67]. Coating with functionalized carbon nanotubes, which enhance the roughness, wettability and cell adhesion of zirconia, contributed to the osseointegrative properties of the material [68]. Attempts have been made to produce bioactive glass coatings on zirconia substrates, but with limited success. These coatings have poor adhesion to the substrate, as a result of which they are often subject to delamination and destruction. To overcome these problems, a strategy based on a functionally graded glass/zirconia system has been proposed [69]. To improve the mechanical characteristics and wear resistance of zirconia implants, the use of graphene as a coating has been studied [70].

Creation of bioactive ceramics compatible with living tissues has been currently developed. By synthesizing biomaterials with appropriate biophysical and biochemical characteristics, it is possible to modulate the cellular response of peri-implant tissues. This property of bioactive materials, such as the release of bioactive ions (Ca, Mg, Sr, Zn, Cr, Ag, La, etc.) can be used to induce phenotypic changes in cells or modulate the immune microenvironment to control tissue healing and regeneration [71]. It has been proven that the biophysical characteristics of biomaterials, such as topography, charge, size, electrostatic interactions and stiffness, can be modulated by the addition of inorganic micro- and nanoparticles [72]. Current research shows that inert ZrO_2 can be converted into a bioactive system comprising various molecules that can mimic the structural and compositional properties of bone tissue at the macro-, micro- and nanoscale, improving implant osseointegration [73]. Considerable efforts have been made by researchers to modify zirconia in terms of morphology and improve biological activity for better cell attachment, proliferation and differentiation during the formation of peri-implant bone [74, 75]. Pardun et al. added magnesium oxide or magnesium fluoride to yttrium-stabilized zirconium dioxide. The presence of Mg^{2+} ions

improved the proliferation and differentiation of osteoblast cells [75]. Mushahary et al. also showed that the introduction of magnesium promotes the proliferation of osteoblasts, increasing the biological activity of zirconium dioxide [76].

It is known that the crystal lattice of lanthanum zirconate ($La_2Zr_2O_7$) is tolerant to various types of substitutions, in particular, calcium and strontium ions. During the process of osseointegration, the release of lanthanum, zirconium, calcium, and strontium cations is possible. The interaction of free cations with bone tissue can have a beneficial effect on the process of osseointegration and promote cell adhesion and proliferation on the surface of zirconium implants. An in vivo experimental study of the newly synthesized material $La_{1.95}Ca_{0.05}Zr_2O_7$ as an implant showed that fully featured bone tissue is formed in the peri-implant area, the architectonics of which can effectively resist the action of mechanical stresses, which may indicate the compatibility of the material and bone tissue in terms of physicochemical and structural characteristics. A new material based on lanthanum zirconate seems promising for use in traumatology and orthopaedics [77]. The synthesis and properties of complex oxides based on lanthanum zirconate were studied ($La_2Zr_2O_7$, $La_{0.9}Ca_{0.1}Zr_2O_{6.95}$ and $La_{0.9}Sr_{0.1}Zr_2O_{6.95}$). It has been proven that the method of materials synthesis has an impact on the density and porosity of the samples. Determination of the cytocompatibility of ceramics based on undoped and doped lanthanum zirconate showed that during the interaction of human fibroblasts with the studied ceramic materials, cell viability changes within acceptable values and is sufficient to maintain their recovery potential. However, additional research is needed to optimize the integration of implants made of this material into bone tissue [78, 79].

CONCLUSION

Ceramic materials based on zirconium dioxide with exceptional mechanical properties and biocompatibility, which do not cause cytotoxic effects and allergic reactions in surrounding tissues, feature perspectives for being used as bone substitute materials in traumatology and orthopaedics. Such materials appear to be a promising alternative to titanium implants in terms of mechanical strength, biological functionality, chemical stability, osseointegration, and antibacterial properties.

Various strategies have been used in order to improve the integration of zirconia implants into bone tissue: improving the surface of the material using physical and chemical methods, obtaining volumetric porosity, including using additive technologies; various composite materials and bioactive coatings have been also developed. New methods of creating zirconium ceramics compatible with living tissues containing bioactive ions that promote both osseointegration and bone tissue regeneration have been actively studied.

Further in vitro and in vivo studies and long-term clinical trials should evaluate ceramic implants in terms of stability, risks of inflammation, infection and mechanical complications. It will provide a clearer picture of recommendations for improving zirconia ceramics.

Conflict of interests *The authors declare that there are no obvious or potential conflicts of interest related to the publication of this study.*

Source of funding *The study was supported by the grant of the Russian Science Foundation No. 22-25-20037, https://rscf.ru/project/22-25-20037*

Ethical statement *Approval of the institutional ethics committee is not required for this type of study.*

Informed consent *Not required.*

REFERENCES

1. Schade AT, Mbowuwa F, Chidothi P, et al. Epidemiology of fractures and their treatment in Malawi: Results of a multicentre prospective registry study to guide orthopaedic care planning. *PLoS One*. 2021;16(8):e0255052. doi: 10.1371/journal.pone.0255052

2. Laurencin C, Khan Y, El-Amin SF. Bone graft substitutes. Expert Rev Med Devices. 2006;3(1):49-57. doi: 10.1586/17434440.3.1.49
3. Yalochkina TO, Belaya ZhE. Fragility fractures and bone remodeling in type 2 diabetes mellitus. *Obesity and metabolism*. 2017;14(3):11-18. (In Russ.) doi: 10.14341/OMET2017311-18
4. Khan SN, Cammisa FP Jr, Sandhu HS, et al. The biology of bone grafting. *J Am Acad Orthop Surg*. 2005;13(1):77-86.
5. McKee MD. Management of segmental bony defects: the role of osteoconductive orthobiologics. *J Am Acad Orthop Surg*. 2006;14(10 Spec No.):S163-167. doi: 10.5435/00124635-200600001-00036
6. Amini AR, Laurencin CT, Nukavarapu SP. Bone tissue engineering: recent advances and challenges. *Crit Rev Biomed Eng*. 2012;40(5):363-408. doi: 10.1615/critrevbiomedeng.v40.i5.10
7. Taniguchi N, Fujibayashi S, Takemoto M, et al. Effect of pore size on bone ingrowth into porous titanium implants fabricated by additive manufacturing: An in vivo experiment. *Mater Sci Eng C Mater Biol Appl*. 2016;59:690-701. doi: 10.1016/j.msec.2015.10.069
8. Chauhan A, Bhatt AD. A review on design of scaffold for osteoinduction: Toward the unification of independent design variables. *Biomech Model Mechanobiol*. 2023;22(1):1-21. doi: 10.1007/s10237-022-01635-9
9. Gilev MV, Zaitsev D., Izmodenova MY, et al. Comparative characteristic of the methods of certification of deformed microstructure of trabecular bone tissue. *Russian Journal of Biomechanics*. 2019;23(2):242-250. (In Russ.) doi: 10.15593/RZhBiomeh/2019.2.06
10. Parikh SN. Bone graft substitutes: past, present, future. *J Postgrad Med*. 2002;48(2):142-148.
11. Muscolo DL, Ayerza MA, Aponte-Tinao LA. Massive allograft use in orthopedic oncology. *Orthop Clin North Am*. 2006;37(1):65-74. doi: 10.1016/j.ocl.2005.08.003
12. Yi S, Xu L, Gu X. Scaffolds for peripheral nerve repair and reconstruction. *Exp Neurol*. 2019;319:112761. doi: 10.1016/j.expneurol.2018.05.016
13. Kaur G, Kumar V, Baino F, et al. Mechanical properties of bioactive glasses, ceramics, glass-ceramics and composites: State-of-the-art review and future challenges. *Mater Sci Eng C Mater Biol Appl*. 2019;104:109895. doi: 10.1016/j.msec.2019.109895
14. Vaiani L, Boccaccio A, Uva AE, et al. Ceramic Materials for Biomedical Applications: An Overview on Properties and Fabrication Processes. *J Funct Biomater*. 2023;14(3):146. doi: 10.3390/jfb14030146
15. Jitaru S, Hodisan I, Timis L, et al. The use of bioceramics in endodontics - literature review. *Clujul Med*. 2016;89(4):470-473. doi: 10.15386/cjmed-612
16. Kulbakin DE, Choynzonov EL, Buyakova SP, et al. Selection of reconstructive material for the restoration of the maxillofacial region bone defects in oncological practice. *Head and neck*. 2018;6(4):64-69. (In Russ.)
17. Hench LL, Thompson I. Twenty-first century challenges for biomaterials. *J R Soc Interface*. 2010;7 Suppl 4(Suppl 4):S379-S391. doi: 10.1098/rsif.2010.0151.focus
18. de Ruiter A, Dik E, van Es R, et al. Micro-structured calcium phosphate ceramic for donor site repair after harvesting chin bone for grafting alveolar clefts in children. *J Craniomaxillofac Surg*. 2014;42(5):460-468. doi: 10.1016/j.jcms.2013.05.042
19. Whitehouse MR, Dacombe PJ, Webb JC, Blom AW. Impaction grafting of the acetabulum with ceramic bone graft substitute: high survivorship in 43 patients with a mean follow-up period of 4 years. *Acta Orthop*. 2013;84(4):371-376. doi: 10.3109/17453674.2013.824801
20. Warreth A, Elkareimi Y. All-ceramic restorations: A review of the literature. *Saudi Dent J*. 2020;32(8):365-372. doi: 10.1016/j.sdentj.2020.05.004
21. Collins MN, Ren G, Young K, et al, Oliveira J.M. Scaffold fabrication technologies and structure/function properties in bone tissue engineering. *Adv Func Mater*. 2021;31(21):2010609. doi: 10.1002/adfm.202010609
22. Yanyan S, Guangxin W, Guoqing S, et al. Effects of amino acids on conversion of calcium carbonate to hydroxyapatite. *RSC Adv*. 2020;10(61):37005-37013. doi: 10.1039/d0ra07636h
23. Yu X, Tang X, Gohil SV, Laurencin CT. Biomaterials for Bone Regenerative Engineering. *Adv Healthc Mater*. 2015;4(9):1268-85. doi: 10.1002/adhm.201400760
24. De Aza AH, Chevalier J, Fantozzi G, et al. Crack growth resistance of alumina, zirconia and zirconia toughened alumina ceramics for joint prostheses. *Biomaterials*. 2002;23(3):937-45. doi: 10.1016/s0142-9612(01)00206-x
25. Chevalier J. What future for zirconia as a biomaterial? *Biomaterials*. 2006;27(4):535-43. doi: 10.1016/j.biomaterials.2005.07.034
26. Abyzov A.M. Aluminum oxide and alumina ceramics (Review). Part 1. Properties of Al2O3 and industrial production of dispersed Al2O3. *New refractories*. 2019;(1):16-23. (In Russ.) doi: 10.17073/1683-4518-2019-1-16-23
27. Vult von Steyern P. All-ceramic fixed partial dentures. Studies on aluminum oxide- and zirconium dioxide-based ceramic systems. *Swed Dent J Suppl*. 2005;(173):1-69.
28. Hernigou P, Bahrami T. Zirconia and alumina ceramics in comparison with stainless-steel heads. Polyethylene wear after a minimum ten-year follow-up. *J Bone Joint Surg Br*. 2003;85(4):504-509. doi: 10.1302/0301-620x.85b4.13397
29. Denry I, Abdelaal M, Dawson DV, et al. Effect of crystalline phase assemblage on reliability of 3Y-TZP. *J Prosthet Dent*. 2021;126(2):238-247. doi: 10.1016/j.prosdent.2020.05.023
30. Yin L, Nakanishi Y, Alao AR, et al. A review of engineered zirconia surfaces in biomedical applications. *Procedia CIRP*. 2017;65:284-290. doi: 10.1016/j.procir.2017.04.057
31. Ulyanov YuA, Zaripova EM, Mingazova EN. On the issue of biocompatibility of ceramic implants in the provision of orthopedic care. *Healthcare manager*. 2023;(9):18-22. (In Russ.) doi: 10.21045/1811-0185-2023-9-18-22
32. Depprich R, Zipprich H, Ommerborn M, et al. Osseointegration of zirconia implants compared with titanium: an in vivo study. *Head Face Med*. 2008;4:30. doi: 10.1186/1746-160X-4-30

33. Gahlert M, Roehling S, Sprecher CM, et al. In vivo performance of zirconia and titanium implants: a histomorphometric study in mini pig maxillae. *Clin Oral Implants Res*. 2012;23(3):281-286. doi: 10.1111/j.1600-0501.2011.02157.x
34. Han JM, Hong G, Lin H, et al. Biomechanical and histological evaluation of the osseointegration capacity of two types of zirconia implant. *Int J Nanomedicine*. 2016;11:6507-6516. doi: 10.2147/IJN.S119519
35. Kohal RJ, Weng D, Bächle M, Strub JR. Loaded custom-made zirconia and titanium implants show similar osseointegration: an animal experiment. *J Periodontol*. 2004;75(9):1262-8. doi: 10.1902/jop.2004.75.9.1262
36. Scarano A, Di Carlo F, Quaranta M, Piattelli A. Bone response to zirconia ceramic implants: an experimental study in rabbits. *J Oral Implantol*. 2003;29(1):8-12. doi: 10.1563/1548-1336(2003)029<0008:BRTZCI>2.3.CO;2
37. Roehling S, Astasov-Frauenhoffer M, Hauser-Gerspach I, et al. In Vitro Biofilm Formation on Titanium and Zirconia Implant Surfaces. *J Periodontol*. 2017;88(3):298-307. doi: 10.1902/jop.2016.160245
38. Gahlert M, Gudehus T, Eichhorn S, et al. Biomechanical and histomorphometric comparison between zirconia implants with varying surface textures and a titanium implant in the maxilla of miniature pigs. *Clin Oral Implants Res*. 2007;18(5):662-668. doi: 10.1111/j.1600-0501.2007.01401.x
39. Bacchelli B, Giavaresi G, Franchi M, et al. Influence of a zirconia sandblasting treated surface on peri-implant bone healing: An experimental study in sheep. *Acta Biomater*. 2009;5(6):2246-2257. doi: 10.1016/j.actbio.2009.01.024
40. Flamant Q, García Marro, Roa Rovira JJ, Anglada M. Hydrofluoric acid etching of dental zirconia. Part 1: etching mechanism and surface characterization. *J Eur Ceram Soc*. 2016;36(1):121-134. doi: 10.1016/j.jeurceramsoc.2015.09.021
41. Vu VT, Oh GJ, Yun KD, et al. Acid etching of glass-infiltrated zirconia and its biological response. *J Adv Prosthodont*. 2017;9(2):104-109. doi: 10.4047/jap.2017.9.2.104
42. Henningsen A, Smeets R, Heuberger R, et al. Changes in surface characteristics of titanium and zirconia after surface treatment with ultraviolet light or non-thermal plasma. *Eur J Oral Sci*. 2018;126(2):126-134. doi: 10.1111/eos.12400
43. Brezavšček M, Fawzy A, Bächle M, et al. The Effect of UV Treatment on the Osteoconductive Capacity of Zirconia-Based Materials. *Materials* (Basel). 2016;9(12):958. doi: 10.3390/ma9120958
44. Yang Y, Zhou J, Liu X, et al. Ultraviolet light-treated zirconia with different roughness affects function of human gingival fibroblasts in vitro: the potential surface modification developed from implant to abutment. *J Biomed Mater Res B Appl Biomater*. 2015;103(1):116-24. doi: 10.1002/jbm.b.33183
45. Kirilova IA, Sadovoy MA, Podorozhnaya VT, et al. Ceramic and osteoceramic implants: upcoming trends. *Russian Journal of Spine Surgery*. 2013;(4):052-062. (In Russ.) doi: 10.14531/ss2013.4.52-62
46. Kalinina MV, Kovalko NYu, Suslov DN, et al. Effect of highly porous bioceramics based on $ZrO_2 – Y_2O_3 – CeO_2$ system on the biological tissues of experimental animals. *J Perspektivnye Materialy*. 2020;(7):29-39. (In Russ.) doi: 10.30791/1028-978X-2020-7-29-39
47. Rogozhnikov A.G. Production methods and physical and mechanical tests domestic ceramic materials based on zirconium dioxide from nanostructured powders. *Ural Medical Journal*. 2015;(10):113-119. (In Russ.)
48. Kovalko NY, Kalinina MV, Arsentyev MY, et al. Effect of t-ZRO2-based ceramic samples on the condition of muscular and connecting tissues in experimental animals with intramuscular introduction. *Inorganic Materials: Applied Research*. 2019;(5):1109-1114. doi: 10.30791/1028-978X-2019-5-41-49
49. Buyakova SP, Khlusov IA, Kulkov SN. Porous zirconium-based ceramics for endoprothesis of bone tissue. *Physical mesomechanics J*. 2004;7(Spec 2):127-130. doi: 10.24411/1683-805X-2004-00097
50. Li T, Chang J, Zhu Y, Wu C. 3D Printing of Bioinspired Biomaterials for Tissue Regeneration. *Adv Healthc Mater*. 2020:e2000208. doi: 10.1002/adhm.202000208
51. Zafar MJ, Zhu D, Zhang Z. 3D Printing of Bioceramics for Bone Tissue Engineering. *Materials* (Basel). 2019;12(20):3361. doi: 10.3390/ma12203361
52. Ma H, Feng C, Chang J, Wu C. 3D-printed bioceramic scaffolds: From bone tissue engineering to tumor therapy. *Acta Biomater*. 2018;79:37-59. doi: 10.1016/j.actbio.2018.08.026
53. Lughi V, Sergo V. Low temperature degradation -aging- of zirconia: A critical review of the relevant aspects in dentistry. *Dent Mater*. 2010;26(8):807-820. doi: 10.1016/j.dental.2010.04.006
54. Ricco Pa, de Carvalho Ramos N, Bastos Campos TM, et al. The roles of microstructure and surface energy on subcritical crack growth in glass-ceramics. *Ceramics International*. 2021;47(5)6827-6833. doi: 10.1016/j.ceramint.2020.11.025
55. Chevalier J, Deville S, Münch E, et al. Critical effect of cubic phase on aging in 3mol% yttria-stabilized zirconia ceramics for hip replacement prosthesis. *Biomaterials*. 2004;25(24):5539-5545. doi: 10.1016/j.biomaterials.2004.01.002
56. Gremillard L, Chevalier J, Martin L, et al. Sub-surface assessment of hydrothermal ageing in zirconia-containing femoral heads for hip joint applications. *Acta Biomater*. 2018;68:286-295. doi: 10.1016/j.actbio.2017.12.021
57. Boniecki M, Sadowski T, Gołębiewski P, et al. Mechanical properties of lumina/zirconia composites. *Ceramics International*. 2020;46(1):1033-1039. doi: 10.1016/j.ceramint.2019.09.068
58. Abbas MKG, Ramesh S, Lee KYS, et al. Effects of sintering additives on the densification and properties of alumina-toughened zirconia ceramic composites. *Ceramics International*. 2020;46(17): 27539-27549. doi: 10.1016/j.ceramint.2020.07.246
59. Abbas MKG, Ramesh S, Tasfy SFH, Lee KYS. A state-of-the-art review on alumina toughened zirconia ceramic composites. *Materials Today Communications*. 2023;37:106964. doi: 10.1016/j.mtcomm.2023.106964
60. Patil S, Patil DR, Jung IC, Ryu J. Effect of cooling rates on mechanical properties of alumina-toughened zirconia composites. *Ceramics International*. 2022;48:21048-21053. doi: 10.1016/j.ceramint.2022.04.127
61. Sequeira S, Fernandes MH, Neves N, Almeida MM. Development and characterization of zirconia–alumina composites for orthopedic implants. *Ceramics International*. 2017;43:693-703. doi: 10.1016/j.ceramint.2016.09.216
62. Plushev AL, Gavryushenko NS, Golev SN. Features of ceramic bearing in hip arthroplasty in patients with dysplastic osteoarthritis. *Moscow Surgical Journal*. 2008;(2):47-55. (In Russ.)

63. Aboushelib MN, Shawky R. Osteogenesis ability of CAD/CAM porous zirconia scaffolds enriched with nano-hydroxyapatite particles. *Int J Implant Dent*. 2017 Dec;3(1):21. doi: 10.1186/s40729-017-0082-6
64. Pardun K, Treccani L, Volkmann E, et al. Mixed zirconia calcium phosphate coatings for dental implants: tailoring coating stability and bioactivity potential. *Mater Sci Eng C Mater Biol Appl*. 2015;48:337-346. doi: 10.1016/j.msec.2014.12.031
65. Panteleenko FI, Okovityi VA, Kylak AI, Okovityi VV. The composite powder obtained based coprecipitation of hydroxyapatite and hydrated zirconia for applying plasma coatings. *Strengthening technologies and coatings*. 2015;(6):38-40.
66. Yang J, Sultana R, Ichim P, et al. Micro-porous calcium phosphate coatings on load-bearing zirconia substrate: Processing, property and application. *Ceramics International*. 2013;39(6):6533-6542. doi: 10.1016/j.ceramint.2013.01.086
67. Silva ADR, Pallone EMJA, Lobo AO. Modification of surfaces of alumina-zirconia porous ceramics with Sr^{2+} after SBF. *J Aust Ceram Soc*. 2020;56:517-524. doi: 10.1007/s41779-019-00360-4
68. Kou W, Akasaka T, Watari F, Sjögren G. An in vitro evaluation of the biological effects of carbon nanotube-coated dental zirconia. *ISRN Dent*. 2013;2013:296727. doi: 10.1155/2013/296727
69. Fabris D, Souza JCM, Silva FS, et al. The bending stress distribution in bilayered and graded zirconia-based dental ceramics. *Ceramics International*. 2016;42(9):11025-11031. doi: 10.1016/j.ceramint.2016.03.245
70. Li H, Xie Y, Li K, L. et al Microstructure and wear behavior of graphene nanosheets-reinforced zirconia coating. *Ceramics International*. 2014;40(8):12821-12829. doi: 10.1016/j.ceramint.2014.04.136
71. Brokesh AM, Gaharwar AK. Inorganic Biomaterials for Regenerative Medicine. *ACS Appl Mater Interfaces*. 2020;12(5):5319-5344. doi: 10.1021/acsami.9b17801
72. Zhao Y, Zhang Z, Pan Z, Liu Y. Advanced bioactive nanomaterials for biomedical applications. *Exploration* (Beijing). 2021;1(3):20210089. doi: 10.1002/EXP.20210089
73. Schünemann FH, Galárraga-Vinueza ME, Magini R, et al. Zirconia surface modifications for implant dentistry. *Mater Sci Eng C Mater Biol Appl*. 2019;98:1294-1305. doi: 10.1016/j.msec.2019.01.062
74. Yin L, Nakanishi Y, Alao AR, et al. A review of engineered zirconia surfaces in biomedical applications. *Procedia CIRP*. 2017;65:284-290. doi: 10.1016/j.procir.2017.04.057
75. Pardun K, Treccani L, Volkmann E, et al. Magnesium-containing mixed coatings on zirconia for dental implants: mechanical characterization and in vitro behavior. *J Biomater Appl*. 2015;30(1):104-118. doi: 10.1177/0885328215572428
76. Mushahary D, Wen C, Kumar JM, et al. Collagen type-I leads to in vivo matrix mineralization and secondary stabilization of Mg-Zr-Ca alloy implants. *Colloids Surf B Biointerfaces*. 2014;122:719-728. doi: 10.1016/j.colsurfb.2014.08.005
77. Izmodenova MYu, Gilev MV, Ananyev MV, et al. Bone tissue properties after lanthanum zirconate ceramics implantation: experimental study. *Traumatology and Orthopedics of Russia*. 2020;26(3):130-14. doi: 10.21823/2311-2905-2020-26-3-130-140
78. Tarasova N, Galisheva A, Belova K, et al. Ceramic materials based on lanthanum zirconate for the bone augmentation purposes: materials science approach. *Chimica Techno Acta*. 2022;9(2), No. 20229209. doi: 10.15826/chimtech.2022.9.2.09.
79. Ulitko M, Antonets Y, Antropova I, et al. Ceramic materials based on lanthanum zirconate for the bone augmentation purposes: cytocompatibility in a cell culture model. *Chimica Techno Acta*. 2023;10(4), No. 202310402. doi: 10.15826/chimtech.2023.10.4.02

The article was submitted 23.10.2023; approved after reviewing 28.11.2023; accepted for publication 28.11.2023.

