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Dear colleagues,

The year 2024 was marked by interesting events in the world of traumatology and orthopaedics. In Russia, the trend towards substitution of imported goods has been maintained in the development of applied science. Much attention was paid to the application and development of the Ilizarov method both in our country and abroad.

At the beginning of 2024, the ASAMICON India conference was held, bringing together Ilizarov followers from the Asian region (India, China, Bangladesh, the Philippines, Indonesia). As part of the conference, the Ilizarov Center participants (members of the ASAMI-Russia) held master classes, gave lectures and presented reports on the application of the Ilizarov transosseous osteosynthesis method.

The annual international conference the *Ilizarov Readings*, held in June and dedicated to the birthday of G.A. Ilizarov, was devoted to staged orthopaedic surgery: planned and revision interventions. The conference program included scientific and practical sessions and training master classes on transosseous osteosynthesis in the treatment of bone defects and various issues of bone and joint infection. The event was attended by representatives of the regions of our country and foreign colleagues from India, Bangladesh, Myanmar, Burkina Faso, Oman, Uzbekistan.

The VI World Congress of ASAMI & ILLRS was held in Beijing with the participation of representatives from more than 40 countries. For almost a week, from September 17 to September 22, leading experts of the world orthopaedic community discussed various aspects of the Ilizarov method application. At the opening ceremony, the Ilizarov Center was distinguished with an award for its significant contribution to the development of external fixation.

The events continued with a congress on gunshot wounds, at which much attention was paid to external fixation, and the name of Academician Ilizarov was most frequently mentioned. The speakers presented reports on the application of the Ilizarov method in the acute and late periods of combat injuries of the musculoskeletal system, its consequences and complications. Prospects were also discussed, including the organization of educational events on the application of the Ilizarov method.

We are confident that external fixation methods will continue to attract much interest in 2025. We have planned to hold scientific and practical events on the Ilizarov method. The main event will be the *Ilizarov Week in Russia*. It will start with a cadaver course in Yekaterinburg, continue with the *Ilizarov Readings* conference and educational events in Kurgan, followed by scientific, practical and educational sections held at the EOF site under the auspices of ASAMI-Russia.

I would like to highlight the undying interest of domestic and foreign trauma- and orthopaedic surgeons in the Ilizarov method on the eve of the anniversary dates of 2026 (105 years since the birth of Academician G.A. Ilizarov, 75 years of the Ilizarov method, 55 years of the Ilizarov Center). I believe we are in the phase of professional rethinking of traumatological and orthopaedic approaches and are increasingly aware of the continuing importance of the Ilizarov method in the world of orthopaedics not only as a technology, but also as a philosophy.

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

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Original article
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Role of serum lactoferrin and calprotectin in the inflammatory response in patients with bone fractures

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Abstract

Introduction Elevated concentrations of serum calprotectin and lactoferrin were observed to make prediction about microvascular changes in patients with bone fractures.

The **aim** of the present study was to assess the diagnostic value of serum calprotectin and lactoferrin in the development of inflammatory response in patients with bone fractures.

Material and Methods Seventy patients were included in the study between October 2021 and January 2022; of these, 40 had bone fractures and 30 were healthy participants (control group). Calprotectin and lactoferrin were measured by immunosorbent assay.

Results 12 patients (30 %) had open bone fractures while 28 (70 %) had closed bone fractures. The study revealed that levels of serum calprotectin significantly increased in patients with bone fractures as compared to healthy subjects, while lactoferrin exhibited a borderline but not significant increase ($P = 0.06$). Patients with open bone fractures had higher levels of serum calprotectin compared to those with closed fractures ($P = 0.05$). The correlation matrix exhibited that there was a strong positive correlation between calprotectin and lactoferrin in patients with bone fractures.

Discussion Calprotectin is classified as a potent pro-inflammatory marker that has been noted to be elevated in chronic inflammation such as irritable bowel syndrome (IBS), atherosclerotic lesions, different types of arthritis, and immunological rejection. The present study may only confirm an increase in calprotectin in patients with bone fractures. Recently published studies indicate the potential new role of calprotectin in bone healing and fracture risk.

Conclusion High serum calprotectin and lactoferrin indicate a strong inflammatory status in bone fracture patients, especially in those with open fractures.

Keywords: calprotectin, lactoferrin, bone fracture, inflammation

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INTRODUCTION

Bone fractures are of both clinical and public health major concern. The complexity entails a dependence of a variety and an array of etiologies. Bone fractures manifest as a range in types that are classified either as open or closed fractures. An open fracture is the one in which there is an open wound or break through to the skin near the site of a broken bone; it has higher risk potential for infection while a closed fracture does not break through to the skin.

Healing of bone fractures is biological and can be influenced by several complexities, one of which is the presence of an adaptive immune system. D. Toben et al. stated that without an adaptive immune system the healing of a fracture would be accelerated in an enormous manner, thus providing a potential role for immune modulation in clinical treatments for fractures [1]. Consistent with the finding above, more evidence was also reported that though the inflammatory response is essential to the initial stages of bone healing, too much inflammation inhibits recovery [2]. Dendritic cells and macrophages are immune effector cells expressing a variety of membrane-bound receptors for self-molecules such as calprotectin. In this context, calprotectin is hypothesized to act as an endogenous differentiation biomarker for phagocytes as well as an extrinsic protein complex, hence classified as a DAMP (danger-associated molecular pattern). Serum levels of calprotectin have been shown to be elevated in patients with skeletal damage that reflects vascular damage as well. Bone fractures do indeed elevate serum calprotectin. The serum calprotectin level is dramatically elevated in early OA stages, with a reverse relationship with disease severity [3]. It may thus be proposed as a promising