Information about the authors:

Elena A. Volokitina – Doctor of Medical Sciences, Professor, Leading Researcher, volokitina_elena@rambler.ru, https://orcid.org/0000-0001-5994-8558;

Irina P. Antropova – Doctor of Biological Sciences, Leading Researcher, aip.hemolab@mail.ru, https://orcid.org/0000-0002-9957-2505;

Kirill A. Timofeev – graduate student, kirilltimofeev64166@gmail.com, https://orcid.org/0000-0003-2208-7154;

Roman A. Trufanenko – graduate student, rtrufanenko@gmail.com https://orcid.org/0000-0002-9978-4807.

Contribution of the authors:

Volokitina E.A. – idea and concept of the study, interpretation of the material, final editing of the manuscript text.

Antropova I.P. – search and analysis of publications on the topic of the review, interpretation of the data obtained, preparation and writing of the text, editing of the text of the manuscript.

Timofeev K.A. – search and analysis of publications on the topic of the review, preparation and writing of the text.

Trufanenko R.A. – search and analysis of publications on the topic of the review.

Review article
https://doi.org/10.18019/1028-4427-2024-30-1-124-133

Mesenchymal stem cells and exosomes in bone defects treatment

A.I. Greben[1,2]✉, P.S. Eremin [2], E.Yu. Kostromina[2], P.A. Markov[2], I.R. Gilmutdinova[2]

[1] Pirogov Russian National Research Medical University, Moscow, Russian Federation
[2] National Medical Research Center for Rehabilitation and Balneology, Moscow, Russian Federation

Corresponding author: Anastasiya I. Greben, aik-nastya@mail.ru

Abstract

Introduction Bone defect management is a critical stage of treatment and rehabilitation that still remains a challenging problem for traumatologists and orthopaedists. The need for tissue engineering techniques is due to limited abilities of the human body to correct bone tissue autoregeneration, especially in comorbid and elderly patients with osteoporosis. Bone autografts is a gold standard in those cases but is associated with certain restrictions. Regenerative medicine and stem cell biology development opened up capabilities to employ new methods for enhancement of bone tissue repair. A special interest of researchers is focused on mesenchymal stem cells and extracellular vesicles for bone tissue regeneration optimization.

Purpose of this review was to show mesenchymal stem cells and exosomes effeciency in bone defect treatment.

Materials and methods Open electronic databases of scientific literature, PubMed and e-Library, were used. The literature data search was carried out using the keywords: regenerative medicine, bone defects, exosomes, mesenchymal stem cells.

Results and discussion The review presents current ideas about mesenchymal stem cells, their microenvironment and exosomes influence on bone tissue repair. Clinical need in effective bone regeneration is still high. Mesenchymal stem cells and acellular regenerative treatments have shown good results in bone defects repair and are perspective directions. Productive use of mesenchymal stem cells and exosomes in bone defects treatment requires further study of their mechanisms of action, the regenerative techniques efficacy and safety evaluation in preclinical and clinical studies.

Conclusion The use of mesenchymal stem cells and cell-free regenerative approaches has demonstrated good results in the restoration of bone tissue defects and is a promising direction.

Keywords: regenerative medicine, bone defects, cytotherapy, exosomes, mesenchymal stem cells, bioengineering, tissue engineering

For citation: Greben AI, Eremin PS, Kostromina EYu, Markov PA, Gilmutdinova IR. Mesenchymal stem cells and exosomes in bone defects treatment. *Genij Ortopedii*. 2024;30(1):124-133. doi: 10.18019/1028-4427-2024-30-1-124-133

INTRODUCTION

Despite the improvement of surgical techniques, the treatment of large bone defects caused by trauma, metastatic damage or infectious process still remains a major challenge for orthopaedic surgeons [1, 2]. Such injuries lead to delayed fracture consolidation or nonunion and ultimately impair patient's musculoskeletal function [3, 4]. Currently, bone grafting is the most commonly used treatment in those conditions [5, 6]. However, limited sources of donor tissue, complications and difficulty of graft collection, the risk of transmission of infectious diseases, short-term viability and unpredictable graft resorption restrict the widespread use of this technique and require the development of new approaches to the treatment of this pathology [7, 8]. The use of modern regenerative techniques, in particular tissue engineering, is a promising approach to the treatment of bone defects and has attracted the attention of a large number of researchers in recent years [4, 9]. Thus, the use of cell technologies could overcome osteogenic "insufficiency", which is often found in elderly patients, in whom the body's own resources are not able to restore lost bone tissue [10-12]. The angiogenic effect of exosomes would lead to improved blood supply to the developing bone tissue, thereby optimizing the process of osteogenesis [13-15].

The purpose of the study was to discuss the effectiveness of mesenchymal stem cells and exosomes to stimulate bone tissue regeneration.

MATERIALS AND METHODS

Open electronic databases of scientific literature Pubmed and e-Library were used for preparing the review. The literature search was carried out using the following keywords: regenerative medicine, bone defects, exosomes, mesenchymal stem cells. The inclusion criteria were review articles, systematic reviews, meta-analyses, multicentre studies, controlled cohort studies, uncontrolled cohort studies. Exclusion criteria were articles without a full-text version and duplicate articles. Preference was given to works published within the last five years.

RESULTS

Way to stimulate bone regeneration

Tissue engineering is an interdisciplinary field aimed at developing new biological approaches to treat a wide range of diseases [12]. The need for tissue engineering techniques in bone regeneration is due to the limited abilities of the human body for correct autoregeneration, especially in comorbid and elderly patients with osteoporosis [10].

Mesenchymal stem cells (MSCs) play a significant role in the process of bone tissue remodeling, since they are the precursors of the key regulators of this process, osteoblasts and osteoclasts, and are also able to migrate to the defect area [16]. Significant advances in the study of stem cell biology have provided new therapeutic regenerative strategies that avoid the use of autologous bone tissue [17].

The shortage of tissue grafts has also stimulated the development of regenerative medicine technologies that apply natural biomaterials that have positive properties such as biocompatibility, bioactivity, controlled degradation and structural similarity to native tissue extracellular matrix [18]. One of the philosophies of regenerative medicine is creation of such scaffold biomaterials that simultaneously mimic the extracellular matrix and positively modulate the activity of proper/exogenous stem cells to achieve maximum regenerative potential [19].

Currently, the following materials have been used to improve bone regeneration [10]:

1. Tissue grafts of:
   – autologous origin (bone grafts, cancellous grafts);
   – allogeneic origin (bone grafts, bone graft product);

2. Components of the extracellular matrix:
   – collagen (types 1, 2 and 4);
   – fibronectin;
   – laminin;
3. Decellularized extracellular matrix:
   – demineralized bone matrix;
   – decellularized bone extracellular matrix;
   – calcined bovine bone;
4. Ex vivo cultured therapeutic cells:
   – MSC transplantation;
   – extracellular matrix formed by cells;
   – exosomes.

The use of mesenchymal stem cells and extracellular vesicles as strategies to optimize bone tissue regeneration is of particular interest to researchers [4].

Mesenchymal stem cells

Currently, there are two main strategies for using MSCs to improve bone tissue regeneration: the release-mobilization of endogenous MSCs and the use of exogenous stem cells [20]. The use of exogenous stem cells is possible in several ways: systemic administration by intravenous infusion [21] and local application of cell suspensions, sheets and spheroids [22]. In systemic use of MSCs, in addition to the osteogenic effect, modulation of the immune status and, accordingly, restoration of the microenvironment have been demonstrated; however, the percentage of cells that reach the bone defect remains low thus decreasing the therapeutic efficacy [21, 23]. The use of cell sheets [24] and spheroids [25] with an extracellular matrix formed by stem cells promotes the release of a large number of growth factors and cytokines that improve bone tissue regeneration, which is successfully used in the treatment of bone defects [26] and to improve the bone-to-graft bonds [27]. Thus, the study of Vishnevsky et al. [28] showed that the addition of MSCs to bone grafts in a rabbit rib cage defect model promoted an increase in the proportion of mature bone matrix and more intense osteogenic differentiation.

In recent years, much attention has been paid to the microenvironment of cells, since its significant influence on the functional activity of stem cells and their reproducible therapeutic effects has been discovered [6]. In a pathological microenvironment, the viability and differentiation of MSCs decreases; thus, during cytotherapy, both the donor microenvironment and the recipient microenvironment play a significant role in determining the therapeutic effectiveness of transplanted stem cells [29]. Important systemic factors affecting bone regeneration and cell microenvironment include the level of steroid hormones [30] and blood glucose [31], as well as the activity of the inflammatory process [32]. Decreased estrogen levels in postmenopausal women have been shown to result in decreased proliferation and osteogenic differentiation of bone marrow (BM) MSCs, decreased bone mineralization, accumulation of reactive oxygen species, adipogenic cell differentiation, imbalance between osteoblastogenesis and osteoclastogenesis, and ultimately, in bone loss [33]. Elevated levels of corticosteroids also suppress the proliferation and osteogenic potential of BM MSCs [34]. At the cell level, the energy metabolic profile has a significant impact on the functions of stem cells, so increased glucose concentration causes dysfunction of BM MSCs [35]. Oxidative stress and accumulation of advanced glycation end products lead to decreased viability and osteogenic differentiation of stem cells [36]. Despite the essential role of inflammation

in bone healing, the proinflammatory microenvironment is a key pathogenetic mechanism underlying various osteopenic disorders, as inflammatory cytokines lead to impaired proliferation and osteogenic differentiation, excess production of reactive oxygen species and apoptosis of stem cells [31]. Thus, to improve the regenerative potential of stem cells, it is necessary to analyze and adjust the level of steroid hormones and glucose in both the donor and the recipient, as well as modulate the inflammatory microenvironment [36]. For this purpose, gene expression regulators, such as rapamycin, a signaling inhibitor of mTOR, can be used in the clinic [37]; DAPT, Notch signaling inhibitor [38]; PDTC, nuclear transcription factor-kappaB (NF-κB) signaling inhibitor [39]; GSK2606414, PERK inhibitor [40]; antioxidant NAC [41]; licochalcone A [42], etc. The effectiveness they demonstrated indicates the potential use of the technique of normalizing the microenvironment of stem cells in order to increase the efficiency of MSC-mediated bone healing [43].

At the moment, the use of adipose tissue MSCs (ADSCs) has become increasingly attractive for clinical specialists as it is the least traumatic method for the patient [44]. However, the limited potential of ADSCs for osteogenic differentiation and the natural tendency towards adipogenic differentiation hinder their widespread use in bone tissue regeneration [45]. At the same time, it is known from the literature that circular RNAs (circRNAs) play a significant role in determining the further path of development of stem cells and progenitor cells [46]. A study by D Zhang et al. [44] assessed the modulating effect of circRNA on the osteogenic differentiation of adipose tissue stem cells. CircRNA is a closed, continuous ring of RNA, which makes it more stable than linear RNA due to the absence of a free end available for enzymatic degradation [47]. Some effects of circRNA are reproduced by acting on microRNAs (miRs) that regulate the expression of target genes [48]. Thus, in the course of this review, it was found that circRNA-vgll3 directly binds to miR-326-5p in the cytoplasm of cells like a “sponge” and inhibits its activity, which leads to an increase in the expression of integrin α5 (Itga5) [44]. Itga5 is known to play a significant role in cell adhesion to the extracellular matrix, improves the functional activity and survival of osteoprogenitors, and also carries out some mechanisms of osteogenic growth factors, such as BMP2, TGFβ and PTH [49]. Increased expression of Itga5 through the circRNA-vgll3/miR-326-5p/integrin α5 signaling pathway leads to improved ADSC homing, recruitment of osteoprogenitor cells, and improved osteogenic differentiation of adipose tissue stem cells [44]. The use of a circRNA-vgll3 inhibitor led to a decrease in the mRNA expression of ADSC osteogenic differentiation genes (Runx2, OSX, Col1a1, OPN, OCN and BSP) [44]. The therapeutic effect of a combined use of circRNA-vgll3-modified calcium phosphate scaffolds and ADSCs was also assessed in a rat model of bone defect of the skull [44]. An increase in mineral density and an increase in the volume of newly formed bone tissue were revealed when compared to the control group [44]. The results of that study show the promise of using circular RNAs, namely circRNA-vgll3, to improve the osteogenic differentiation of adipose tissue stem cells and their further use for the treatment of bone defects [44].

Literature data on research into the effectiveness of stem cells in bone tissue restoration are not limited to animal trials alone. Thus, VN Bordakov et al. [50] provided data on the successful use in their clinical practice of tissue-engineered constructs based on calcium hydroxyapatite, fibrin glue and bone marrow MSCs in the treatment of defects of long bones. A histological assessment of the regenerate one month after grafting discovered developing bone tissue, and the result of treatment was subsequent consolidation of the fracture and functional recovery. However, the authors emphasize the importance of further studying this combination of biologically active components in subsequent studies [50].

Exosomes

Traditional tissue engineering is based on the use of scaffolds, cultured cells, and growth factors [51]. However, the use of cells has a number of disadvantages: limited sources, insufficient cell activity, immunological reactions and high costs for clinical use [52]. Nevertheless, the therapeutic potential

of exosomes is similar to the paracrine functions of stem cells and overcomes the limitations associated with their transplantation [1]. This is why safer acellular tissue engineering may become an alternative to cell therapy [2, 53, 54]. Thus, the studies of the regenerative potential of MSC exosomes on a model of bone defect in rats performed by IV Mayborodin et al. [55, 56] demonstrated faster healing and an increase in bone density, as well as the formation of less rough callus compared to the control group.

Monocytes and macrophages are known to be key regulators of tissue healing processes, and different macrophage phenotypes have different effects on repair processes [57]. During the repair process, the recruitment of monocyte macrophages occurs, a transition from the M_1-phenotype, pro-inflammatory, to the M_2-phenotype, anti-inflammatory [58]. Current research is focused on studying the influence of different macrophage phenotypes on tissue regeneration [59]. Thus, F Loi et al. [60] suggested that consistent changes in macrophage phenotypes make a significant contribution to the process of osteogenesis. Macrophages control the physiological process of bone repair by secreting various factors that are osteoinductive and, conversely, inhibiting bone regeneration [61]. Intercellular interactions are mediated by the release into the local environment of exosomes (Exos) that are extracellular vesicles ranging in size from 40 to 150 nm, containing proteins, lipids and nucleic acids, including miRs [62, 63]. Exosomes captured by target cells have a biological effect on them, change their behavior pattern and activate signaling pathways [64]. The study of M Kang et al. [59] investigated the functional role of paracrine factors, Exos M_0, M_1 and M_2 macrophages, in the treatment of critical size defects in a rat calvarial defect model. It was revealed that Exos M_0 and M_2-macrophages promote bone repair while Exos M_1 affects bone regeneration [59]. Exos M_1, and namely miR-155, may affect RUNX2 and BMP signal ways, in particular BMP2 and BMP9 that result in the decrease of osteogenic differentiation of MSC, while Exos M_0 and M_2, miR 378a, promote expression of osteoinductive genes of MSC [59]. CT evaluation conducted after 3 weeks showed impairment in bone formation in Exos M_1 group and improvement in Exos M_0 and M_2-macrophages group [59]. Other studies demonstrated that osteogenesis improved as a result of common cultivation of M_2-macrophages with osteoprogenitors while M_1-macrophages decreased expression of osteogenic markers and impaired bone tissue mineralization [65, 66]. The study confirms the results of other studies and indicates the differential and opposite effects of polarized macrophages and their exosomes on bone tissue regeneration, and also provides grounds for the prospects of using exosomes of M_0 and M_2-macrophages as osteogenesis stimulators [67-69].

The pathogenetically important anti-inflammatory effect of exosomes was demonstrated in a study by X Wang et al. [70], where the effect of a polycaprolactone (PCL) scaffold in combination with MSC exosomes and S-nitrosoglutathione (GSNO) on bone tissue repair was studied. PCL is a biocompatible but bioinert polymer, what limits its stand-alone application in bone engineering [71]. Nevertheless, GSNO, which is a donor of NO, regulates the activity of the blood coagulation system, has an anti-inflammatory effect and prevents the destruction of bone tissue [72]. The work demonstrated a decrease in the expression of pro-inflammatory genes (IL-6, TNF-α, iNOS и Il-1β), an improvement in the osteogenic differentiation of BM MSCs, what was manifested by an increase in the expression of mRNA ALP, Col-I and Runx2, as well as an increase in ALP activity [70]. Researchers have suggested a synergistic effect of GSNO and exosomes on the expression of pro-inflammatory cytokines [70]. The results of that study show the promise of using bioactive agents such as GSNO and exosomes in combination with scaffolds to improve bone tissue regeneration [70].

Filling of large bone tissue defects is often accompanied by insufficient vascularization of the resulting tissue [73]. Angiogenesis plays a significant role in the process of bone tissue remodeling; therefore, for effective healing, improvement of both osteogenesis and angiogenesis is necessary [13]. A study by Y Zha et al. [2] examined an acellular tissue engineering system using encapsulated vascular endothelial growth factor (VEGF) gene in exosomes on the surface of a 3D-modulated PCL scaffold in a radius bone defect model in rats. Micro-CT analysis after 6 and 12 weeks revealed a significant

improvement in bone regeneration in the experimental group, and histological analysis showed the presence of more mature collagen fibers compared to the control group [2]. The study demonstrated the dual role of exosome-modified scaffolds: as an inducer of osteogenic differentiation of BM MSCs and as a VEGF depot that ensures remodeling of the vascular network [2]. That work demonstrated the possibility of using exosomes as a biovector for the delivery of biologically active substances to improve bone tissue regeneration [2].

It was previously shown that BMSC-Exos and magnetic nanoparticles (Fe_3O_4, γ-Fe_2O_3) in combination with a static magnetic field (SMF) have a positive effect on both osteo- and angiogenesis [74, 75]. Wu et al. [1] assessed the effect of magnetic nanoparticle-modified exosomes (BMSC- Fe_3O_4-Exos) in combination with SMF on the functional characteristics of human umbilical vein endothelial cells (HUVEC) and BMSC, as well as the restoration of calvar defect on rat models. Researchers have demonstrated the osteogenic effect of this modification of exosomes in combination with a static magnetic field, which was manifested by improved mineralization of bone tissue, increased ALP secretion and mRNA expression of osteogenic markers (OPN, RUNX2, COL-1) [1]. When co-cultured with HUVEC, effects such as accelerated cell migration, a greater number of tube-like structures, and an increase in the expression of mRNA of pro-angiogenic factors (VEGF, ANG-1, HIF-1α) were noted, which confirms the angiogenic effect of BMSC-Fe_3O_4-Exos-SMF [1]. Micro-CT analysis demonstrated an increase in the amount of newly formed bone and blood vessels in the experimental group, which is confirmed by the results of other studies [76-81]. The positive effect on osteo- and angiogenesis was explained by an increase in the concentration of miR-1260a and its effect on the transcription of certain genes [1]. Thus, in BMSC, miR-1260a inhibits the expression of HDAC7 and thereby reduces its suppressive effect on the expression of OPN, RUNX2, OCN, ALP and COL-1, a similar mechanism of action is observed in HUVEC, where miR-1260a inhibits COL4A2, thus increasing secretion of VEGF, ANG-1 and HIF-1α [1, 75, 82]. This kind of angiogenic effect was demonstrated in the work of Lu et al. [14]. The study showed that miR-29a-3p, through post-transcriptional inhibition of VASH-1 which negatively affects angiogenesis, contributed to improved proliferation and migration of endothelial cells, and an increase in the number of osteocalcin-positive osteoblasts, bone mineral density and trabecular bone volume was noted, compared with the control group [14]. The results of this study demonstrate the therapeutic potential of exosomes in the repair of bone defects [1].

DISCUSSION

Management of large bone defects remains a challenging problem for orthopaedic surgeons, and therefore there is an active search for methods to increase the efficiency of bone regeneration [1, 4]. A large number of studies have been focused on the use of mesenchymal stem cells and exosomes as stimulators of osteogenesis. Analysis of current medical literature allows us to draw definite conclusions:

– All the studies we reviewed show a positive effect of mesenchymal stem cells and exosomes on the process of bone tissue remodeling.

– Local use of mesenchymal stem cells is characterized by a more pronounced regenerative effect compared to systemic administration [21, 23, 26, 28].

– Developing methods for increasing the differentiation of mesenchymal stem cells of adipose tissue in the osteogenic direction would enable to use alternative sources of multipotent cells to bone marrow in the future, and, accordingly, reduce the traumatic nature of the procedure, which is especially important in the case of a severe patient's condition [44].

– To improve the regenerative potential of mesenchymal stem cells, it is necessary to consider the endocrine status of both the donor and the recipient, as well as carry out anti-inflammatory therapy to create an optimal microenvironment of transplanted cells [31-36].

– Exosomes of anti-inflammatory phenotypes of macrophages have a positive effect on the process of bone repair [60, 65-69].

– Exosomes of mesenchymal stem cells have an anti-inflammatory, angiogenic and osteogenic effect that ensure a more efficient bone tissue regeneration process [1, 2, 14, 55, 56, 70, 74, 75].

CONCLUSION

Despite the active development of medicine, the clinical need for effective bone regeneration still remains at a high level. The use of mesenchymal stem cells and acellular regenerative approaches has demonstrated good results in bone defect management and is a promising direction. Further study of the mechanisms of action is necessary for the productive use of mesenchymal stem cells and exosomes in the treatment of bone defects along with assessment of the effectiveness and safety of these regenerative techniques in preclinical and clinical studies.

Conflict of interest *The authors declare no apparent or potential conflicts of interest related to the publication of this paper.*

Funding *The study had no sponsorship.*

REFERENCES

1. Wu D, Chang X, Tian J, et al. Bone mesenchymal stem cells stimulation by magnetic nanoparticles and a static magnetic field: release of exosomal miR-1260a improves osteogenesis and angiogenesis. *J Nanobiotechnology*. 2021;19(1):209. doi: 10.1186/s12951-021-00958-6
2. Zha Y, Li Y, Lin T, et al. Progenitor cell-derived exosomes endowed with VEGF plasmids enhance osteogenic induction and vascular remodeling in large segmental bone defects. *Theranostics*. 2021;11(1):397-409. doi: 10.7150/thno.50741
3. Herberg S, McDermott AM, Dang PN, et al. Combinatorial morphogenetic and mechanical cues to mimic bone development for defect repair. *Sci Adv*. 2019;5(8):eaax2476. doi: 10.1126/sciadv.aax2476
4. Shang F, Yu Y, Liu S, et al. Advancing application of mesenchymal stem cell-based bone tissue regeneration. *Bioact Mater*. 2020;6(3):666-683. doi: 10.1016/j.bioactmat.2020.08.014
5. Lopes D, Martins-Cruz C, Oliveira MB, Mano JF. Bone physiology as inspiration for tissue regenerative therapies. *Biomaterials*. 2018;185:240-275. doi: 10.1016/j.biomaterials.2018.09.028
6. Sui BD, Hu CH, Liu AQ, et al. Stem cell-based bone regeneration in diseased microenvironments: Challenges and solutions. *Biomaterials*. 2019;196:18-30. doi: 10.1016/j.biomaterials.2017.10.046
7. Liang B, Liang JM, Ding JN, et al. Dimethyloxaloylglycine-stimulated human bone marrow mesenchymal stem cell-derived exosomes enhance bone regeneration through angiogenesis by targeting the AKT/mTOR pathway. *Stem Cell Res Ther*. 2019;10(1):335. doi: 10.1186/s13287-019-1410-y
8. Ho-Shui-Ling A, Bolander J, Rustom LE, et al. Bone regeneration strategies: Engineered scaffolds, bioactive molecules and stem cells current stage and future perspectives. *Biomaterials*. 2018;180:143-162. doi: 10.1016/j.biomaterials.2018.07.017
9. Naudot M, Garcia Garcia A, Jankovsky N, et al. The combination of a poly-caprolactone/nano-hydroxyapatite honeycomb scaffold and mesenchymal stem cells promotes bone regeneration in rat calvarial defects. *J Tissue Eng Regen Med*. 2020;14(11):1570-1580. doi: 10.1002/term.3114
10. Thormann U, Ray S, Sommer U, et al. Bone formation induced by strontium modified calcium phosphate cement in critical-size metaphyseal fracture defects in ovariectomized rats. *Biomaterials*. 2013;34(34):8589-8598. doi: 10.1016/j.biomaterials.2013.07.036
11. Deev R. Cellular technologies in traumatology and orthopedics of osteogenesis. *Traumatology and Orthopaedics of Russia*. 2007;46(4):18-30. (in Russ.)
12. Kim BC, Bae H, Kwon IK, et al. Osteoblastic/cementoblastic and neural differentiation of dental stem cells and their applications to tissue engineering and regenerative medicine. *Tissue Eng Part B Rev*. 2012;18(3):235-244. doi: 10.1089/ten.TEB.2011.0642
13. Watson EC, Adams RH. Biology of bone: the vasculature of the skeletal system. *Cold Spring Harb Perspect Med*. 2018;8(7):a031559. doi: 10.1101/cshperspect.a031559
14. Lu GD, Cheng P, Liu T, Wang Z. BMSC-Derived Exosomal miR-29a Promotes Angiogenesis and Osteogenesis. *Front Cell Dev Biol*. 2020;8:608521. doi: 10.3389/fcell.2020.608521
15. Olfert IM, Baum O, Hellsten Y, Egginton S. Advances and challenges in skeletal muscle angiogenesis. *Am J Physiol Heart Circ Physiol*. 2016;310(3):H326-H336. doi: 10.1152/ajpheart.00635.2015
16. Fierro FA, Nolta JA, Adamopoulos IE. Concise review: stem cells in osteoimmunology. *Stem Cells*. 2017;35(6):1461-1467. doi: 10.1002/stem.2625
17. Naik S, Larsen SB, Cowley CJ, Fuchs E. Two to tango: dialog between immunity and stem cells in health and disease. *Cell*. 2018;175(4):908-920. doi: 10.1016/j.cell.2018.08.071
18. Renth AN, Detamore MS. Leveraging "raw materials" as building blocks and bioactive signals in regenerative medicine. *Tissue Eng Part B Rev*. 2012;18(5):341-362. doi: 10.1089/ten.TEB.2012.0080
19. Chen P, Tao J, Zhu S, et al. Radially oriented collagen scaffold with SDF-1 promotes osteochondral repair by facilitating cell homing. *Biomaterials*. 2015;39:114-123. doi: 10.1016/j.biomaterials.2014.10.049

20. Gao C, Peng S, Feng P, Shuai C. Bone biomaterials and interactions with stem cells. *Bone Res*. 2017;5:17059. doi: 10.1038/boneres.2017.59
21. Liu Y, Yang R, Shi S. Systemic infusion of mesenchymal stem cells improves cell-based bone regeneration via upregulation of regulatory T cells. *Tissue Eng Part A*. 2015;21(3-4):498-509. doi: 10.1089/ten.tea.2013.0673
22. Zheng CX, Sui BD, Hu CH, et al. Reconstruction of structure and function in tissue engineering of solid organs: Toward simulation of natural development based on decellularization. *J Tissue Eng Regen Med*. 2018;12(6):1432-1447. doi: 10.1002/term.2676
23. Zinchenko EV. Changes in the mineral composition of the skeletal bones during the application of a tibial defect and intravenous administration of mesenchymal stem cells on the 10th day of the bone regenerate formation. *Current issues of anatom : Materials Of the International Scientific and practical conference*. Vitebsk : VSMU. 2020:127-129. (in Russ.)
24. Sui BD, Chen J, Zhang XY, et al. Gender-independent efficacy of mesenchymal stem cell therapy in sex hormone-deficient bone loss via immunosuppression and resident stem cell recovery. *Exp Mol Med*. 2018;50(12):1-14. doi: 10.1038/s12276-018-0192-0
25. Ahrens CC, Dong Z, Li W. Engineering cell aggregates through incorporated polymeric microparticles. *Acta Biomater*. 2017;62:64-81. doi: 10.1016/j.actbio.2017.08.003
26. Yan J, Zhang C, Zhao Y, et al. Non-viral oligonucleotide antimiR-138 delivery to mesenchymal stem cell sheets and the effect on osteogenesis. *Biomaterials*. 2014;35(27):7734-7749. doi: 10.1016/j.biomaterials.2014.05.089
27. Jiang Z, Wang H, Yu K, et al. Light-Controlled BMSC Sheet-Implant Complexes with Improved Osteogenesis via an LRP5/β-Catenin/Runx2 Regulatory Loop. A*CS Appl Mater Interfaces*. 2017;9(40):34674-34686. doi: 10.1021/acsami.7b10184
28. Vishnevskii AA, Lutsai VI, Usha BV. Stimulation of reparative osteogenesis by multipotent stem cells during the replacement of bone defects in the rib cage in the experiment. *Agricultural Science*. 2012;10:23-24. (in Russ.)
29. Sui BD, Hu CH, Zheng CX, et al. Recipient Glycemic Micro-environments Govern Therapeutic Effects of Mesenchymal Stem Cell Infusion on Osteopenia. *Theranostics*. 2017;7(5):1225-1244. doi: 10.7150/thno.18181
30. Wei P, Dove KK, Bensard C, et al. The force is strong with this one: Metabolism (over)powers stem cell fate. *Trends Cell Biol*. 2018;28(7):551-559. doi: 10.1016/j.tcb.2018.02.007
31. Liao L, Su X, Yang X, et al. TNF-α Inhibits FoxO1 by Upregulating miR-705 to Aggravate Oxidative Damage in Bone Marrow-Derived Mesenchymal Stem Cells during Osteoporosis. *Stem Cells*. 2016;34(4):1054-1067. doi: 10.1002/stem.2274
32. Almeida M, Laurent MR, Dubois V, et al. Estrogens and Androgens in Skeletal Physiology and Pathophysiology. *Physiol Rev*. 2017;97(1):135-187. doi: 10.1152/physrev.00033.2015
33. Li J, Zhang N, Huang X, et al. Dexamethasone shifts bone marrow stromal cells from osteoblasts to adipocytes by C/EBPalpha promoter methylation. *Cell Death Dis*. 2013;4(10):e832. doi: 10.1038/cddis.2013.348
34. Napoli N, Chandran M, Pierroz DD, et al. Mechanisms of diabetes mellitus-induced bone fragility. *Nat Rev Endocrinol*. 2017;13(4):208-219. doi: 10.1038/nrendo.2016.153
35. Riddle RC, Clemens TL. Bone cell bioenergetics and skeletal energy homeostasis. *Physiol Rev*. 2017;97(2):667-698. doi: 10.1152/physrev.00022.2016
36. Ono T, Takayanagi H. Osteoimmunology in bone fracture healing. *Curr Osteoporos Rep*. 2017;15(4):367-375. doi: 10.1007/s11914-017-0381-0
37. Liu Y, Kou X, Chen C, et al. Chronic high dose alcohol induces osteopenia via activation of mTOR signaling in bone marrow mesenchymal stem cells. *Stem Cells*. 2016;34(8):2157-2168. doi: 10.1002/stem.2392
38. Liu S, Liu D, Chen C, et al. MSC transplantation improves osteopenia via epigenetic regulation of notch signaling in lupus. *Cell Metab*. 2015;22(4):606-618. doi: 10.1016/j.cmet.2015.08.018
39. Li C, Li B, Dong Z, et al. Lipopolysaccharide differentially affects the osteogenic differentiation of periodontal ligament stem cells and bone marrow mesenchymal stem cells through Toll-like receptor 4 mediated nuclear factor κB pathway. *Stem Cell Res. Ther*. 2014;5(3):67. doi: 10.1186/scrt456
40. Xue P, Li B, An Y, et al. Decreased MORF leads to prolonged endoplasmic reticulum stress in periodontitis-associated chronic inflammation. *Cell Death Differ*. 2016;23(11):1862-1872. doi: 10.1038/cdd.2016.74
41. Geissler S, Textor M, Schmidt-Bleek K, et al. In serum veritas-in serum sanitas? Cell non-autonomous aging compromises differentiation and survival of mesenchymal stromal cells via the oxidative stress pathway. *Cell Death Dis*. 2013;4(12):e970. doi: 10.1038/cddis.2013.501
42. Ming L, Jin F, Huang P, et al. Licochalcone A up-regulates of FasL in mesenchymal stem cells to strengthen bone formation and increase bone mass. *Sci Rep*. 2014;4:7209. doi: 10.1038/srep07209
43. Zhang X, Li Y, Chen YE, et al. Cell-free 3D scaffold with two-stage delivery of miRNA-26a to regenerate critical-sized bone defects. *Nat Commun*. 2016;7:10376. doi: 10.1038/ncomms10376
44. Zhang D, Ni N, Wang Y, et al. CircRNA-vgII3 promotes osteogenic differentiation of adipose-derived mesenchymal stem cells via modulating miRNA-dependent integrin α5 expression. *Cell Death Differ*. 2021;28(1):283-302. doi: 10.1038/s41418-020-0600-6
45. Tabatabaei Qomi R, Sheykhhasan M. Adipose-derived stromal cell in regenerative medicine: a review. *World J Stem Cells*. 2017;9(8):107-117. doi: 10.4252/wjsc.v9.i8.107
46. Betz VM, Kochanek S, Rammelt S, et al. Recent advances in gene-enhanced bone tissue engineering. *J Gene Med*. 2018;20(6):e3018. doi: 10.1002/jgm.3018
47. Kristensen LS, Okholm TLH, Venø MT, Kjems J. Circular RNAs are abundantly expressed and upregulated during human epidermal stem cell differentiation. *RNA Biol*. 2018;15(2):280-291. doi: 10.1080/15476286.2017.1409931
48. Ashwal-Fluss R, Meyer M, Pamudurti NR, et al. circRNA biogenesis competes with pre-mRNA splicing. *Mol Cell*. 2014;56(1):55-66. doi: 10.1016/j.molcel.2014.08.019
49. Liu Y, Ma Y, Zhang J, et al. MBG-modified β-TCP scaffold promotes mesenchymal stem cells adhesion and osteogenic differentiation via a FAK/MAPK signaling pathway. *ACS Appl Mater Interfaces*. 2017;9(36):30283- 30296. doi: 10.1021/acsami.7b02466

50. Bordakov VN, Derkachev VS, Rudenok VV, et at. Tissue engineering in the treatment of long bone defects. *Surgery. Eastern Europe*. 2018;7(1): 67-73. (in Russ.)
51. Ostrovidov S, Salehi S, Costantini M, et al. 3D Bioprinting in Skeletal Muscle Tissue Engineering. *Small*. 2019;15(24):e1805530. doi: 10.1002/smll.201805530
52. Wang Q, Cheng H., Peng H, et al. Non-genetic engineering of cells for drug delivery and cell-based therapy. *Adv Drug Deliv Rev*. 2015;91:125-140. doi: 10.1016/j.addr.2014.12.003
53. Liao W, Ning Y, Xu HJ, et al. BMSC-derived exosomes carrying microRNA-122-5p promote proliferation of osteoblasts in osteonecrosis of the femoral head. *Clin Sci* (Lond). 2019;133(18):1955-1975. doi: 10.1042/CS20181064
54. Liu L, Liu Y, Feng C, et al. Lithium-containing biomaterials stimulate bone marrow stromal cell-derived exosomal miR-130a secretion to promote angiogenesis. *Biomaterials*. 2019;192:523-536. doi: 10.1016/j.biomaterials.2018.11.007
55. Maiborodin IV, Shevela AA, Marchukov SV, et al. Regeneration of a bone defect under conditions of experimental use of extracellular microvesicles of multipotent stromal cells. *News of Surgery*. 2020;28(4):359-369. (in Russ.) doi: 10.18484/2305-0047.2020.4.359
56. Shevela AA, Shevela AI, Matveeva VA, et al. Exosomes of multipotent stromal cells and experimental osseointegration of dental implants. *Materials of the II International Scientific and Practical Conference*. 2020;2:41-55. (in Russ.)
57. Minutti CM, Knipper JA, Allen JE, Zaiss DM. Tissue-specific contribution of macrophages to wound healing. *Semin Cell Dev Biol*. 2017;61:3-11. doi: 10.1016/j.semcdb.2016.08.006
58. Murray PJ. Macrophage Polarization. Annu Rev Physiol. 2017;79:541-566. doi: 10.1146/annurev-physiol-022516-034339
59. Kang M, Huang CC, Lu Y, et al. Bone regeneration is mediated by macrophage extracellular vesicles. *Bone*. 2020;141:115627. doi: 10.1016/j.bone.2020.115627
60. Loi F, Córdova LA, Zhang R, et al. The effects of immunomodulation by macrophage subsets on osteogenesis in vitro. *Stem Cell Res Ther*. 2016;7:15. doi: 10.1186/s13287-016-0276-5
61. Miron RJ, Bosshardt DD. OsteoMacs: Key players around bone biomaterials. *Biomaterials*. 2016;82:1-19. doi: 10.1016/j.biomaterials.2015.12.017
62. Tkach M, Théry C. Communication by Extracellular Vesicles: Where We Are and Where We Need to Go. *Cell*. 2016;164(6):1226-1232. doi: 10.1016/j.cell.2016.01.043
63. Kalluri R, LeBleu VS. The biology, function, and biomedical applications of exosomes. *Science*. 2020;367(6478):eaau6977. doi: 10.1126/science.aau6977
64. Barile L, Vassalli G. Exosomes: Therapy delivery tools and biomarkers of diseases. *Pharmacol Ther*. 2017;174:63-78. doi: 10.1016/j.pharmthera.2017.02.020
65. Nathan K, Lu LY, Lin T, et al. Precise immunomodulation of the M1 to M2 macrophage transition enhances mesenchymal stem cell osteogenesis and differs by sex. *Bone Joint Res*. 2019;8(10):481-488. doi: 10.1302/2046-3758.810.BJR-2018-0231.R2
66. Gong L, Zhao Y, Zhang Y, Ruan Z. The Macrophage Polarization Regulates MSC Osteoblast Differentiation in vitro. *Ann Clin Lab Sci*. 2016;46(1):65-71.
67. Cappariello A, Loftus A, Muraca M, et al. Osteoblast-Derived Extracellular Vesicles Are Biological Tools for the Delivery of Active Molecules to Bone. *J Bone Miner Res*. 2018;33(3):517-533. doi: 10.1002/jbmr.3332
68. Huang CC, Kang M, Lu Y, et al. Functionally engineered extracellular vesicles improve bone regeneration. *Acta Biomater*. 2020;109:182-194. doi: 10.1016/j.actbio.2020.04.017
69. Curtale G, Rubino M, Locati M. MicroRNAs as Molecular Switches in Macrophage Activation. *Front Immunol*. 2019;10:799. doi: 10.3389/fimmu.2019.00799
70. Wang X, Ao J, Lu H, et al. Osteoimmune Modulation and Guided Osteogenesis Promoted by Barrier Membranes Incorporated with S-Nitrosoglutathione (GSNO) and Mesenchymal Stem Cell-Derived Exosomes. *Int J Nanomedicine*. 2020;15:3483-3496. doi: 10.2147/IJN.S248741
71. Shahrezaee M, Salehi M, Keshtkari S, et al. In vitro and in vivo investigation of PLA/PCL scaffold coated with metformin-loaded gelatin nanocarriers in regeneration of critical-sized bone defects. *Nanomedicine*. 2018;14(7):2061-2073. doi: 10.1016/j.nano.2018.06.007
72. Corpas FJ, Alché JD, Barroso JB. Current overview of S-nitrosoglutathione (GSNO) in higher plants. *Front Plant Sci*. 2013;4:126. doi: 10.3389/fpls.2013.00126
73. Stegen S, Carmeliet G. The skeletal vascular system – Breathing life into bone tissue. *Bone*. 2018;115:50-58. doi: 10.1016/j.bone.2017.08.022
74. Huang Z, He Y, Chang X, et al. A magnetic iron oxide/polydopamine coating can improve osteogenesis of 3D-printed porous titanium scaffolds with a static magnetic field by upregulating the TGFβ-Smads pathway. *Adv Healthc Mater*. 2020;9(14):e2000318. doi: 10.1002/adhm.202000318
75. Takeuchi R, Katagiri W, Endo S, Kobayashi T. Exosomes from conditioned media of bone marrow-derived mesenchymal stem cells promote bone regeneration by enhancing angiogenesis. *PLoS One*. 2019;14(11):e0225472. doi: 10.1371/journal.pone.0225472
76. He Y, Yu L, Liu J, et al. Enhanced osteogenic differentiation of human bone-derived mesenchymal stem cells in 3-dimensional printed porous titanium scaffolds by static magnetic field through up-regulating Smad4. *FASEB J*. 2019;33(5):6069-6081. doi: 10.1096/fj.201802195R
77. Kim EC, Leesungbok R, Lee SW, et al. Effects of static magnetic fields on bone regeneration of implants in the rabbit: micro-CT, histologic, microarray, and real-time PCR analyses. *Clin Oral Implants Res*. 2017;28(4):396-405. doi: 10.1111/clr.12812
78. Lee JR, Park BW, Kim J, et al. Nanovesicles derived from iron oxide nanoparticles-incorporated mesenchymal stem cells for cardiac repair. *Sci Adv*. 2020;6(18):eaaz0952. doi: 10.1126/sciadv.aaz0952

79. Zhu Y, Li Z, Zhang Y, et al. The essential role of osteoclast-derived exosomes in magnetic nanoparticle-infiltrated hydroxyapatite scaffold modulated osteoblast proliferation in an osteoporosis model. *Nanoscale*. 2020;12(16):8720-8726. doi: 10.1039/d0nr00867b
80. Kim HY, Kim TJ, Kang L, et al. Mesenchymal stem cell-derived magnetic extracellular nanovesicles for targeting and treatment of ischemic stroke. *Biomaterials*. 2020;243:119942. doi: 0.1016/j.biomaterials.2020.119942
81. Wu D, Kang L, Tian J, et al. Exosomes derived from bone mesenchymal stem cells with the stimulation of Fe_3O_4 nanoparticles and static magnetic field enhance wound healing through upregulated miR-21-5p. *Int J Nanomedicine*. 2020;15:7979-7993. doi: 10.2147/IJN.S275650
82. Okada M, Yamawaki H. A current perspective of canstatin, a fragment of type IV collagen alpha 2 chain. *J Pharmacol Sci*. 2019;139(2):59-64. doi: 10.1016/j.jphs.2018.12.001

The article was submitted 18.01.2023; approved after reviewing 21.03.2023; accepted for publication 01.12.2023.

Information about the authors:

Anastasiya I. Greben – Resident, aik-nastya@mail.ru, https://orcid.org/0000-0002-2423-523X, aik-nastya@mail.ru;

Petr S. Eremin – Researcher, ereminps@gmail.com, https://orcid.org/0000-0001-8832-8470;

Elena Yu. Kostromina – Candidate of Medical Sciences, Senior Researcher, bioimed07@hotmail.com, https://orcid.org/0000-0002-9728-7938;

Pavel A. Markov – Candidate of Biological Sciences, Senior Researcher, p.a.markov@mail.ru, https://orcid.org/0000-0002-4803-4803;

Ilmira R. Gilmutdinova – Candidate of Medical Science, Head of the Department, gilm.ilmira@mail.ru, https://orcid.org/0000-0001-6743-2615.

Contribution of the authors:

Greben A.I. – review of publications on the topic of the article, analysis and interpretation of data, writing and scientific editing of the text of the article, review of critical content.

Eremin P.S., Kostromina E.Yu., Markov P.A. – writing and scientific editing of the article text, checking the critical content.

Gilmutdinova I.R. – review of critical content, approval of the article for publication.

Review article
https://doi.org/10.18019/1028-4427-2024-30-1-134-141

Failed distractional bone regeneration as a complication of distraction osteosynthesis: risk factors, preventive diagnosis, treatment

K.I. Novikov[1,2]✉, E.V. Klintsov[1], O.V. Klimov[1], K.S. Sergeev[2]

[1] Ilizarov National Medical Research Centre for Traumatology and Orthopedics, Kurgan, Russian Federation
[2] Tyumen State Medical University, Tyumen, Russian Federation

Corresponding author: Konstantin I. Novikov, kinovikov@mail.ru

Abstract

Introduction Despite the large number of articles on complications associated with surgical lengthening, information about such a complication of transosseous distraction osteosynthesis as failed bone regenerate (called hypoplastic in foreign literature) is extremely rare. There are no methods for predicting the restructuring of the regenerate and clinical recommendations for the management of patients at various stages of reconstruction of the distraction regenerate. This entails a long period of immobilization and severe complications.

The objective of the work was to define the notion of inadequate ("ischemic"/hypoplastic) bone regeneration and the problem of its formation as a complication during surgical limb lengthening

Material and methods The PubMed database and the eLIBRARY scientific electronic library were used to select sources for a systematic literature review. The sources published between 1997 and 2020 were selected

Results and discussion Ineffective distraction bone regenerate is a complication of surgical segment lengthening with the shape and/or structure of the newly formed bone preventing functional load on the segment. There is a general tendency with bone elongations being greater than 15-20 % to significantly reduce biomechanical properties of the distractional regenerate bone. Patients' age at surgical lengthening is not reported as a risk factor for distraction regenerate fractures and a history of adverse events and complications is regarded as an additional risk factor. Inadequate (unstable) distraction regenerate bone includes morphotypes III-V and structural types 1, 5, 7 as classified by Ru Li. There are no clinical guidelines for operational strategy. Failed distraction bone regeneration as a complication of distraction osteosynthesis was reported by different authors between 1997 and 2020. There are conflicting statistically unreliable data regarding a risk for regenerate bone to develop into a less stable type. The surgical options presented have no statistical significance (occasional case reports) and do not describe all possible clinical scenarios.

Conclusion The problem of failed distraction regeneration and impaired organotypic restructuring remains one of the most important problems in limb lengthening. Inadequate formation and restructuring of newly formed bone can be caused by many factors including anatomical, physiological and technological aspects that would require further comprehensive study.

Keywords: hypoplastic/ischemic/atrophic distractional regenerate bone, complications of distraction osteosynthesis, classification of distraction regenerate bone

For citation: Novikov KI, Klintsov EV, Klimov OV, Sergeev KS. Failed distractional bone regeneration as a complication of distraction osteosynthesis: risk factors, preventive diagnosis, treatment. *Genij Ortopedii*. 2024;30(1):134-141. doi: 10.18019/1028-4427-2024-30-1-134-141

INTRODUCTION

There are no statistical data on the number of limb lengthening surgeries performed worldwide due to the lack of the national healthcare reports with no possibility to authenticate the information. With a large number of articles and reports on complications associated with surgical limb lengthening there is a paucity of publications reporting failed bone regeneration, called hypoplastic in foreign literature, as a complication of transosseous distraction osteosynthesis (1-4.8 % of all surgical limb lengthening cases). There is no clear definition of the adverse event which cannot be prevented due to the lack of methods for predicting the restructuring of the regenerate bone into an unstable type. There are no recommendations for management of patients at various stages of reconstruction of the distraction bone regeneration to be followed by a long period of immobilization and severe complications (muscle atrophy, joint contracture, severe decrease in the mobility and quality of life, mental health adverse effect).

The objective was to define the notion of inadequate ("ischemic"/hypoplastic) regenerate bone and explore the phenomenon as a complication of surgical limb lengthening based on literature data.

MATERIAL AND METHODS

An internet search of eLIBRARY and PubMed databases using the search terms: bone regenerate complications during lengthening, ischemic regenerate bone, classification of distraction bone regeneration, treatment of ischemic bone regenerate, fractures after bone lengthening was performed.

Exclusions included publications reporting maxillofacial surgery (mandibular lengthening, maxillar bone correction), animal experiments, lengthening of short cancellous bones, case/control reports and paid content.

Overall, 1207 contributions were identified including 808 with eLIBRARY and 399 with PubMed. 37 sources were selected, including 5 patents.

RESULTS

Definition of the term

The definition of ischemic distraction regenerate in their study was given by D. Borzunov et al. [1]. The authors used the radiological classification offered by R. Li to evaluate hypoplastic types of distraction regenerate [2]. This classification includes five callus shapes of distraction osteogenesis:

– Fusiform (the regenerate is wider than the original bone);

– Cylindrical (the regenerate is the same width as the original bone);

– Concave (the regenerate tends to produce an hourglass appearance);

– Lateral (the regenerate show a callus defect);

– Central (the regenerate is a thin pillar in the central portion).

According to the authors, types 3 and 5 can be classified as "ischemic" distraction regenerate formed as a hypoplastic type. Type 4 (with the formation of a marginal defect and a hypoplastic bone formation) cannot be classified as an "ischemic" regenerate. It is usually associated with an impaired integrity of the bone due to the osteotomy. The authors differentiate between "ischemic" regenerate and "hypoplastic" regenerate based on the following characteristics: a) the connective tissue area prevailing over the osseous area of the regenerate; b) the the original bone area prevailing over the regenerate area; c) no tendency to increasing the length and area of bone sections (according to radiological investigations in dynamics); d) formation of endplates at the ends of the osseous regenerate parts with signs of nonunion (like an atrophic nonunion); e) disparity between organotypical restructuring of the regenerate and bone fixation length in combination with

maintained pathological mobility observed with clinical testing; f) formation of a soft tissue defect in the projection of the "ischemic" regenerate. In the treatment of patients with this pathology. The authors suggested osteotomy to be produced in the proximal and distal original bone to be followed by compression and compaction [1].

F. Schiedel et al. reported 67 patients (101 cases of femoral lengthening) with 11 developing unstable regenerate between 2008 and 2010. The authors reported no cases where intramedullary reinforcement could not be used. The appearance of the regenerate using the Li classification scheme was not a predictive value for the probability of a fracture after frame removal. The authors classified morphotypes 4 and 5 and structural types 1-4 of the regenerate as "unstable" types [3]. J. Kenwright et al. classified fractures after surgical lengthening of the segment and identified 4 types: Ia, compression of the regenerate zone; Ib, fracture of the regenerate and displacement; II, fracture in the "base" of the regenerate; III, fracture of the parent bone proximally/distally off the regenerate zone; IV, fracture of the adjacent bone segment [4].

Preventive diagnosis and risk factors

In 2003, G.V. Dyachkova et al. reported outcomes of 149 patients who underwent distraction osteosynthesis, and found that if the height of the radiolucent zone (connective tissue layer) was more than 20 % of the height of the diastasis, the reasons for that were to be identified and adjustments made during the distraction; if the diameter of the regenerate at the "growth radiolucent zone" was 20 % less than the diameter of the bone fragments, the reasons for that were to be identified and adjustments made to the elongation process due to the risk of an hourglass regenerate [5].

A.L. Shastov reported a history of repeated and unsuccessful surgical interventions, angioneurological disorders, cicatricial degeneration of soft tissues, traumatic disruption of bone integrity during osteotomy, inadequate distraction rate, lack of timely monitoring as risk factors of "ischemic" distraction regenerate [6].

The C-reactive protein level was practical for predicting poor regeneration during Ilizarov segment lengthening. The serum CRP of less than 6 mg/l in the first 10 days of distraction was a prognostic sign indicating high probability of poor regeneration [7].

Outcomes of lower limb lengthening in patients with systemic skeletal diseases and pathologically short stature showed that the rate of poor results increased with repeated segment lengthening in patients aged 14 years and older, in adults aged 20 years and older, with the length gain of more than 50 % of the initial segment length, with osteosynthesis index (OI) being less than 20 days/cm with the femur lengthened secondarily at the cross-lengthening stage, and in patients with Shereshevsky-Turner syndrome [8].

K.A. Dyachkov suggested that the regenerate "growth zone" should not exceed 23-33 % of the total regenerate area during the distraction period, otherwise it would result in complications in most cases [9].

White blood cells CD3++ and CD19++ more than 6.6 units and the serum immunoglobulin A of more than 3.3 would slow down fracture healing and transosseous distraction osteosynthesis with the Ilizarov healing [10].

K.N. Devmurari et al. explored radiographs of 28 cases of femoral lengthening by 30-55 % of the original length and reported callus fractures in 14 patients within 440-545 days of frame removal. No callus fracture was seen in segment lengthening of 30 %; the atypical shape of the callus and its optical properties corresponded to the parameters of the femur [11].

L. Zaka et al. reviewed outcomes of 19 patients who underwent lower limb lengthening with intramedullary nail. The mean age of the patients was 43 years with a mean distraction distance of 38.9 mm. There was no relationship between the effectiveness of distraction osteosynthesis and the patient's age [12].

In contrast, other authors [13] retrospectively studied 63 patients (aged 3 to 57 years) who had 74 distraction osteogenesis procedures between 2004 and 2009 using circular and monolateral external fixators. Adult age and bone healing index were the most important predictors of complications associated with the distraction regenerate restructuring into unstable types. The use of the cure index as such was uninformative. The index was calculated by dividing the number of days from the beginning of treatment to the patient's complete recovery by absolute or relative length gain (it can be calculated at the end of treatment, and not at the beginning or in the mid, and cannot be used for prediction). Another study [14] indicated 72 cases of segment elongation with 17 fractures observed in 25 patients and occurred in different morphotypes of the regenerate without distinct correlation with the relative segment elongation (from 39 to 66 %).

K.P. Venkatesh et al. [15] reviewed the results of 20 patients who underwent bilateral lengthening with a monolateral external fixator. The patients were divided into 2 groups: 12 patients had lengthening of less than 50 % of the original segment length and 8 of more than 50 % of the initial femoral length. All patients developed stable types of regenerate (70 % fusiform and 30 % cylindrical) in the initial phase of distraction. The regenerate transformed into a less stable type in 85 % of cases of the first group and in 62 % of the second group with 25 % of them restructured into unstable types during advanced distraction phases. The ratio maintained during the consolidation stage.

The regenerate was shown to restructure into a less stable type in all cases of elongation greater than 10 cm. The authors reported a correlation between the regenerate structure and the risk of fracture. Fractures were not associated with a "transparent" regenerate and cylindrical shape (types 4 and 8 as classified by R. Li's and is characterized by a radiological transparent layer in the projection of the growth zone of the regenerate). Li type III regenerate fractures were treated using re-osteosynthesis with an external fixation device; patients with regenerate types IV and V with external transosseous compression-distraction osteosynthesis added by bone grafting with no dynamics for more than 4 months of frame removal.

In 2012, F. Launaya et al. [16] reported retrospectively 111 cases of lower limb lengthening (40 femurs, 71 tibiae in patients aged 5 to 32 years) performed between 2000 and 2010 with a higher rate of femoral fractures compared to the tibia. Most of the fractures were classified as Simpson – Kenwright type II. The incidence of fractures was higher with the surgery performed for patients aged 9 years and younger and with distraction started earlier than 7 days of osteotomy. There was no statistical correlation between the beginning of lengthening and the patient's age.

N. Muzaffar et al. reported 15 cases of femoral lengthening in 15 patients aged 12 to 32 years with 3 "false" cylindrical regenerates and the volume (measured in pixels) risky because if diagnosis is untimely or inaction on the part of the attending physician, the biomechanical properties of the newly formed bone can be completely lost, and repeated surgical intervention would be required [17].

A review of 319 Ilizarov lengthening procedures was performed in 2013 to include patients aged 3 to 50 years and showed a strong relationship between the lengthening index (month/cm of lengthening) and the length of the regenerate (i.e., the greater the lengthening of the segment, the longer the fixation with the frame on). The lowest lengthening index was in younger patients. A significant difference in the lengthening index in different segments was also revealed (16 % less in the femur than in the tibia). The authors were unable to statistically prove longer periods for repeated segment lengthenings [18].

M. Kenawey et al. reported 37 cases of femoral lengthening using the ISKD system with poor regenerate noted in 8 cases (no description of the cases and the definition of the concept provided). Important risk factors were a distraction rate greater than 1.5 mm/day (9.1 times higher risk), age 30 years or older, smoking, and lengthening greater than 4 cm. [19].

In his work N.G. Burkel et al. [20] reported 178 cases of femoral lengthening in 108 patients and a 4.5 % incidence of distraction regenerate fractures. They found no statistically significant relationship between the incidence of fractures and the age of patients, gender, and time of surgery. Lengthening of greater than 5 cm were considered a statistically significant risk factor.

The bone and the structural components of the limb segment are involved in the process of limb lengthening, and the success of treatment depends on their condition. The muscles has an important role. T.I. Menshchikova [21] reported the use of ultrasound diagnosing the reserve capabilities of muscles (echo density) for the maximum lengthening gain without negative consequences.

Treatment options

Upbringing the distraction regenerate and stimulation of distraction osteosynthesis is emphasized by many authors.

S.S. Leonchuk et al. [22] reported an hourglass-shaped regenerate with a height of the middle layer of 10 mm or greater and low bone mineralization as indications for stimulation of osteogenesis. Mechanical stimulation was considered as a simple and most effective method (gradual or immediate compression of the regenerate by 7-10 mm with a certain force applied). The technique ensured compression of the bone regenerate with ischemic connective tissue stimulating angiogenesis. The method facilitated restoration of the regenerate integrity with the diameter and the mechanical strength increasing. The "rotational" compression of the distraction regenerate could be more effective. The bone was subjected to a dosed external rotation of 15-20º during gradual segment lengthening and correction of the limb axis with the apparatus, after 5-7 days of longitudinal-axial bone alignment. Rotation was produced at a rate of 2-3º/day. Biomechanical stimulation was performed using automatic high-frequency distraction. The "accordion maneuver" was used to stimulate osteogenesis by distraction by 0.25 mm in the morning to be followed by compression of 0.25 mm in the afternoon and distraction of 0.25 mm to be produced in the evening. Good results have been shown with use of bioactive implants (combined osteosynthesis using intramedullary wires coated with hydroxyapatite), hyperbaric oxygenation, local application of low-frequency pulsed ultrasound on the regenerate and electrical stimulation of the limb muscles.

A.L. Shastov reported compaction of the regenerate including an additional osteotomy, minimally invasive introduction of autologous bone chips and medullary components or paired fibula as methods of choice for treatment of an "ischemic" distraction regenerate [6].

A retrospective analysis performed by V.I.Shevtsov et al between 1976 and 2020 included 213 literature sources [23] and 564 patients featuring (1) the use of auto- and heteroplasty for bone defect repair; (2) fibular bone grafting to repair bone defects; (3) the use of artificial materials to repair bone defects; (4) application of tissue engineering and cellular technologies. The method developed by G.A. Ilizarov has been recognized as the most biological method for bone defect repair with the effectiveness of 97.7-100 % but it cannot be used for short bone fragments, the need of long-term treatment, limited in-hospital stay, for patients living far from medical centers, etc.).

V.D. Balayan et al. reviewed treatment outcomes of 120 patients aged 23 to 72 year. They were treated with revascularizing osteoperforation, X-shaped longitudinal osteotomy, bone grafting with auto- and allografts in combination with fixation of fragments with a bone fixator, external fixation device, intramedullary osteosynthesis with locking screws (BIOS) and intraosseous Fixion rod to stimulate reparative osteogenesis shortening the period of limb external fixation from 115 ± 12 days to 85 ± 12 days [24].

T.I. Dolganova et al. [25] reported ischemic distraction regenerate observed during polyfocal bone lengthening in patients with long bone defects (ultrasound examination) with distraction regenerates developing independently during sequential multi-level bone lengthening. An additional bone osteotomy and subsequent discrete bone transport can improve reparative processes at the site

of the “ischemic” distraction regenerate with the closure of the marginal defect with newly formed bone tissue and accelerated organotypic restructuring (the latter should be taken into account when choosing surgical treatment strategy).

Methods for stimulation of distraction regeneration that can be used for preventive and therapeutic purposes included a longitudinal split left along the posterior surface of the bone as a source of osteoinductive cells [26], HBOT to address vascular, neurological and biomechanical complications [27],platelet-rich plasma introduced into the distraction regenerate to prevent poor regeneration [28], gradual elongation with spiral longitudinal deflection of fragments to ensure formation of a good volumetric bone regenerate [29], accelerated distraction rate in the first 10 days after osteotomy and the slowdown 10 days before the end of distraction leading to bone regeneration being comparable with the maternal bone fragments [30].

J.J. Jauregui et al. [31] performed meta-analysis of 192 cases of segmental lengthening showing that the use of LIPUS (low-frequency ultrasound stimulation) and PEMF (pulsated electromagnetic field) reduced the HI (healing index) from 45.4 days/cm of lengthening to 33.7 days/cm.

In contrast, A.H.R.W. Simpson et al. [32] conducted a study (32 patients using stimulation with the LIPUS system and 30 placebo) showed no effect of ultrasound on distraction osteoneogenesis. Smoking increased the cure rate by 50 %.

H.I. Balci et al [33] reported the optimal distraction rate of 0.564 mm/day for good morphological quality callus based on the experience of twenty-seven patients with congenital pseudarthrosis of the tibia who underwent limb lengthening surgery between 1997 and 2016.

K.-W. Park et al. [34] reported a higher incidence of complications during femoral lengthening in 148 achondroplasia patients who underwent lower limb lengthening. Tibial lengthening had a significantly lower complication rate and a higher callus formation rate than femoral lengthening. The authors gave an example of the formation of a Li type V regenerate (treatment option included reinforcement with wires and use of an autograft from the iliac crest with a satisfactory result).

DISCUSSION

Ineffective distraction bone regenerate is a complication of surgical segment lengthening when the shape and/or structure of the newly formed bone does not allow functional load on the segment. The complication is a fracture after surgical segment lengthening (types III, IV complications according to Donnan). The reported incidence of fractures after surgical segment lengthening averages 2.9 % (1–4.8 %, with one study reporting a rate of 40 %) [35, 36]. A review of 11 series including 1065 segments of patients of different ages, with various nosologies, different lengthening values included 117 fractures and deformities at the regenerate level amounting for 10.99 % of which patients must be aware signing consent for surgical lengthening intervention.

The trends that can be observed in the majority of publications include: lengthening greater than 15-20 % is associated with higher complication rate (including failed distraction bone regenerate). Data regarding the performance situation are conflicting. In most articles, the age at which surgical lengthening is performed is not a risk for the development of an incompetent distraction regenerate; a history of problems and persistence during previous surgical lengthening of segments is an additional risk factor (the significance of the indicator of its underdevelopment). There are conflicting data regarding the effect of age on the incidence of complications. The age at which surgical lengthening is performed is not a risk factor for the development of a failed distraction regenerate; a history of adverse events during previous surgical segment lengthening is an additional risk factor (the significance is not indicated numerically).

The pathology can be treated surgically and conservatively (plaster/plastic bandage, osteosynthesis with a plate/TEN with/without grafting, bifocal osteosynthesis with an external fixation device).

No uniform recommendations for clinicians have been developed at the moment. Like other researchers, we suggest that R. Li's classification is the most practical grading system for assessing distraction regenerate to identify 5 morphotypes and 10 types of regenerate structure [37]. Most authors evaluate morphotypes III-V and structural types 1, 5, 7 as a failed distraction (unstable) regenerate (if these structures are identified on radiographs, measures should be taken to stimulate regeneration).

CONCLUSION

Failure of the distraction regenerate and impaired organotypic restructuring has been one of the most important problem of limb lengthening. Poor regeneration and restructuring of newly formed bone can be caused by anatomical, physiological and technological events that remain controversial and require further comprehensive study.

REFERENCES

1. Borzunov DY, Shastov AL. Mechanical solutions to salvage failed distraction osteogenesis in large bone defect management. *Int Orthop*. 2019;43(5):1051-1059. doi: 10.1007/s00264-018-4032-6
2. Li R, Saleh M, Yang L, Coulton L. Radiographic classification of osteogenesis during bone distraction. *J Orthop Res*. 2006;24(3):339-47. doi: 10.1002/jor.20026
3. Schiedel F, Elsner U, Gosheger G, et al. Prophylactic titanium elastic nailing (TEN) following femoral lengthening (Lengthening then rodding) with one or two nails reduces the risk for secondary interventions after regenerate fractures: a cohort study in monolateral vs. bilateral lengthening procedures. *BMC Musculoskelet Disord*. 2013;14:302. doi: 10.1186/1471-2474-14-302
4. Launay F, Younsi R, Pithioux M, et al. Fracture following lower limb lengthening in children: a series of 58 patients. *Orthop Traumatol Surg Res*. 2013;99(1):72-9. doi: 10.1016/j.otsr.2012.08.005
5. Diachkova GV, Mikhailov ES, Yerofeyev SA, et al. Qualitative and quantitative indices of roentgenological assessment of a distraction regenerate bone. *Genij Ortopedii*. 2003;(4):11-15. (In Russ.)
6. Shastov AL. *Optimization of recovery processes in patients with false joints and bone defects in conditions of impaired osteogenesis. Avtoref. Kand. Dis*. Kurgan, 2016:24. Available at: https://www.dissercat.com/content/optimizatsiya-vosstanovitelnykh-protsessov-u-patsientov-s-lozhnymi-sustavami-i-kostnymi-defe/read. Accessed Aug 22, 2023. (In Russ.)
7. Aranovich AM, Stogov MV, Tushina NV, Kireeva EA. C-reactive protein as a prognostic marker of distraction osteogene-sis disorders. Preliminary results. *Genij Ortopedii*. 2020;26(3):382-384. doi: 10.18019/1028-4427-2020-26-3-382-384
8. Shchukin AA, Aranovich AM, Popkov AV, Popkov DA. Evaluation of the results of lower limb lengthening in patients with systemic skeletal diseases accompanied by pathologically short stature. *Genij Ortopedii*. 2014;(2):44-51. (In Russ.)
9. Dyachkov KA. *X-ray diagnostics in identifying patterns of distraction regenerate formation and bone quality during limb lengthening. Autoref. Dokt. Dis*. Moscow; 2016:48. Available at: https://www.dissercat.com/content/luchevaya-diagnostika-v-vyyavlenii-zakonomernostei-formirovaniya-distraktsionnogo-regenerata/read. Accessed Aug 22, 2023. (In Russ.)
10. Berdyugina OV. *Immunological criteria for predicting bone remodeling in case of injury. Autoref. Dokt. Dis*. Chelyabinsk; 2008:50. Available at: https://www.dissercat.com/content/immunologicheskie-kriterii-prognoza-kostnogo-remodelirovaniya-pri-povrezhdenii. Accessed Aug 22, 2023. (In Russ.)
11. Devmurari KN, Song HR, Modi HN, et al. Callus features of regenerate fracture cases in femoral lengthening in achondroplasia. *Skeletal Radiol*. 2010 Sep;39(9):897-903. doi: 10.1007/s00256-009-0742-6
12. Zak L, Arnhold R, Tiefenboeck TM, Wozasek GE. The influence of advanced age in bone healing after intramedullary limb lengthening. *Orthop Traumatol Surg Res*. 2021;107(8):103055. doi: 10.1016/j.otsr.2021.103055
13. Liantis P, Mavrogenis AF, Stavropoulos NA, et al. Risk factors for and complications of distraction osteogenesis. *Eur J Orthop Surg Traumatol*. 2014;24(5):693-8. doi: 10.1007/s00590-013-1261-7
14. Kitoh H, Mishima K, Matsushita M, et al. Early and late fracture following extensive limb lengthening in patients with achondroplasia and hypochondroplasia. *Bone Joint J*. 2014;96-B(9):1269-1273. doi: 10.1302/0301-620X.96B9.33840
15. Venkatesh KP, Modi HN, Devmurari K, et al. Femoral lengthening in achondroplasia: magnitude of lengthening in relation to patterns of callus, stiffness of adjacent joints and fracture. *J Bone Joint Surg Br*. 2009;91(12):1612-7. doi: 10.1302/0301-620X.91B12.22418
16. Launay F, Younsi R, Pithioux M, et al. Fracture following lower limb lengthening in children: a series of 58 patients. *Orthop Traumatol Surg Res*. 2013;99(1):72-9. doi: 10.1016/j.otsr.2012.08.005
17. Muzaffar N, Hafeez A, Modi H, Song HR. Callus patterns in femoral lengthening over an intramedullary nail. *J Orthop Res*. 2011;29(7):1106-1113. doi: 10.1002/jor.21353

18. Koczewski P, Shadi M. Factors influencing bone regenerate healing in distraction osteogenesis. *Ortop Traumatol Rehabil*. 2013;15(6):591-9. doi: 10.5604/15093492.1091515
19. Kenawey M, Krettek C, Liodakis E, et al. Insufficient bone regenerate after intramedullary femoral lengthening: risk factors and classification system. *Clin Orthop Relat Res*. 2011;469(1):264-73. doi: 10.1007/s11999-010-1332-6
20. Burke NG, Cassar-Gheiti AJ, Tan J, et al. Regenerate bone fracture rate following femoral lengthening in paediatric patients. *J Child Orthop*. 2017;11(3):210-215. doi: 10.1302/1863-2548.11.160216
21. Menshchikova TI. *Structural and functional aspects in the rationale for surgical lengthening of the lower extremities. Autoref. Dokt. Dis*. Tyumen; 2007:48. Available at: https://earthpapers.net/preview/299350/a?#?page=1. Accessed Aug 22, 2023. (In Russ.)
22. Shevtsov VI, Leonchuk SS. Stimulation of Distraction Osteogenesis in Limb Lengthening: Our Concept. *Traumatology and Orthopedics of Russia*. 2021;27(1):75-85. (In Russ.) doi: 10.21823/2311-2905-2021-27-1-75-85
23. Shevtsov VI. Defects of long bones – a brief history of the development of technology of their compensation. *Ural Medical Journal*. 2022;21(2):43-46. (In Russ.) doi: 10.52420/2071-5943-2022-21-2-43-46
24. Balayan VD, Tishkov NV, Barabash YuA, Kauts OA. Surgical treatment of pseudoarthrosis of long cortical bones with use of additional osteogenesis focuses. *Siberian Medical Journal*. 2009;(7):73-75. (In Russ.)
25. Dolganova TI, Borzunov DYu, Menshchikova TI, Shastov AL. Evaluation of ischemic distraction regenerated bone for polylocal lengthening of fragments in patients with long bone defects (An ultrasound study). *Genij Ortopedii*. 2013;(2):62-66. (In Russ.)
26. Shevtsov VI, Novikov KI, Sklyar LV, Zykov AG. *Method for lengthening long tubular bones*. Patent RF no. 2281707, 2006. Available at: https://www.fips.ru/registers-doc-view/fips_servlet?DB=RUPAT&DocNumber=2281707&TypeFile=html. Accessed Aug 22, 2023. (In Russ.)
27. Novikov KI, Sazonova NV, Aranovich AM, Menshchikova TI. *Method for relief of complications in distraction limb lengthening*. Patent RF no. 2268669, 2006. Available at: https://www.fips.ru/registers-doc-view/fips_servlet?DB=RUPAT&DocNumber=2268669&TypeFile=html. Accessed Aug 22, 2023. (In Russ.)
28. Desyatnichenko KS, Larionov AA, Grebneva OL, et al. *A method for stimulating reparative osteogenesis*. Patent RF no. 2193868. 2002. Available at: https://www.fips.ru/registers-doc-view/fips_servlet?DB=RUPAT&DocNumber=2193868&TypeFile=html. Accessed Aug 22, 2023. (In Russ.)
29. Novikov KI. *A method for lengthening a tubular bone*. Patent RF no. 2271766. 2006. Available at: https://www.fips.ru/registers-doc-view/fips_servlet?DB=RUPAT&DocNumber=2271766&TypeFile=html. Accessed Aug 22, 2023. (In Russ.)
30. Shevtsov VI, Novikov KI, Sklyar LV, et al. *A method for lengthening a long tubular bone*. Patent RF no. 2182471. 2002. Available at: https://www.fips.ru/registers-doc-view/fips_servlet?DB=RUPAT&DocNumber=2182471&TypeFile=html. Accessed Aug 22, 2023. (In Russ.)
31. Jauregui JJ, Ventimiglia AV, Grieco PW, et al. Regenerate bone stimulation following limb lengthening: a meta-analysis. *BMC Musculoskelet Disord*. 2016 Sep 29;17(1):407. doi: 10.1186/s12891-016-1259-5
32. Simpson AH, Keenan G, Nayagam S, et al. Low-intensity pulsed ultrasound does not influence bone healing by distraction osteogenesis: a multicentre double-blind randomised control trial. *Bone Joint J*. 2017;99-B(4):494-502. doi: 10.1302/0301-620X.99B4.BJJ-2016-0559.R1
33. Balci Hİ, Bayram S, Pehlivanoglu T, et al. Effect of lengthening speed on the quality of callus and complications in patients with congenital pseudarthrosis of tibia. *Int Orthop*. 2021;45(6):1517-1522. doi: 10.1007/s00264-021-05011-7
34. Park KW, Garcia RA, Rejuso CA, et al. Limb Lengthening in Patients with Achondroplasia. *Yonsei Med J*. 2015;56(6):1656-62. doi: 10.3349/ymj.2015.56.6.1656
35. Frost MW, Kold S, Rahbek O, et al. Complications in Elective Removal of 271 Bone Lengthening Nails (FITBONE, PRECICE and STRYDE). *Strategies Trauma Limb Reconstr*. 2021;16(2):110-115. doi: 10.5005/jp-journals-10080-1529
36. El-Sayed M., Correll J., Hosny G.A., et al. Bone regenerate complications during lengthening: incidence, predisposing factors, and treatmen. *European Orthopaedics and Traumatology*. 2015;6(4):445-449.
37. Borzunov DYu, Shastov AL. „Ischemic" Distraction Regenerate: Interpretation, Definition, Problems and Solutions. *Traumatology and Orthopedics of Russia*. 2019;25(1):68-76. (In Russ.) doi: 10.21823/2311-2905-2019-25-1-68-76

The article was submitted 22.12.2022; approved after reviewing 25.01.2023; accepted for publication 01.12.2023.

Information about the authors:

Konstantin I. Novikov – Doctor of Medical Sciences, Leading Researcher, kinovikov@mail.ru;

Egor V. Klintsov – graduate student, e.rubisco@mail.ru;

Oleg V. Klimov – Doctor of Medical Sciences, traumatologist-orthopedist;

Konstantin S. Sergeev – Doctor of Medical Sciences, Professor.

Review article
https://doi.org/10.18019/1028-4427-2024-30-1-142-152

Intramedullary osteosynthesis for ankle fractures and distal tibiofibular syndesmotic disruption

F.A. Gafurov[1], I.Yu. Khodzhanov[2], D.Sh. Mansurov[1]✉, Sh.N. Eranov[1]

[1] Samarkand State Medical University, Samarkand, Republic of Uzbekistan
[2] Republican Specialized Scientific-Practical Medical Center of Traumatology and Orthopedics, Tashkent, Republic of Uzbekistan

Corresponding author: Djalolidin Sh. Mansurov, jalolmedic511@gmail.com

Abstract

Introduction The optimal surgical approach for malleolar fractures and distal tibiofibular syndesmotic (DTFS) disruption remains controversial. There is no uniform treatment protocol for this type of injury.

The objective was to review modern surgical treatments of the pathology and determine the optimal option.

Material and methods Articles of French, English, Uzbek, Kazakh, German, Danish, Japanese and Chinese authors were retrospectively reviewed. An internet search of MedLine; PubMed; Scopus; Web of Science, CINAHL, the Cochrane Central Register of Controlled Trials databases was performed.

Results Comparative studies of dynamic fixation and static fixation of the DTFS showed advantages of the dynamic methods enabling precise, anatomical syndesmotic fixation and faster healing. Dynamic fixation methods would require no implant removal, while syndesmotic screw woul be taken off to reduce compression in the ankle joint and minimize a risk of malreduction facilitating mobility of the ankle joint. Dynamic methods are associated with greater stability and less complication rate. However, static methods have the advantages of being more accessible and less expensive, which can be an important factor choosing a treatment method. Static methods are a wide application and can be used in a wide range of clinical cases. Long-term results show no statistically significant differences between dynamic fixation and static fixation.

Discussion Literature review indicates the dynamic method with suture-button, a combined method and titanium cable isotonic annular fixation system as the preferred technique for surgical stabilization of distal syndesmosis associated with ankle fractures with a lower risk of postoperative complications and the possibility of short-term rehabilitation.

Conclusion The choice between dynamic and static methods of distal syndesmosis fixation depends on many factors, including the complexity of the injury, the availability and cost of implants and the experience of the surgeon.

Keywords: ankle fractures, tibiofibular syndesmosis disruption, dynamic fixation, static fixation, instability

For citation: Gafurov FA, Khodzhanov IYu, Mansurov DSh, Eranov ShN. Intramedullary osteosynthesis for ankle fractures and distal tibiofibular syndesmotic disruption. *Genij Ortopedii*. 2024;30(1):142-152. doi: 10.18019/1028-4427-2024-30-1-142-152

INTRODUCTION

Syndesmotic injuries occur during sporting activities, car accidents and other external effects. Once one has determined that syndesmotic injury will require surgical intervention, the surgeon needs to decide the most appropriate method of fixation. Syndesmotic fixation can be provided by bolts, wires, plates, wedges and other tools. Each method has advantages and disadvantages. Treatment would be dependent on the individual patient and injury characteristics. Safe and modern technologies are essential for improving the care of surgical patients. The distal tibia and fibula form the osseous part of the syndesmosis and are linked by the anterior tibiofibular ligament (ATIFL), the posterior tibiofibular ligament (PTIFL), transverse tibiofibular ligament (TTFL) and the interosseus ligament (Fig. 1) [1, 2].

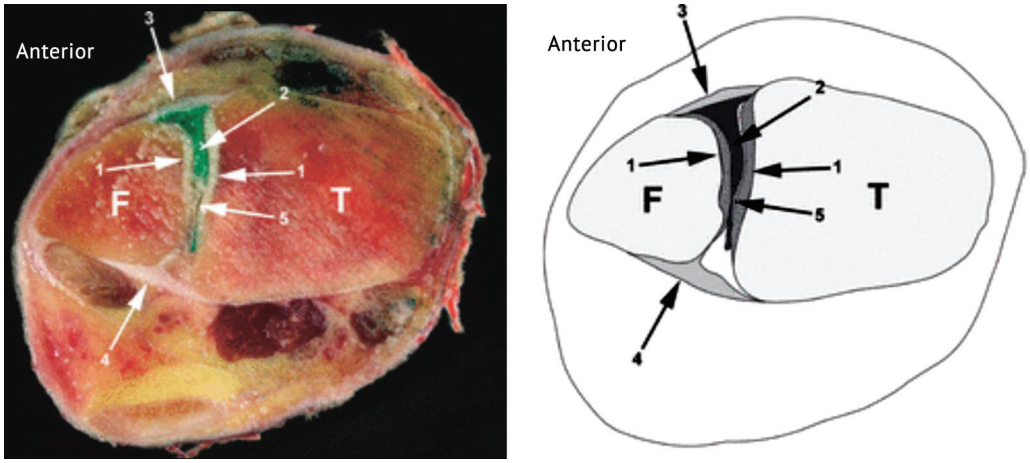

Fig. 1 Anatomical specimen and diagram of the distal tibiofibular syndesmosis: 1, cartilage; 2, syndesmotic recess; 3, anterior tibiofibular ligament; 4, posterior tibiofibular ligament; 5, interosseous ligament

Ankle fractures remain the third most common musculoskeletal injury and account for 5.5 to 7.4 % of all fractures seen in the trauma setting. Syndesmosis injuries account for 25 % of all ankle injuries and may result in significant functional impairment at a long term [3-8]. This applies to the Weber type C ankle fractures that often have an associated syndesmotic injury, the Weber type B ankle fractures that are usually caused by high energy injuries with syndesmosis involved in 37 % of cases [9-14]. Ankle fracture is caused by traumas such as falls, traffic accidents and sports-related injuries. The most common mechanism of injury is falls (66.5 %), with more fractures seen at winter periods [15]. Complications associated with surgical treatment of ankle fractures can have a significant impact on the patient's quality of life. Complications may be temporary and permanent resulting in disability and limited range of motion. If poorly managed, this type of injury can lead to long-term complications such as chronic pain, instability and osteoarthritis of the ankle [16-20].

Jody Litrenta et al. reported a slightly detrimental effect on outcomes of operatively treated ankle fractures in patients of multicenter randomized trial [21]. Surgical intervention is needed in many cases to address an injury and restore the function of the affected joint, which is currently the priority treatment for the pathology [7, 22-24]. This article will review current surgical options for ankle fracture associated with distal syndesmosis injury or rupture and their effectiveness in achieving optimal outcomes. The risks and benefits associated with each approach and the postoperative recovery and rehabilitation process will be discussed. There have been many studies comparing different surgical options. In 2019, Alberto Grassi, Kristian Samuelsson, Annunziato Amendola performed a meta-analysis of studies comparing dynamic fixation and static fixation of acute syndesmosis injuries and reported the superiority of dynamic fixation over static methods [22].

In 2017, Pei Zhang et al. reported advantages of a suture-button device over syndesmotic screw fixation in treatment of distal tibiofibular syndesmotic injuries [25]. Zhaofeng Jia and Jiwu Cheng investigated the clinical effects of a new technique, titanium cable isotonic annular fixation which showed advantages over current treatments of distal tibiofibular syndesmosis injury [26]. With the knowledge of the latest advances in the surgical treatment of ankle fractures involving syndesmosis, patients and healthcare providers can make informed decisions about the most appropriate strategy in a particular case, which is the purpose of this article.

The objective was to review modern surgical treatments of ankle fractures and distal tibiofibular syndesmotic disruption and determine the optimal option.

MATERIAL ANFD METHODS

Search strategy

An internet search of MedLine; PubMed; Scopus; Web of Science, CINAHL, the Cochrane Central Register of Controlled Trials databases was performed using the search terms “ankle fractures”, “rupture – injury to the distal syndesmosis”, “ankle fracture”, “syndesmosis injury”, “syndesmosis fixation”. All stages of selecting material for the article, including literature search, data extraction and quality assessment, were produced by the authors of the literature review, without additional funding or attraction of specialists who are supporters of a particular method of treatment. We also examined references to publications included in peer-reviewed articles, opinions of individual experts, and literature in the field of traumatology. The final search was performed on March 2, 2023.

Analysis and selection of information sources

Single cases of treatment, reports or abstracts were excluded. The search was carried out by each author independently, independently of other participants. The selection of suitable material was carried out through meetings of the authors, by discussing each source and voting for inclusion. In addition, the review included German and Danish studies presented in full text on the topic, including information on statistics and mechanisms of injury. Preference was given to large systematic reviews, randomized clinical trials with a high level of evidence (level 1-3 of the Oxford CEBM level of evidence)

Data collection and study quality assessment

All data were collected by reviewers according to uniform criteria. The study protocol (authors, titles, journals, years, type of studies, study protocol) was documented and the level of evidence considered. Statistical data were found in various regions and taken into account, including patient groups, number of patients, gender and age. Data on timing from injury to treatment, the time spent on surgery, Weber type of fracture, option of surgical fixation of the syndesmosis, long-term results and the number of postoperative complications which included surgical site infection, post-traumatic arthritis of the ankle joint, nonunion, limited range of motion and less common adverse events. The level of evidence was assessed based on the Oxford CEBM classification and the quality of the data. Almost all studies included functional monitoring using AOFAS, OMA, or ROM. The American Orthopedic Foot and Ankle Society (AOFAS) scale combines several patient-reported items concerning pain, function and alignment of the first ray. Each of the nine items is scored, accumulating to a total score ranging from 0 points (indicating severe pain and impairment) to 100 points (no symptoms or impairment).

The Olerud Molander ankle function score was used to evaluate the limb function after surgical treatment using a functional rating scale from 0 (totally impaired) to 100 (completely unimpaired).

The analysis included AOFAS and OMA scores measured at six months of surgery to 2 years. The range of motion of the ankle joint was highly individual for each person. Dorsiflexion, with the foot raising up, was approximately 20 degrees, and plantar flexion, with the foot coming down, was 30 degrees. This ROM was used as a reference for ankle kinematics. These measurements are important for assessment of ROM the range of motion in the affected joint, and a change is a marker of functional disorders of the ankle joint. A complication is defined as an adverse event associated with treatment that worsens treatment results or leads to the use of more complex protocols associated with a worse long-term prognosis and the use of more traumatic methods. An in-depth analysis of the literature resulted in the following data. The literature review included both articles examining various methods of surgical fixation of distal syndesmosis, and the comparative series. Next, the articles were carefully sorted into three groups, with the main sorting criterion being a type of surgical fixation of the distal syndesmosis. Open reduction and internal fixation (ORIF) using syndesmotic screws were reported in the articles on static fixation, ORIF using the suture-button was described in the studies on dynamic fixation, and ORIF in combination of syndesmotic screws and suture-buttons was reported in the articles on combined methods.

RESULTS

Thirty-seven contributions including meta-analyses, randomized controlled trials, cohort studies, which described surgical fixation of the distal tibiofibular joint and the comparison of long-term results, complications and mobility of the joint after a certain period of surgical treatment with the use of suture-button method (an example of dynamic fixation of the syndesmosis), the syndesmosis screw (an example of static fixation) and the combined method (using the syndesmosis screw and the suture-button method simultaneously). There are 3 main types of surgical fixation of the ankle joint. A syndesmotic screw is used for static fixation as a routine method of fixation of the distal syndesmosis. The suture button device using elastic materials offers dynamic fixation of the injured syndesmosis. A combined method has the advantages of both the static method and the dynamic techniques [25, 27-33]. The use of a syndesmotic screw is the gold standard for fixation of distal syndesmotic tears associated with ankle fractures.

All methods are used in traumatological practice and are safe but can be associated with complications, as with any surgical intervention, in the form of wound infections, implant failure, repeated surgical interventions, injury to the neurovascular bundles, chronic instability of the ankle joint, postoperative arthrosis and malreduction, which has a direct impact on the quality of life of patients, long-term results, and the extent of the ankle mobility [34-37]. The results of the studies showed differences in the incidence of complications between surgical treatment options. Static fixation was associated with the highest incidence of joint malreduction, implant failure and reoperation, and the highest incidence of non-anatomic syndesmotic fixation was characteristic of the dynamic group. The lowest rate of complications was observed in the group of combined methods due to syndesmosis fixation at the site of the anterior tibiofibular ligament and the posterior tibiofibular ligament reducing the risk of implant breakage and non-anatomical fusion, but increasing the risk of iatrogenic fracture [38-41].

Long-term results and kinematics of ankle joint movements

The findings showed that the three surgical techniques provided good functional results measured with the AOFAS score at 24 months or with physical examination of ankle ROM at a last follow-up, but there was a significant difference in duration of rehabilitation, where dynamic and combined methods of syndesmosis fixation showed advantages [28, 33, 34, 38]. In 2020, Neel K. Patel, Calvin Chan reported hybrid fixation as most appropriately restore tibiofibular kinematics for early

weightbearing, a lower risk of implant failure and a gap between the fibula and tibia, and limitations related to the age of the patients, bone density and severity of injury, which did not allow its use in routine practice, in older individuals, in particular [42]. N. Ramadanov et al. reported the difference in ankle ROM after static versus dynamic fixation describing a meta-analysis in greater detail. They found no statistically significant difference in dorsiflexion and plantar flexion during at 6 to 12 months of patient management [33].

Risk of re-operations associated with implant removal

Screw fixation of the distal syndesmosis sometimes requires reoperation in some cases to correct screw malposition, breakage, or nonunion. Reoperation may involve removing or repositioning the screw or applying a different type of fixation. The decision on a reoperation depends on the severity of the problem and the individual characteristics of the patient. Careful monitoring and follow-up is important to identify complications and ensure optimal outcome. Most non-specialized hospitals are experienced with routine removal of the syndesmotic screw, even in the absence of indications, which may be the reason for the low effectiveness of the technique in the period up to 6 months [43-47]. The studies showing comparison of button fixation and syndesmotic screws have demonstrated that static fixation methods often require removal of the metal construct due to the risk of implant breakage and decreased joint mobility, while dynamic methods do not require removal of the implant due to insignificant risk of device failure and its elasticity, low pressure at the site of the distal tibiofibular joint and the absence of significant limitation of the ankle mobility [25, 27-33].

Risk of joint malreduction

Ankle malreduction can occur in ankle fractures that involve syndesmosis and cause significant long-term complications such as chronic pain, instability, and early arthritis. Inadequate reduction may occur during fracture or during surgery. Proper reduction and alignment of the ankle joint is essential to maintain mobility. Imaging examination including radiography and computed tomography, can help diagnose and evaluate the extent of malreduction. Surgery may be required to address malreduction and realign the joint. Malreduction of the distal tibiofibular joint plays a role in the long-term results of surgical fixation; malreduction can increase the risk of repeated surgical interventions, development of instability of the distal tibiofibular joint reducing the quality of life of patients [48-50]. Although most studies have not shown a statistically significant superiority in the rate of malreduction of distal syndesmosis in the suture-button group, some systematic reviews and meta-analyses, a study performed by A. Grassi et al. in 2019, and a systematic review by K. Xu et al., conducted in 2021, showed that dynamic fixation is associated with a much lower risk of implant-related complications including malreduction [22, 29].

Risk of implant associated complications

Fixation of the distal syndesmosis with screws can be associated with implant-related complications including inadequate screw position and breakage causing persistent pain, instability and impaired ankle function. Implant-related complications are caused by malplaced screws or incompliance of the patient. Careful monitoring and surgical intervention are important to prevent complications and ensure optimal outcome. Numerous cohort studies, randomized clinical trials, and some meta-analyses have shown that dynamic ankle stabilization is associated with a lower risk of postoperative complications including implant failure, chronic instability, compression syndrome, bone irritation at the implant site, and infectious complications caused by slight compression at the fracture site improving blood supply which is very important for elderly patients [29, 33, 51].

Some meta-analyses, such as a systematic review conducted in 2019 by Alberto Grassi, Kristian Samuelsson showed no statistically significant advantage of dynamic methods with more complications seen in the group of static fixation [22].

Hybrid fixation of the ankle joint

There is a paucity of information on the topic. Hybrid fixation was reported in two articles of 2020 and 2021 [38, 42]. In 2020, Neel K. Patel and Calvin Chan reported lower risk of lateral translation in plantar flexion with postoperative results being comparable to the intact joint [42]. In 2021, hybrid fixation was reported to show a high accuracy of reduction, a low rate of diastasis, and favorable clinical outcomes in Weber type C fractures with syndesmosis injury [38]. Numan Mercan, Ahmet Yıldırım reported at least 15 % lower stress at the implant area with use of hybrid fixation as compared to other methods due to the the load distributed between the two independent fixation systems [52].

New Surgical Treatments for Ankle Instability

Over the years, surgical techniques for distal syndesmosis fixation have been improved, leading to improved results and fewer complications. A new technique employes taut cable bracing using a synthetic ligament to stabilize the ankle joint. This technique has shown promising results with good functional outcomes and lower complication rate compared with traditional screw fixation. The use of 3D printed implants can be practical for distal syndesmosis fixation. These implants are custom-made to fit each patient's unique anatomy, resulting in improved stability and a reduced risk of implant-related complications. Zhaofeng Jia, Jiwu Cheng, Haiyan Zhong developed a new technique using isotonic annular fixation. This technique has no disadvantages, unlike the suture-button and screw methods, and can restore the normal kinetics of the joint and resistance to load in the joint area. The technique is associated with a lower risk of implant failure, does not require routine removal, and allows the use of loading methods of rehabilitation early in the postoperative period [26]. In general, the study allowed us to conclude that the three surgical techniques are effective in the treatment of ankle fractures with injury to the syndesmosis, but each technique has advantages associated with the specific surgical method, type of implant, and disadvantages due to the characteristics of complications, long-term results and indications for use. Dynamic and hybrid methods of syndesmosis fixation are more practical in terms of rehabilitation and early weight-bearing on the limb. The static fixation is the method of choice for elderly patients with a lower risk of chronic joint instability, no need for rehabilitation and early loading on the joint, and no difference in the long-term period. Hybrid fixation is appropriate for younger patients with the possibility of early rehabilitation and early recovery of working capacity. Innovative methods can be considered for surgical fixation which may become new standards for the treatment of the pathology. Surgeons must carefully consider the patient's individual needs and extent of injury selecting a most appropriate surgical technique.

DISCUSSION

Comparison of different surgical treatments of ankle fractures with syndesmotic injuries is essential, as the selection of a most appropriate surgical technique can have a significant impact on patient outcomes. Comparisons in the series included open reduction and internal fixation (ORIF) using screws, ORIF with suture button fixation, and ORIF with a combination of screws and suture button fixation. New techniques that are not routinely used in everyday practice were also discussed. Surgical treatments of ankle fractures were presented in many studies. The button-suture method and the syndesmotic screw fixation were presented in a meta-analysis reported by Keteng Xu,

Jiale Zhang in 2020. Although the authors reported no statistically significant differences in radiological findings and clinical parameters with use of the methods at a long term however, the suture-button method was associated with a lower risk of bone damage at the implant site, implant failure and a decreased risk of malreduction. In addition to that, the duration of the rehabilitation period was shorter in the suture-button group [29]. Similar results were obtained in a meta-analysis performed by Nikolai Ramadanov, Simon Bueschges, Dobromir Dimitrov who also compared the button-suture method and the syndesmotic screw fixation of the ankle fracture with more detail to rehabilitation and risks of postoperative complications. The American Orthopedic Foot and Ankle Society score was identical in the groups at 6 months with long-term results being superior in the suture-button at 12 months but ultimately there was no significant difference in the outcomes at 24-month follow-up. Analysis of postoperative complications showed reduced risk of implant failure, bone damage at the site of implantation, joint malreduction and repeated operations with the use of the suture-button showing advantages of dynamic methods of syndesmosis fixation [33].

In 2019, Xiao Fan and Peng Zheng examined long-term outcomes and complications in a meta-analysis and reported no statistically significant difference in postoperative complications or long-term outcomes. The frequency of syndesmotic screw removal was the only significant difference [32]. In 2019, Alberto Grassi, Kristian Samuelsson reported significant evidence of a risk of complications reduced by 24 % compared to static fixation methods, the risk of implant-associated complications reduced by 25 %, higher AOFAS scores at a long term, greater ROM in the joint and effectiveness of early rehabilitation [22]. No significant difference in long-term results was reported in a systematic review performed by Pei Zhang, Yuan Liang in 2017 with advantages of the dynamic fixation observed in reducing the risk of postoperative complications, low cost, and low risk of malreduction of the syndesmosis, with no need to remove hardware [25]. In 2022, Jan Niklas Altmeppen, Christian Colcuc, et al. performed a prospective study and examined the results of surgical fixation of the distal syndesmosis over 10 years at a single clinic. The study showed no differences in the long-term results with various fixation methods and in the period of working rehabilitation did not differ and measured 10 weeks, regardless of the type of surgical treatment [27].

There are many studies reporting the need of the distal syndesmosis fixation and routine placement of metal constructs. In 2015, Jody Litrenta, David Saper and Paul Tornetta examined the effect of distal syndesmosis injury on long-term outcomes. They found that although the outcomes of patients without damage to the syndesmosis were better than those in the group with injury to the distal tibiofibular joint, the difference was slightly higher than the statistical threshold [21]. In 2021, Nuno Corte-Real, João Caetano reported the distal syndesmosis playing the major role in the ankle stabilization [16], the authors also confirmed The role of the distal syndesmosis fixation was reported in a retrospective cohort study performed in 2022, reducing the risk of chronic instability and rehabilitation period [53]. May Fong Mak, Richard Stern reported the use of an anatomical approach in restoration of the distal tibiofibular joint and showed promising results as compared with intraosseous fixation methods [28]. In 2020, FA Gafurov reported the need of surgical fixation of the distal syndesmosis is necessary [54].

The effectiveness of early postoperative weight-bearing on the involved joint is debatable. Ramy Khojaly, Fiachra E Rowan performed meta-analysis in 2022 and reported good functional outcome of early weight-bearing at 6 weeks with insignificant results observed at 6 and at 12 months of surgery [55]. Kiera A Kingston, Ye Lin produced a retrospective study in 2023 and reported the quality of life of patients with chronic ankle instability improved by more than 70 % [56]. VA Selivanov, MO Zhumagulov used an arthroscopic method for restoring syndesmosis with the

posterior inferior tibiofibular ligament being intact; the method provided the possibility of early weight-bearing on the joint and a lower risk of complications [57]. Although a study conducted by Sai-Kit Lim, Yui-Chung Ho in 2021 showed worse long-term results of ligament restoration as compared to routine fixation of the distal articulation using various methods of surgical correction for its instability [58].

Methods of the distal syndesmosis fixation have been developing with every decade, and isotonic annular fixation devised by Zhaofeng Jia, Jiwu Cheng, Haiyan Zhong is one of the methods. The results with the method are similar to those with hybrid fixation due to easy performance being associated with a lower risk of postoperative complications as compared to other surgical treatments of ankle instability [26]. Using only one surgical strategy as a priority in the treatment of this pathology would be a wrong decision. The use of each technique can be significantly limited considering the mechanism of injury, the time period with the greater risk of occurrence of this pathology, as well as associated factors, such as the Weber type of fracture, body mass index, age, the presence of osteoporosis.

The choice of surgical technique should rely on several factors, including the severity of the injury, the patient's age and the surgeon's experience and preference. For example, younger patients with more severe injuries may benefit from ORIF combined with screws and button suture, and older patients with less severe injuries may benefit from ORIF using screws alone. A combined technique using a syndesmotic screw and suture-button can be practical for athletes who can initiate early rehabilitation. A relatively small sample size of the data and its relatively low quality are one of the limitations of the study, which may confine generalizability of the findings. Studies with levels of evidence 1-3, with larger cohort of patients and longer follow-up are needed to confirm these results.

In conclusion, the choice of surgical technique for ankle fractures with syndesmotic injury should be individualized based on the patient's needs and the extent of injury. The three surgical techniques compared in the study are effective in achieving good functional results, but each technique has advantages and disadvantages in terms of complication rates. Surgeons must carefully consider these factors when selecting the most appropriate surgical technique.

CONCLUSION

Surgical treatment of distal syndesmotic tears associated with ankle fractures is a complex and multi-staged process that requires selection of the most optimal fixation. Various methods of static fixation using screws and plates and new approaches of dynamic fixation are employed for the surgery. Dynamic fixation uses flexible devices that allow a degree of movement and flexibility during the healing process, as opposed to static fixation, which immobilizes the joint with rigid devices. Dynamic fixation is beneficial in maintaining normal range of motion during the healing process, which can improve functional outcomes and reduce the risk of postoperative stiffness and pain. It may also reduce the risk of postoperative complications including screw breakage or loosening, joint space widening or joint instability during healing. However, dynamic fixation cannot be applied for all patients. The choice of fixation method depends on the severity and location of the fracture, individual characteristics and preferences of the patient. Careful evaluation of each case and the choice of the most optimal fixation are essential. Overall, dynamic fixation and hybrid fixation represent a promising approach to the treatment of distal syndesmotic tears that may improve patient outcomes and reduce complications. More research is needed to evaluate the effectiveness and safety of these methods.

Conflict of interest *The authors declare no conflict of interest.*

Funding *The study was conducted without sponsorship.*

Ethical review *Not applicable.*

Informed consent *Not applicable.*

REFERENCES

1. Hermans JJ, Beumer A, de Jong TA, Kleinrensink GJ. Anatomy of the distal tibiofibular syndesmosis in adults: a pictorial essay with a multimodality approach. *J Anat*. 2010;217(6):633-645. doi: 10.1111/j.1469-7580.2010.01302.x
2. Yammine K, Jalloul M, Assi C. Distal tibiofibular syndesmosis: A meta-analysis of cadaveric studies. *Morphologie*. 2022;106(355):241-251. doi: 10.1016/j.morpho.2021.10.004
3. Bilge O, Dündar ZD, Atılgan N, et al. The epidemiology of adult fractures according to the AO/OTA fracture classification. *Ulus Travma Acil Cerrahi Derg*. 2022;28(2):209-216. doi: 10.14744/tjtes.2020.26374
4. van Zuuren WJ, Schepers T, Beumer A, Sierevelt I, van Noort A, van den Bekerom MPJ. Acute syndesmotic instability in ankle fractures: A review. *Foot Ankle Surg*. 2017;23(3):135-141. doi: 10.1016/j.fas.2016.04.001
5. Zhang YW, Rui YF. A systematic review of the "Logsplitter" injury: how much do we know? *Injury*. 2021;52(3):358-365. doi: 10.1016/j.injury.2020.11.043
6. Ibrahim IO, Velasco BT, Ye MY, et al. Syndesmotic screw breakage may be more problematic than previously reported: increased rates of hardware removal secondary to pain with Intraosseous screw breakage. *Foot Ankle Spec*. 2022;15(1):27-35. doi: 10.1177/1938640020932049
7. Vander Maten JW, McCracken M, Liu J, Ebraheim NA. Syndesmosis screw breakage: An analysis of multiple breakage locations. *J Orthop*. 2022 22;29:38-43. doi: 10.1016/j.jor.2022.01.004
8. Li JK, Yu Y, Wu YH, et al. Does the level of syndesmotic screw insertion affect clinical outcome after ankle fractures with syndesmotic instability? *Orthop Surg*. 2023;15(1):247-255. doi: 10.1111/os.13569
9. Cornu O, Manon J, Tribak K, Putineanu D. Traumatic injuries of the distal tibiofibular syndesmosis. *Orthop Traumatol Surg Res*. 2021;107(1S):102778. doi: 10.1016/j.otsr.2020.102778
10. Bible JE, Sivasubramaniam PG, Jahangir AA, et al. High-energy transsyndesmotic ankle fracture dislocation - the "Logsplitter" injury. *J Orthop Trauma*. 2014;28(4):200-204. doi: 10.1097/01.bot.0000435605.83497.53
11. Gruenewald LD, Leitner DH, Koch V, et al. Diagnostic value of DECT-based collagen mapping for assessing the distal tibiofibular syndesmosis in patients with acute trauma. *Diagnostics* (Basel). 2023;13(3):533. doi: 10.3390/diagnostics13030533
12. Alvarez-López A, Valdebenito-Aceitón V, Soto-Carrasco SR. Tibioperoneal syndesmosis: diagnosis, fixation methods and arthroscopy. *Revista Información Científica*. 2023;102:4087. (In Span.) doi: 10.5281/zenodo.7768163
13. Rammelt S, Obruba P. An update on the evaluation and treatment of syndesmotic injuries. *Eur J Trauma Emerg Surg*. 2015;41(6):601-614. doi: 10.1007/s00068-014-0466-8
14. Lou Z, Wang Z, Liu C, Tang X. Outcomes of tibial pilon fracture fixation based on four-column theory. *Injury*. 2023;54 Suppl 2:S36-S42. doi: 10.1016/j.injury.2022.08.017
15. Rydberg EM, Wennergren D, Stigevall C, et al. Epidemiology of more than 50,000 ankle fractures in the Swedish Fracture Register during a period of 10 years. *J Orthop Surg Res*. 2023;18(1):79. doi: 10.1186/s13018-023-03558-2
16. Corte-Real N, Caetano J. Ankle and syndesmosis instability: consensus and controversies. *EFORT Open Rev*. 2021;6(6):420-431. doi: 10.1302/2058-5241.6.210017
17. Cogan C, Liu T, Toogood P. An assessment of normal tibiofibular anatomy on lateral fluoroscopy. *Foot Ankle Int*. 2020;41(7):866-869. doi: 10.1177/1071100720917639
18. Carrozzo M, Vicenti G, Pesce V, et al. Beyond the pillars of the ankle: A prospective randomized CT analysis of syndesmosis' injuries in Weber B and C type fractures. *Injury*. 2018;49 Suppl 3:S54-S60. doi: 10.1016/j.injury.2018.10.005
19. Kaiser PB, Bejarano-Pineda L, Kwon JY, et al. The syndesmosis, Part II: Surgical treatment strategies. *Orthop Clin North Am*. 2021;52(4):417-432. doi: 10.1016/j.ocl.2021.05.011
20. Dean DM, Ho BS, Lin A, et al. Predictors of patient-reported function and pain outcomes in operative ankle fractures. *Foot Ankle Int*. 2017;38(5):496-501. doi: 10.1177/1071100716688176
21. Litrenta J, Saper D, Tornetta P 3rd, et al. Does syndesmotic injury have a negative effect on functional outcome? A multicenter prospective evaluation. *J Orthop Trauma*. 2015;29(9):410-413. doi: 10.1097/BOT.0000000000000295
22. Grassi A, Samuelsson K, D'Hooghe P, et al. Dynamic stabilization of syndesmosis injuries reduces complications and reoperations as compared with screw fixation: a meta-analysis of randomized controlled trials. *Am J Sports Med*. 2020;48(4):1000-1013. doi: 10.1177/0363546519849909
23. Regauer M, Mackay G, Nelson O, Böcker W, Ehrnthaller C. Evidence-based surgical treatment algorithm for unstable syndesmotic injuries. *J Clin Med*. 2022;11(2):331. doi: 10.3390/jcm11020331
24. Elabd A, Abdullah S, Kandel W, Hegazy M. Syndesmotic stabilization: syndesmotic screw versus flexible fixation: a systematic review. *J Foot Ankle Surg*. 2021;60(5):998-1007. doi: 10.1053/j.jfas.2020.09.021

25. Zhang P, Liang Y, He J, et al. A systematic review of suture-button versus syndesmotic screw in the treatment of distal tibiofibular syndesmosis injury. *BMC Musculoskelet Disord*. 2017;18(1):286. doi: 10.1186/s12891-017-1645-7
26. Jia Z, Cheng J, Zhong H, et al. Titanium cable isotonic annular fixation system for the treatment of distal tibiofibular syndesmosis injury. *Am J Transl Res*. 2019;11(8):4967-4975.
27. Altmeppen JN, Colcuc C, Balser C, et al. A 10-year follow-up of ankle syndesmotic injuries: prospective comparison of knotless suture-button fixation and syndesmotic screw fixation. *J Clin Med*. 2022;11(9):2524. doi: 10.3390/jcm11092524
28. Mak MF, Stern R, Assal M. Repair of syndesmosis injury in ankle fractures: Current state of the art. *EFORT Open Rev*. 2018;3(1):24-29. doi: 10.1302/2058-5241.3.170017
29. Xu K, Zhang J, Zhang P, et al. Comparison of suture-button versus syndesmotic screw in the treatment of distal tibiofibular syndesmosis injury: a meta-analysis. *J Foot Ankle Surg*. 2021;60(3):555-566. doi: 10.1053/j.jfas.2020.08.005
30. Schulte SS, Oplinger SL, Graver HR, et al. Suture button versus screw fixation for distal tibiofibular injury and expected value decision analysis. *Cureus*. 2021;13(11):e19890. doi: 10.7759/cureus.19890
31. Lurie BM, Paez CJ, Howitt SR, Pennock AT. Suture-button versus screw fixation in adolescent syndesmotic injuries: functional outcomes and maintenance of reduction. *J Pediatr Orthop*. 2021;41(6):e427-e432. doi: 10.1097/BPO.0000000000001803
32. Fan X, Zheng P, Zhang YY, Hou ZT. Dynamic fixation versus static fixation in treatment effectiveness and safety for distal tibiofibular syndesmosis injuries: a systematic review and meta-analysis. *Orthop Surg*. 2019;11(6):923-931. doi: 10.1111/os.12523
33. Ramadanov N, Bueschges S, Dimitrov D. Comparison of outcomes between suture button technique and screw fixation technique in patients with acute syndesmotic diastasis: a meta-analysis of randomized controlled trials. *Foot Ankle Orthop*. 2021;6(4):24730114211061405. doi: 10.1177/24730114211061405
34. Pogliacomi F, De Filippo M, Casalini D, et al. Acute syndesmotic injuries in ankle fractures: From diagnosis to treatment and current concepts. *World J Orthop*. 2021;12(5):270-291. doi: 10.5312/wjo.v12.i5.270
35. Kodirkulov ZhSh, Zhamatov AK, Gafurov FA, Yarmatov EI. Current concept of treatment of patients with injuries of the tibiofibular syndesmosis. *Scientific Progress*. 2021;2(7):944-951. (In Russ.)
36. Hosin S, Vermesan D, Prejbeanu R, et al. Avoiding the removal of syndesmotic screws after distal tibiofibular diastasis repair: a benefit or a drawback? *J Clin Med*. 2022;11(21):6412. doi: 10.3390/jcm11216412
37. Saad BN, Rampertaap Y, Menken LG, et al. Direct versus indirect posterior malleolar fixation in the treatment of trimalleolar ankle fractures: Is there a difference in outcomes? *OTA Int*. 2022;5(4):e219. doi: 10.1097/OI9.0000000000000219
38. Kim GB, Park CH. Hybrid fixation for Danis-Weber type C fractures with syndesmosis injury. *Foot Ankle Int*. 2021;42(2):137-144. doi: 10.1177/1071100720964799
39. Bartoníček J, Rammelt S, Tuček M. Maisonneuve fractures of the ankle: a critical analysis review. *JBJS Rev*. 2022;10(2). doi: 10.2106/JBJS.RVW.21.00160
40. Harris MC, Lause G, Unangst A, et al. Prospective results of the modified glide path technique for improved syndesmotic reduction during ankle fracture fixation. *Foot Ankle Int*. 2022;43(7):923-927. doi: 10.1177/10711007221081868
41. Çağlar C, Akçaalan S, Akkaya M. Anatomically fixed posterior malleolar fractures in syndesmosis injuries without transsyndesmotic screw fixation. *Foot Ankle Int*. 2022;43(4):486-494. doi: 10.1177/10711007211060067
42. Patel NK, Chan C, Murphy CI, et al. Hybrid fixation restores tibiofibular kinematics for early weightbearing after syndesmotic injury. *Orthop J Sports Med*. 2020;8(9):2325967120946744. doi: 10.1177/2325967120946744
43. Sanders FRK, Birnie MF, Dingemans SA, et al. Functional outcome of routine versus on-demand removal of the syndesmotic screw: a multicentre randomized controlled trial. *Bone Joint J*. 2021;103-B(11):1709-1716. doi: 10.1302/0301-620X.103B11.BJJ-2021-0348.R2
44. Gennis E, Koenig S, Rodericks D, et al. The fate of the fixed syndesmosis over time. *Foot Ankle Int*. 2015;36(10):1202-1208. doi: 10.1177/1071100715588186
45. Hennings R, Fuchs C, Spiegl UJ, et al. "Flexible nature of fixation" in syndesmotic stabilization of the inferior tibiofibular joint affects the radiological reduction outcome. *Int Orthop*. 2022;46(11):2649-2657. doi: 10.1007/s00264-022-05550-7
46. Dingemans SA, Rammelt S, White TO, et al. Should syndesmotic screws be removed after surgical fixation of unstable ankle fractures? a systematic review. *Bone Joint J*. 2016;98-B(11):1497-1504. doi: 10.1302/0301-620X.98B11.BJJ-2016-0202.R1
47. Pfeifer CG, Grechenig S, Frankewycz B, et al. Analysis of 213 currently used rehabilitation protocols in foot and ankle fractures. *Injury*. 2015;46 Suppl 4:S51-S57. doi: 10.1016/S0020-1383(15)30018-8
48. Futamura K, Baba T, Mogami A, et al. Malreduction of syndesmosis injury associated with malleolar ankle fracture can be avoided using Weber's three indexes in the mortise view. *Injury*. 2017;48(4):954-959. doi: 10.1016/j.injury.2017.02.004
49. Lampridis V, Gougoulias N, Sakellariou A. Stability in ankle fractures: Diagnosis and treatment. *EFORT Open Rev*. 2018;3(5):294-303. doi: 10.1302/2058-5241.3.170057

50. van den Heuvel SB, Dingemans SA, Gardenbroek TJ, Schepers T. Assessing quality of syndesmotic reduction in surgically treated acute syndesmotic injuries: a systematic review. *J Foot Ankle Surg*. 2019;58(1):144-150. doi: 10.1053/j.jfas.2018.08.038
51. Cehic MG, Jaarsma R, Whitehorn A. Effectiveness of suture button fixation versus screw fixation for the management of acute distal tibiofibular syndesmotic injuries: a systematic review protocol. *JBI Evid Synth*. 2023;21(5):977-984. doi: 10.11124/JBIES-22-00219
52. Mercan N, Yıldırım A, Dere Y. Biomechanical analysis of tibiofibular syndesmosis injury fixation methods: a finite element analysis. *J Foot Ankle Surg*. 2023;62(1):107-114. doi: 10.1053/j.jfas.2022.05.007
53. Wu CC, Yeh WL, Lee PC, et al. Should diastatic syndesmosis be stabilized in advanced pronation-external rotation ankle injuries? A retrospective cohort comparison. *Orthop Surg*. 2022;14(7):1447-1456. doi: 10.1111/os.13331
54. Gafurov FA. Experience of surgical treatment with ruptures of distal tibiofibular syndesmosis. *Bulletin of Science and Education*. 2020;(18):78-80. (In Russ.)
55. Khojaly R, Rowan FE, Hassan M, et al. Weight-bearing allowed following internal fixation of ankle fractures, a systematic literature review and meta-analysis. *Foot Ankle Int*. 2022;43(9):1143-1156. doi: 10.1177/10711007221102142
56. Kingston KA, Lin Y, Bradley AT, et al. Salvage of chronic syndesmosis instability: a retrospective review with mid-term follow-up. *J Foot Ankle Surg*. 2023;62(2):210-217. doi: 10.1053/j.jfas.2022.06.010
57. Selivanov VA, Zhumagulov MO, Omirzak EJ, et al. Arthroscopic syndesmotic repair for syndesmotic injury of ankle. *Vestnik KazNMU*. 2016;3-1:295-300. (In Russ.)
58. Lim SK, Ho YC, Ling SK, Yung PS. Functional outcome of fusion versus ligament reconstruction in patients with a syndesmosis injury: A narrative review. *Asia Pac J Sports Med Arthrosc Rehabil Technol*. 2021;25:53-59. doi: 10.1016/j.asmart.2021.05.002

The article was submitted 25.04.2023; approved after reviewing 27.04.2023; accepted for publication 01.12.2023.

Information about the authors:

Farrukh A. Gafurov – assistant of the department;

Iskandar Yu. Khodzhanov – Doctor of Medical Sciences, Professor, Head of the Clinic, https://orcid.org/0000-0001-9420-3623;

Djalolidin Sh. Mansurov – Candidate of Medical Sciences, Head of the Department, jalolmedic511@gmail.com; https://orcid.org/0000-0002-1799-641X;

Sherzod N. Eranov – Candidate of Medical Sciences, Assistant of the Department, https://orcid.org/0000-0001-6544-5375.

Contribution of the authors:

Gafurov F.A. – conceptualization, validation, investigation, data curation, writing – original draft.

Khodzhanov I.Yu. – methodology, control.

Mansurov D.Sh. – writing – original draft and final draft, formal analysis, project management.

Eranov Sh.N. – writing – original draft, visualization.

Review article
https://doi.org/10.18019/1028-4427-2024-30-1-153-162

Mechanisms of musculoskeletal consequences of COVID-19

N.N. Grigorieva[1]✉, G.A. Airapetov[2]

[1] Regional Clinical Antituberculosis Dispensary, Stavropol, Russian Federation
[2] St. Petersburg Research Institute of Phthisiopulmonology, St. Petersburg, Russian Federation

Corresponding author: Natalya N. Grigorieva, natash2015@bk.ru

Abstract

Introduction A coronavirus, SARS-CoV-2, called COVID-19 by the WHO has caused a pandemic of respiratory illness killed more than 6 million people. The severe infection has a significant negative impact on the entire musculoskeletal system.

The objective was to summarize literature data on the mechanisms of the condition and identify musculoskeletal symptoms of COVID-19.

Material and methods An internet search of PubMed, MedLine and eLIBRARY library databases using the search terms: COVID-19, aseptic osteonecrosis, post-COVID-19 syndrome, arthropathy, musculoskeletal system, spondylitis, osteoporosis was performed.

Results and discussion Musculoskeletal symptoms of COVID-19 are reported in 31-59% of cases. Mechanisms of musculoskeletal involvement of coronavirus infection include cytotoxic effect of the virus on osteogenesis cells, vascular inflammation and coagulopathy, "cytokine storm", side effects of drug therapy and hypoxia. According to an etiological factor, musculoskeletal manifestations of SARS-CoV-2 include autoimmune (reactive arthritis, sacroiliitis, ankylosing spondylitis, axial spondyloarthritis, psoriatic arthritis) conditions caused by impaired circulation of bone tissue (aseptic osteonecrosis), infectious (septic arthritis, spondylitis, spondylodiscitis) and metabolic (osteopenia, osteoporosis) conditions.

Conclusion It has been established that COVID-19 infection has a negative impact on the musculoskeletal, endocrine and immune systems increasing the risk of degenerative diseases of the musculoskeletal system and infectious complications in orthopaedic patients early post surgery.

Keywords: COVID-19, aseptic osteonecrosis, post-Covid syndrome, arthropathy, musculoskeletal system, spondylitis, osteoporosis

For citation: Grigorieva NN, Airapetov GA. Mechanisms of musculoskeletal consequences of COVID-19. *Genij Ortopedii*. 2024;30(1):153-162. doi: 10.18019/1028-4427-2024-30-1-153-162

INTRODUCTION

A coronavirus, SARS-CoV-2, called COVID-19 by the WHO has caused a pandemic of respiratory illness killed more than 6 million people [1]. Despite the general understanding of the symptoms and consequences of COVID-19, the full spectrum of the disease's impact on the human body is still unknown. In the future, patients who have suffered from COVID-19 may face long-term consequences of the disease. In December 2020, the UK National Institute for Health and Care Excellence published guidance on the long-term effects of COVID-19, and based on relapsing nature of post-COVID symptoms the following integrative classification was proposed [2]:

1) acute COVID-19: signs and symptoms of COVID-19 for up to 4 weeks;

2) ongoing symptomatic COVID-19: signs and symptoms of COVID-19 from 4 to 12 weeks;

3) post-COVID-19 syndrome: signs and symptoms that develop during or after an infection consistent with COVID-19, continue for more than 12 weeks and are not explained by an alternative diagnosis.

COVID-19 can significantly impact the respiratory system. Many patients suffer the effects of lung damage during the acute phase, including shortness of breath and coughing. Long COVID-19 can affect virtually any organ in the body. SARS-CoV-2 uses the angiotensin-converting enzyme 2 (ACE 2) as the receptor for entry into host cells. ACE2 is present in many cell types and tissues including the lungs, the intestine, the endothelium of small vessels, smooth muscle tissue, skeletal muscles and in synovial tissue [3, 4]. ACE2 is expressed in keratinocytes, fibroblasts, endothelial cells, osteoblasts, and osteoclasts [5]. Numerous organs are potential targets for SARS-CoV-2 infection [3]. Clinical manifestations of COVID-19 pain vary from headache, abdominal pain, arthralgia, to myalgia. CWS Hoong et al. hypothesised that viral arthralgia is an uncommon but distinct manifestation of COVID-19 infection in patients with and without respiratory symptoms. The presence of musculoskeletal complaints was not associated with the risk of developing viral pneumonia. COVID-19 arthralgia was often more severe and had variable onset, while generalised body ache and myalgia were milder and coincided with the occurrence of fever or respiratory symptoms. Viral arthralgia was reported as a novel clinical manifestation of COVID-19, and untypical of a viral prodrome or a reactive arthropathy [6]. Musculoskeletal symptoms are common COVID-19 symptoms with reported prevalence of 31-59 % but have not yet been systematically investigated [7]. A retrospective cohort study of COVID-19 patients with long-term COVID progression reported by PR Sinha, N Mallick showed a significant (27 %) increase in the incidence of orthopaedic conditions such as myalgia, arthralgia, low back pain, bone infection, AVN, and joint disease [8].

One of the most important factors in the pathogenesis of COVID-19 musculoskeletal symptoms is a cytotoxic effect of the virus on osteo- and chondrogenesis, and the negative effect of drugs on the bone and the cartilage during treatment of acute COVID-19. An increased level of pro-inflammatory cytokines (tumor necrosis factor-α, interleukin-6, interleukin-1β and chemokines) persisting in patients with asymptomatic COVID-19 for 6 months after recovery plays a role [9]. A high prevalence of musculoskeletal disorders is reported in patients who suffered from COVID-19, manifested by musculoskeletal pain and structural changes in bone tissue and tendon-capsular apparatus. The timing of the onset of a COVID-19 musculoskeletal pathology is an important issue [6, 8]. In a systematic review, O.B. Khoja et al. reported musculoskeletal pain in 62.5 % of COVID-19 survivors 16 weeks after recovery [10]. C. Fernández-de-Las-Peñas et al. reported COVID-19 patients suffering from musculoskeletal consequences 4 weeks after illness [11].

COVID-19 musculoskeletal conditions are the largest contributors to the global burden of disability in younger and working aged people [1, 12]. Detection and treatment of SARS-CoV-2 infection in the early stages have a great social and economic role. Although post-Covid musculoskeletal disorders are widely discussed, there is no consensus regarding the chronology and definition of the main types of musculoskeletal conditions associated with COVID-19.

The objective was to summarize literature data on the mechanisms of the condition and identify common musculoskeletal symptoms of COVID-19.

MATERIAL AND METHODS

An internet search of PubMed, MedLine and eLIBRARY library databases using the search terms: COVID-19, aseptic osteonecrosis, post-COVID-19 syndrome, arthropathy, musculoskeletal system, spondylitis, osteoporosis was performed. Publications reporting pathogenesis of post-Covid syndrome, musculoskeletal disorders associated with COVID-19 infection and the effect of the SARS-CoV-2 virus on bone and cartilage tissue were collected.

RESULTS AND DISCUSSION

The main mechanisms of musculoskeletal disorders associated with COVID-19 infection

Cytotoxic effects on osteogenesis cells

The effect of the SARS-Cov-2 virus on osteogenesis is widely discussed. A research model of mice infected with COVID-19 demonstrated a bone mass decreased by 24.4 % (p = 0.0009), trabeculae decreased by 19.0 % (p = 0.004) and thickness of trabecular bone decreased by 6.2 % (p = 0.04). Surviving infected mice also showed osteoclasts increased by 64 %, their surface area increased by 27 %, and osteoclasts on the bone surface increased by 38 % [13]. It is hypothesized that the SARS-CoV specific protein, 3a/X1, promotes osteoclastogenesis by accelerating the differentiation of osteoclasts from monocyte/macrophage precursors, enhancing the expression of receptor activator of NF-kB ligand (RANKL) and inflammatory cytokines such as TNF-α facilitating osteoclastogenesis. SARS-CoV-2 can directly infect erythroid progenitor cells in human bone marrow [14]. Specifically, a decrease in lymphocyte count was observed when hematopoietic stem cells treated with SARS-CoV-2 S protein reduced the number of multipotent lymphoid progenitor cells (MPCs) [15]. Incubation of MPC with protein S increased the monocyte population and contributed to a marked increase in osteoclastogenesis [16]. Interestingly, the results show that SARS-CoV-2 remains in erythroid progenitor cells after 14 days of the initial infection [15]. Individuals who have had COVID-19 infection are likely to be diagnosed with osteoporosis, which is associated with a high risk of fractures and progression of degenerative changes in the musculoskeletal system [14].

«Cytokine storm»

A hyperinflammatory reaction of the immune system, which is more pronounced in patients with moderate and severe forms of COVID-19 infection, has an adverse effect on osteo- and chondrogenesis. Although the inflammatory response of the immune system can be observed in mild cases and in asymptomatic carriers, to a less pronounced extent compared to severe forms of the disease [16]. S.W.X. Ong et al. conducted a prospective multicenter cohort study and reported an elevated level of pro-inflammatory cytokines at 6 months compared with healthy controls, regardless of the severity of the coronavirus infection and persistent symptoms. Recovered COVID-19 patients had elevated levels of pro-inflammatory T cell-associated cytokines such as IL-17A, IL-12p70, IL-1β and SCF that continued to increase after recovery [9]. It is known that inflammatory cytokines such as IL-1β, IL-6, IL-17, chemokine ligand CXCL10, tumor necrosis factor (TNF-α) and vascular endothelial growth factor A (VEGF-A) are elevated in patients with infection COVID-19 having a damaging effect on osteo- and chondrogenesis. IL-1β, IL-6 and tumor necrosis factor (TNF-α) activate chondrocytes of the superficial layer of cartilage leading to increased synthesis of matrix metalloproteinases (MMPs) and, ultimately, to increased degradation of the articular cartilage. IL-1β, IL-6 increase bone resorption by stimulating osteoclast activity. Although IL-17 was originally thought to affect only immune cells, it has been shown to stimulate osteoclastogenesis in patients with rheumatoid arthritis (RA) by inducing the formation of OC-like multinucleated cells through prostaglandin E2 and expression of OC differentiation factor (ODF) [3].

Vascular inflammation and coagulopathy

Vascular inflammation plays a key role in the pathogenesis of COVID-19 [17]. SARS-CoV-2 infects vascular endothelial cells by interacting with angiotensin-converting enzyme 2 receptors [18]. The body's immune response to viral invasion leads to a disruption of homeostasis in the form of hypercoagulation. Vascular changes associated with COVID-19 include endotheliitis, vasoconstriction and rupture, thrombotic microangiopathy, capillary dysfunction accompanied by poor oxygenation of bone tissue, can cause avascular osteonecrosis [19, 20].

Hypoxia

Patients with pneumonia mediated by acute coronavirus infection and extensive damage to the lung tissue can develop hypoxia. H Tao et al. hypothesized that oxygen deprivation signaling impairs osteoclast differentiation and osteoblast formation [21]. Hypoxia enhances the hyperproduction of pro-osteoclastogenic cytokines, including receptor activator of nuclear factor B ligand (RANKL), vascular endothelial growth factor (VEGF), macrophage colony-stimulating factor (M-CSF) leading to activation of osteoclasts [22]. Hypoxia-inducible factor (HIF-1) increases osteoclast differentiation through overexpression of RANKL and nuclear factor, activated cytoplasmic T cell 1 (NFATc1) [23]. Hypoxia signaling appears to inactivate osteogenesis capacity of osteoblasts [24]. In recent years, the negative effects of oxidative stress on bone metabolism have received much attention. Multiple mechanisms are involved in osteoclast activation, including regulation of mitogen-activated protein kinases (MAPKs) and intracellular Ca2+ levels[25]. In addition, excess free radicals interfere with osteoblast adhesion impairing bone homeostasis. Hypoxemia can also lead to impaired Ca2+ metabolism and damage to osteocytes [21].

Iatrogenic effects on the musculoskeletal system in patients who suffered acute coronavirus infection

There is no specific therapy for COVID-19. The action of drugs recommended by health systems in various countries of Western Europe, the USA and Russia for the treatment of COVID-19 is based on blocking the hyperproduction of pro-inflammatory cytokines and preventing viral replication. They have many side effects that cause long-term complications in many organs and systems, including the musculoskeletal system.

JAK kinase inhibitors may have an adverse effect on bone tissue by inhibiting osteoclastogenesis, since selective inhibition of Janus kinase 2 leads to a decrease in RANKL-induced osteoclast differentiation [26]. A number of cohort studies and meta-analyses describe the risks of osteonecrosis from protease inhibitors. S.O. Lee et al. reported 54 % of patients taking protease inhibitors for more than a year to treat HIV infection developed aseptic osteonecrosis [27]. Glucocorticosteroids are also associated with a greater risk of metabolic disorders and blood supply to bone tissue. Their use in the treatment of COVID-19 is based on the suppressed expression of pro-inflammatory cytokines, such as IL-1, IL-2, IL-6, TNF-α and IFN-γ, and leukocytes migrated to inflammation sites, which prevents the development of a “cytokine storm” [28]. The negative effect of glucocorticosteroids is based on bone resorption by enhancing osteoclast differentiation and reducing osteoblastogenesis. They can also cause apoptosis of osteoblasts and osteocytes and reduce production of growth hormone. It is generally accepted that the risk of pathological fractures due to osteoporosis and avascular necrosis is associated with the dose and duration of use, decreasing upon cessation. Osteonecrosis can develop in 9-40 % of patients taking glucocorticosteroids for a long time with the risk of avascular necrosis increasing by 3.6 % with the dose increasing with every 10 mg/day [29]. The unfavorable effect of glucocorticosteroids

is based on lipid metabolism disorders associated with their use. Accumulation of low-density lipoproteins results in the formation of fat emboli leading to blockage of peripheral blood vessels and ischemic necrosis of bone tissue [30]. Large doses of glucocorticosteroids can cause peripheral vascular thrombosis by reducing the activity of tissue plasminogen activator (t-PA) and increasing the level of plasminogen activator inhibitor antigen-1 (PAI-1) in plasma [31].

Types of musculoskeletal disorders associated with COVID-19 infection

Based on an analysis of the available literature, musculoskeletal disorders associated with COVID-19 infection can be divided into 4 main groups: autoimmune, bone circulatory disorders, infectious, metabolic according to the leading etiological factor (Table 1).

Table 1

Types of musculoskeletal disorders associated with COVID-19 infection

Etiology	Nosology	Publications
Autoimmune	Reactive arthritis, sacroiliitis, ankylosing spondylitis, axial spondyloarthritis, psoriatic arthritis	[4, 32, 33, 34, 35, 36, 37, 38]
Bone circulatory disorders	Aseptic osteonecrosis	[17, 19, 20, 39, 40]
Infectious	Septic arthritis, spondylitis, spondylodiscitis	[41, 42, 43, 44, 45]
Metabolic	Osteopenia, osteoporosis	[46, 47, 48, 49]

Autoimmune musculoskeletal disorders associated with COVID-19 infection

Analysis of literature data shows that patients with COVID-19 may develop a wide variety of autoimmune disorders. G.G. Tardine et al. reported 25 clinical observations of reactive arthritis developed after a new coronavirus infection. More than half of the patients had a mild course of the disease, and three were treated in the intensive care unit. Four were positive for the HLA-B27 antigen, one had antinuclear antibodies (ANA), two had RF, and one had AB-CCP [4]. D. Colatutto et al. reported the natural history of reactive arthritis and sacroiliitis in two patients who developed COVID-19 infection. Blood samples showed a slight increase in the cytokine profile; the HLA-B27 antigen was negative in both patients [32]. L. Novelli et al. reported psoriatic spondyloarthritis triggered by SARS-CoV-2 infection in a 27-year-old patient [33]. There were several reports of ankylosing spondylitis and axial spondyloarthritis attributed to COVID-19 [34, 35]. Three main pathophysiologic pathways have been proposed by I.M. Omar et al. to explain the effects of COVID-19 in the musculoskeletal system, including the cytokine storm, development of a prothrombotic state, and autoimmunity [36]. Up to 45 % of COVID-19 patients exhibit at least one circulating autoantibody. Higher concentrations of autoantibodies often result in more severe symptoms, suggesting that autoimmunity plays a role in the pathogenesis of COVID-19. SARS-CoV-2 has several epitopes that cross-react with host antigens and could result in autoimmune conditions. There are also studies that describe cases of increased levels of antibodies to cyclic citrullinated peptide (ACCP) after COVID-19, which were not examined prior to involvement in some cases, and which were negative in other cases, and could suggest an association between COVID-19 infection and rheumatoid arthritis developed in the post-Covid period [37, 38].

Mechanisms leading to autoimmune disorders of the musculoskeletal system triggered by COVID-19 may include:

a) excessive synthesis of angiotensin II induced by coronavirus, which leads to synovial hyperplasia by activating its receptors located on the synovial membrane. Angiotensin II increases expression of inflammatory cytokines, chemokines and production of reactive oxygen species [38];

b) activation of pro-inflammatory subpopulations of T cells [36, 37];

c) activation of Toll-like receptor-7 synovial membranes initiating an inflammatory response [37, 38];

d) "cytokine storm" [36, 38].

Aseptic osteonecrosis

Avascular osteonecrosis occurs in 5-58 % of cases affecting the head of the femur, humerus, vertebral bodies, calcaneus and talus [39]. There is no consensus on the mechanism of osteonecrosis triggered by COVID-19. Drug therapy is essential in treatment of COVID-19 [17, 26, 40]. S.R. Agarwala et al. report a series of three cases in which patients developed AVN of the femoral head after being treated for COVID-19 infection. The mean dose of prednisolone used in these cases was 758 mg (400-1250 mg), which is less than the mean cumulative dose of around 2000 mg steroid, documented in the literature as causative for AVN. Patients were symptomatic and developed early AVN presentation at a mean of 58 days after COVID-19 diagnosis as compared with the literature which shows that it generally takes 6 months to 1 year to develop AVN post steroid exposure. The authors suggest a greater risk of osteonecrosis associated with COVID-19 viral infection, when treated with low doses of steroids [17]. Many authors report circulatory disorders due to thrombotic microangiopathy and vascular inflammation and the cytotoxic effect of the virus on osteogenesis cells as the main mechanisms of this pathology [19]. M.A. Panin et al. reported a series of clinical observations of osteonecrosis of the femoral head triggered by COVID-19 with a patient receiving no glucocorticosteroids during treatment for coronavirus infection and who was diagnosed with bilateral osteonecrosis of the femoral heads after 180 days [20].

Secondary musculoskeletal infections associated with SARS-Cov-2

According to the literature, infectious lesions of post-COVID musculoskeletal sequelae are common. V. Bagaria reported a high incidence of periprosthetic joint infections, soft tissue abscesses, and septic arthritis at 1 year in 12 of 90 patients admitted for COVID-19 [41]. M.V. Ardakani et al. reported a series of five cases in which patients developed septic arthritis concomitant with AVN after being treated for COVID-19 infection. An average time period of onset of hip symptoms from the beginning of the COVID-19 infection was 41.6 days [42]. I.V. Esin et al. described the clinical manifestations of infectious spondylitis in 4 patients who suffered from COVID-19, reporting a higher frequency of multi-level lesions and a greater risk of death after surgery due to the generalization of the infectious process and progression of multiple organ failure [43]. I.I. Ustenko et al. and G. Talamonti et al. reported cases of spinal epidural abscess purulent spondylodiscitis and epiduritis in patients who suffered a severe form of COVID-19 [44, 45]. Secondary immunodeficiency caused by a damaging effect of the SARS-CoV-2 virus on the immune system is the most likely cause of infectious damage to the musculoskeletal system [50]. It is capable of damaging lymphocytes, including B cells, T cells and Nk cells, leading to suppression of the immune system during illness. A decrease in lymphocytes and host immune function is the main reason contributing to the development of secondary bacterial infection [51]. An increase in bacterial adhesion due to viral infection; cell destruction by viral enzymes; release of planktonic bacteria from biofilms; synergy in viral-bacterial co-infections; an increased number of immature phagocytes; dysregulation of nutritional immunity; modulation of apoptosis and inflammation can be alternative mechanisms of infectious damage to the musculoskeletal system in the post-Covid period [52]. There is a high probability of developing secondary immunodeficiency mediated by the immunosuppressive effect of drugs used to treat moderate and severe forms of COVID-19 [44].

Risk factors of infectious lesions of the musculoskeletal system may include age over 60 years, long-term hospital stay and mechanical ventilation, stay in the intensive care unit (severe COVID-19), a history of chronic bacterial infections, chronic renal failure with the need for hemodialysis [43].

Metabolic disorders of bone tissue associated with COVID-19

There are several mechanisms of bone metabolism disorders including the direct cytotoxic effect of the virus on bone marrow cells, hyperinflammation reaction and hypoxia enhancing osteoclastogenesis [3, 13, 22]. Side effects of drugs used to treat the condition are one of the risk factors for osteoporosis and osteopenia after COVID-19 infection [26, 46]. L. Sapra et al. report the role of various factors in the risk of developing skeletal disorders in viral diseases including COVID-19. The authors suggest that SARS-CoV-2 has direct and indirect effects on bone metabolism [47]. Experiments performed by B. Mi et al. in a mouse model demonstrated overexpression of microRNA (miR-5106) triggered by SARS-CoV-2 in fracture healing *in vitro* and *in vivo* [48]. A retrospective cohort study performed at San Raffaele University Hospital in Milan showed that thoracic vertebral fractures were detected in 36 % of COVID-19 patients with osteoporosis beng previously diagnosed in 3 % of the patients [49]. Endocrine pathology plays an important role in disturbed osteometabolism due to coronavirus infection. Cases of primary hypoparathyroidism and decompensation of hypoparathyroidism due to COVID-19 were reported in numerous studies. PTH deficiency contributes to a decreased rate of bone tissue remodeling and associated with decreased markers of the bone turnover in the blood and iliac bone biopsy [53]. In 2020, S. Elkattawy et al. reported the first case of primary hypoparathyroidism caused by SARS-CoV2 infection in a 46-year-old male patient with no history of parathyroid pathology who was hospitalized with respiratory failure and had a long-term inpatient stay [52]. S. Bossoni et al. reported a case of a 72-year-old female patient with a history of thyroidectomy who presented with mild COVID-19 infection and acute perioral paresthesia and dysarthria. Laboratory studies revealed low calcium levels, increased serum phosphorus and decreased parathyroid-stimulating hormone, suggesting that SARS-CoV-2 infection caused severe hypocalcemia in the context of subclinical postoperative hypoparathyroidism [55].

V.E. Georgakopoulou et al. reported a case of a 53-year-old patient with hypoparathyroidism that developed due to COVID-19. The patient had no symptoms associated with this condition and had a normal serum calcium level of 8.9 mg/dL [56]. In some studies, hypocalcemia was identified as a biochemical marker of the aggressive course of SARS-CoV-2 [57]. Vitamin D plays an important role in the regulation of osteogenesis and is one of the risk factors for the development of osteoporosis [58]. Much evidence suggests that vitamin D deficiency is closely associated with the incidence of COVID-19. Patients with osteoporosis were found to be more susceptible to SARS-COV-2 infection and the manifestations of the condition exacerbated after exposure to COVID-19. Some COVID-19 patients develop decreased bone density as a complication [59]. F. Liu et al identified and characterized 42 common targets for VitD on both COVID-19 and osteoporosis. Further bioinformatic analysis revealed 8 core targets in the VitD-COVID-19-osteoporosis network. These VitD targets involved in the ErbB and MAPK signaling pathways are critical for fibrotic diseases such as COVID-19 and ossification due to the bidirectional regulatory role of this pathway in profibrotic/antifibrotic disorders and bone formation/bone resorption, respectively. These results identified new mechanistic insights into the functional role and molecular network of VitD in both COVID-19 and osteoporosis [60].

CONCLUSION

The mechanism by which COVID-19 affects the musculoskeletal system include the cytotoxic effect of the virus on osteogenesis cells, hyperinflammation reaction, vascular disorders and coagulopathy, hypoxia and drug therapy for coronavirus infection. Based on an analysis

of the available literature, four most common etiological factors of the musculoskeletal consequences of COVID-19 infection have been identified to include autoimmunity, bone circulatory disorders, infection and metabolic disorders.

The SARS-CoV-2 virus causes direct damage to the immune system, to B cells, T cells and Nk cells and leads to the development of secondary immunodeficiency and infectious pathology of the musculoskeletal system. Immunodeficiency mediated by COVID-19 increases the risks of early infectious postoperative complications in patients operated on for impaired locomotion. Patients who have had coronavirus infection may develop osteopenia and osteoporosis due to a cytotoxic effect of the virus on bone marrow cells and due to endocrine disorders increasing the risk of fractures and progression of degenerative changes in the osteoarticular system. An analysis of the available literature did not establish an accurate chronology of the development of persistent musculoskeletal symptoms associated with COVID-19, which was likely due to the short observation period of this cohort of patients.

Conflict of interest *The authors declare that they have no competing interests.*

Funding *This research received no external funding.*

REFERENCES

1. Polozhikhina M.A. Mortality during the Covid-19 pandemic and risk reduction directions: preliminary results for 2020. *Economic and social problems of Russia*. 2021;(2):50-73. (In Russ.) doi: 10.31249/espr/2021.02.03
2. National Academies of Sciences, Engineering, and Medicine; Health and Medicine Division; Board on Health Care Services. *Long COVID: Examining Long-Term Health Effects of COVID-19 and Implications for the Social Security Administration: Proceedings of a Workshop*. Forstag EH, Denning LA, editors. Washington (DC): National Academies Press (US); 2022. doi: 10.17226/26619
3. Zheng KI, Feng G, Liu WY, et al. Extrapulmonary complications of COVID-19: A multisystem disease? *J Med Virol*. 2021;93(1):323-335. doi: 10.1002/jmv.26294
4. Taradin GG, Kugler TE, Malovichko IS, Kononenko LV. Acute arthritis associated with COVID-19. *Almanac of Clinical Medicine*. 2022; 50 (2): 139–148. doi: 10.18786/2072-0505-2022-50-015
5. Shchegolev AI, Tumanova UN. Persistenciya koronavirusa SARS-CoV-2 v telah umershih i mery zashchity ot inficirovaniya. *Bulletin of Russian State Medical University*. 2021;(3):5-12. doi: 10.24075/vrgmu.2021.029
6. Hoong CWS, Amin MNME, Tan TC, Lee JE. Viral arthralgia a new manifestation of COVID-19 infection? A cohort study of COVID-19-associated musculoskeletal symptoms. Int J Infect Dis. 2021;104:363-369. doi: 10.1016/j.ijid.2021.01.031
7. Cipollaro L, Giordano L, Padulo J, et al. Musculoskeletal symptoms in SARS-CoV-2 (COVID-19) patients. *J Orthop Surg Res*. 2020;15(1):178. doi: 10.1186/s13018-020-01702-w
8. Sinha PR, Mallick N, Sahu RL. Orthopedic Manifestations and Post-COVID-19 Infection. *J Pharm Bioallied Sci*. 2023 Jul;15(Suppl 1):S665-S668. doi: 10.4103/jpbs.jpbs_88_23
9. Ong SWX, Fong SW, Young BE, et al. Persistent Symptoms and Association With Inflammatory Cytokine Signatures in Recovered Coronavirus Disease 2019 Patients. *Open Forum Infect Dis*. 2021;8(6):ofab156. doi: 10.1093/ofid/ofab156
10. Khoja O, Silva Passadouro B, Mulvey M, et al. Clinical Characteristics and Mechanisms of Musculoskeletal Pain in Long COVID. *J Pain Res*. 2022;15:1729-1748. doi: 10.2147/JPR.S365026
11. Fernández-de-Las-Peñas C, Palacios-Ceña D, Gómez-Mayordomo V, et al. Defining Post-COVID Symptoms (Post-Acute COVID, Long COVID, Persistent Post-COVID): An Integrative Classification. *Int J Environ Res Public Health*. 2021;18(5):2621. doi: 10.3390/ijerph18052621
12. Gasparotto M, Framba V, Piovella C, et al. Post-COVID-19 arthritis: a case report and literature review. *Clin Rheumatol*. 2021;40(8):3357-3362. doi: 10.1007/s10067-020-05550-1
13. Awosanya OD, Dalloul CE, Blosser RJ, et al. Osteoclast-mediated bone loss observed in a COVID-19 mouse model. *Bone*. 2022;154:116227. doi: 10.1016/j.bone.2021.116227
14. Minasov TB, Baikov DE, Khafizov MM, Yakupova ER, The features of bone metabolism in COVID-19. *Journal of Family Medicine*. 2021;(5). (In Russ.) doi: 10.33920/med-10-2105-04
15. Huerga Encabo H, Grey W, Garcia-Albornoz M, et al. Human Erythroid Progenitors Are Directly Infected by SARS-CoV-2: Implications for Emerging Erythropoiesis in Severe COVID-19 Patients. *Stem Cell Reports*. 2021;16(3):428-436. doi: 10.1016/j.stemcr.2021.02.001
16. Ropa J, Cooper S, Capitano ML, et al. Human Hematopoietic Stem, Progenitor, and Immune Cells Respond Ex Vivo to SARS-CoV-2 Spike Protein. *Stem Cell Rev Rep*. 2021;17(1):253-265. doi: 10.1007/s12015-020-10056-z
17. Agarwala SR, Vijayvargiya M, Pandey P. Avascular necrosis as a part of 'long COVID-19'. *BMJ Case Rep*. 2021;14(7):e242101. doi: 10.1136/bcr-2021-242101
18. Murkamilov IT, Aitbaev KA, Kudaibergenova IO, et al. Damage of the Muscle System in Covid-19. *The Russian Archives of Internal Medicine*. 2021;11(2):146-153. doi: 10.20514/2226-6704-2021-11-2-146-153
19. Kingma TJ, Hoch V, Johnson C, Chaudhry B. Avascular Necrosis of the Hip: A Post COVID-19 Sequela. *Cureus*. 2022;14(10):e29976. doi: 10.7759/cureus.29976

20. Panin MA, Petrosyan AS, Hadjicharalambous KK, Boiko AV. Avascular Necrosis of the Femoral Head After COVID-19: A Case Series. *Traumatology and Orthopedics of Russia*. 2022;28(1):110-117. doi: 10.17816/2311-2905-1687
21. Tao H, Ge G, Li W, et al. Dysimmunity and inflammatory storm: Watch out for bone lesions in COVID-19 infection. *Med Hypotheses*. 2020;145:110332. doi: 10.1016/j.mehy.2020.110332
22. Hiraga T. Hypoxic Microenvironment and Metastatic Bone Disease. *Int J Mol Sci*. 2018;19(11):3523. doi: 10.3390/ijms19113523
23. Samarpita S, Doss HM, Ganesan R, Rasool M. Interleukin 17 under hypoxia mimetic condition augments osteoclast mediated bone erosion and expression of HIF-1α and MMP-9. *Cell Immunol*. 2018;332:39-50. doi: 10.1016/j.cellimm.2018.07.005
24. Utting JC, Robins SP, Brandao-Burch A, et al. Hypoxia inhibits the growth, differentiation and bone-forming capacity of rat osteoblasts. *Exp Cell Res*. 2006;312(10):1693-1702. doi: 10.1016/j.yexcr.2006.02.007
25. Callaway DA, Jiang JX. Reactive oxygen species and oxidative stress in osteoclastogenesis, skeletal aging and bone diseases. *J Bone Miner Metab*. 2015;33(4):359-370. doi: 10.1007/s00774-015-0656-4
26. Tsed AN, Mushtin NE, Dulaev AK, Shmelev AV. Pathological changes in the osteoarticular system during COVID-19 drug therapy (review of literature). *Grekov's Bulletin of Surgery*. 2022;181(2):85-91. (In Russ.) doi: 10.24884/0042-4625-2022-181-2-85-91
27. Lee SO, Lee JE, Lee S, et al. Osteonecrosis of the Femoral Head in Korean Patients with Human Immunodeficiency Virus Infection. *Infect Chemother*. 2020;52(4):592-599. doi: 10.3947/ic.2020.52.4.592
28. Strehl C, Ehlers L, Gaber T, Buttgereit F. Glucocorticoids-All-Rounders Tackling the Versatile Players of the Immune System. *Front Immunol*. 2019;10:1744. doi: 10.3389/fimmu.2019.01744
29. Bialik V.E., Makarov M.A., Byalik E.I., et al. Avascular necrosis of bone tissue: Definition, epidemiology, types, risk factors, pathogenesis of the disease. Analytical review of the literature. *Rheumatology Science and Practice*. 2023;61(2):220-235. (In Russ.) doi: 10.47360/1995-4484-2023-220-235
30. Koo KH, Kim R, Kim YS, et al. Risk period for developing osteonecrosis of the femoral head in patients on steroid treatment. *Clin Rheumatol*. 2002;21(4):299-303. doi: 10.1007/s100670200078
31. Kerachian MA, Séguin C, Harvey EJ. Glucocorticoids in osteonecrosis of the femoral head: a new understanding of the mechanisms of action. *J Steroid Biochem Mol Biol*. 2009;114(3-5):121-128. doi: 10.1016/j.jsbmb.2009.02.007
32. Colatutto D, Sonaglia A, Zabotti A, et sl. Post-COVID-19 Arthritis and Sacroiliitis: Natural History with Longitudinal Magnetic Resonance Imaging Study in Two Cases and Review of the Literature. *Viruses*. 2021;13(8):1558. doi: 10.3390/v13081558
33. Novelli L, Motta F, Ceribelli A, et al. A case of psoriatic arthritis triggered by SARS-CoV-2 infection. *Rheumatology* (Oxford). 2021;60(1):e21-e23. doi: 10.1093/rheumatology/keaa691
34. Sagitova ER, Kravcova ON. Coronavirus is a trigger for ankylosing spondylitis? *Practical medicine*. 2022;20(3);133-135. doi: 10.32000/2072-1757-2022-3-133-135
35. Coath FL, Mackay J, Gaffney JK. Axial presentation of reactive arthritis secondary to COVID-19 infection. *Rheumatology* (Oxford). 2021;60(7):e232-e233. doi: 10.1093/rheumatology/keab009
36. Omar IM, Weaver JS, Samet JD, et al. Musculoskeletal Manifestations of COVID-19: Currently Described Clinical Symptoms and Multimodality Imaging Findings. *Radiographics*. 2022;42(5):1415-1432. doi: 10.1148/rg.220036
37. Aronova ES, Belov BS, Gridneva GI. Rheumatological manifestations of post-COVID syndrome (literature review). *Medical alphabet*. 2022;(15):20-25. (In Russ.) doi: 10.33667/2078-5631-2022-15-20-25
38. Kamyshnikova LA, Pisankina DS, Payudis AN, et al. Post-COVID musculo-articular syndrome and COVID-19 association with rheumatoid arthritis. *Ural Medical Journal*. 2023;22(1):104-110. (In Russ.) doi: 10.52420/2071-5943-2023-22-1-104-110
39. Beketova TV, Levina NO, Ladygina DO, et al. Avascular necrosis as a part of post-COVID syndrome. Case reports. *Rheumatology Science and Practice*. 2022;60(4):420-426 (In Russ.) doi: 10.47360/1995-4484-2022-420-426
40. Torgashin A.N., Rodionova S.S. Osteonecrosis in Patients Recovering from COVID-19: Mechanisms, Diagnosis, and Treatment at Early-Stage Disease (Review). *Traumatology and Orthopedics of Russia*. 2022;28(1):128-137. doi: 10.17816/2311-2905-1707
41. Bagaria V. Usual and Unusual Musculoskeletal Sequalae of COVID 19! *Indian J Orthop*. 2021;55(Suppl 2):518-519. doi: 10.1007/s43465-021-00412-7
42. Ardakani MV, Parviz S, Ghadimi E, et al. Concomitant septic arthritis of the hip joint and femoral head avascular necrosis in patients with recent COVID-19 infection: a cautionary report. *J Orthop Surg Res*. 2022;17(1):302. doi: 10.1186/s13018-022-03192-4
43. Yesin IV, Perecmanas EO, Tulkova TE. Clinical features of infectious spondylitis in patients with COVID-19. *Russian Journal of Spine Surgery*. 2023;20(1):85-92. doi: 10.14531/ss2023.1.85-92
44. Ustenko II, Kushnir YB, Amelin AV, et al. Case reports: spondylodiscitis and epiduritis after suffering COVID-19. *Journal of Clinical Practice*. 2023;20(1):85-92. doi: 10.14531/ss2023.1.85-92
45. Talamonti G, Colistra D, Crisà F, et al. Spinal epidural abscess in COVID-19 patients. *J Neurol*. 2021;268(7):2320-2326. doi: 10.1007/s00415-020-10211-z
46. Evcik D. Musculoskeletal involvement: COVID-19 and post COVID 19. *Turk J Phys Med Rehabil*. 2023;69(1):1-7. doi: 10.5606/tftrd.2023.12521
47. Sapra L, Saini C, Garg B, et al. Long-term implications of COVID-19 on bone health: pathophysiology and therapeutics. *Inflamm Res*. 2022;71(9):1025-1040. doi: 10.1007/s00011-022-01616-9
48. Mi B, Xiong Y, Zhang C, et al. SARS-CoV-2-induced Overexpression of miR-4485 Suppresses Osteogenic Differentiation and Impairs Fracture Healing. *Int J Biol Sci*. 2021;17(5):1277-1288. doi: 10.7150/ijbs.56657
49. di Filippo L, Formenti AM, Doga M, et al. Radiological Thoracic Vertebral Fractures are Highly Prevalent in COVID-19 and Predict Disease Outcomes. *J Clin Endocrinol Metab*. 2021;106(2):e602-e614. doi: 10.1210/clinem/dgaa738
50. Komarov VT, Khichina NS, Filatova MA. Features of the course of post-infectious arthritis after a new coronavirus infection COVID-19. *Modern Rheumatology Journal*. 2022;16(S1):10. (In Russ.)
51. Bavykin AS. Cell and molecular level of strategy of COVID-19 to induce immunodeficiency. Possible therapeutic solution. *Journal of microbiology, epidemiology and immunobiology*. 2021;98(4):450-467. doi: 10.36233/0372-9311-119

52. Karoli NA, Rebrov AP. The Frequency and the character of bacterial infection in patients with COVID-19. *South Russian Journal of Therapeutic Practice*. 2023;4(1):28-39. (In Russ.) doi: 10.21886/2712-8156-2023-4-1-28-39
53. Grebennikova TA, Belaya ZE, Melnichenko GA. Hypoparathyroidism: disease update and new methods of treatment. *Endocrine Surgery*. 2017;11(2):70-80. (In Russ.) doi: 10.14341/serg2017270-80
54. Elkattawy S, Alyacoub R, Ayad S, et al. A Novel Case of Hypoparathyroidism Secondary to SARS-CoV-2 Infection. *Cureus*. 2020;12(8):e10097. doi: 10.7759/cureus.10097
55. Bossoni S, Chiesa L, Giustina A. Severe hypocalcemia in a thyroidectomized woman with Covid-19 infection. *Endocrine*. 2020;68(2):253-254. doi: 10.1007/s12020-020-02326-0
56. Georgakopoulou VE, Avramopoulos P, Papalexis P, et al. COVID-19 induced hypoparathyroidism: A case report. *Exp Ther Med*. 2022;23(5):346. doi: 10.3892/etm.2022.11276
57. di Filippo L, Formenti AM, Doga M, et al. Hypocalcemia is a distinctive biochemical feature of hospitalized COVID-19 patients. *Endocrine*. 2021;71(1):9-13. doi: 10.1007/s12020-020-02541-9
58. Capozzi A, Scambia G, Lello S. Calcium, vitamin D, vitamin K2, and magnesium supplementation and skeletal health. *Maturitas*. 2020;140:55-63. doi: 10.1016/j.maturitas.2020.05.020
59. Zhang JY, Wang XM, Xing X, et al. Single-cell landscape of immunological responses in patients with COVID-19. *Nat Immunol*. 2020;21(9):1107-1118. doi: 10.1038/s41590-020-0762-x
60. Liu F, Song C, Cai W, et al. Shared mechanisms and crosstalk of COVID-19 and osteoporosis via vitamin D. *Sci Rep*. 2022;12(1):18147. doi: 10.1038/s41598-022-23143-7

The article was submitted 15.11.2023; approved after reviewing 27.11.2023; accepted for publication 01.12.2023.

Information about the authors:

Natalya N. Grigoryeva – traumatologist-orthopedist, natash2015@bk.ru, https://orcid.org/0009-0000-4318-6173;

Georgy A. Airapetov – Doctor of Medical Sciences, Associate Professor, airapetovga@yandex.ru, https://orcid.org/0000-0001-7507-7772.

Contribution of the authors:

Grigorieva N.N. – development of the concept, collection and analysis of literary sources, preparation and writing of the text of the article.

Airapetov G.A. – development of the concept, collection and analysis of literary sources, writing the text and editing the article..

The authors confirm that they meet the international ICMJE criteria for authorship (all authors made a significant contribution to the development of the concept, conduct of the study and preparation of the article, read and approved the final version before publication).

Главный редактор А.В. Бурцев

Компьютерная верстка М.А. Беляева

Перевод Т.А. Малкова, И.А. Саранских

Информационная поддержка сайта журнала О.Б. Борзунова, Е.А. Дворянцева

Журнал зарегистрирован Федеральной службой по надзору в сфере связи, информационных технологий и массовых коммуникаций
ПИ № ФС77-68207 от 30 декабря 2016 года

Территория распространения: Российская Федерация, зарубежные страны

Подписано в печать 16.02.2024. Дата выхода 29.02.2024
Формат 60 × 84 1/8. Усл. печ. л. 19
Тираж 75 экз. Заказ № 09570. Свободная цена

Адрес издателя, редакции журнала «Гений ортопедии»
640014, Россия, г. Курган, ул. М. Ульяновой, 6
http://ilizarov-journal.com

Отпечатано в Типографии «Эталон». 198097, г. Санкт-Петербург, ул. Трефолева, 2 литера БН, помещение 3-Н, офис 1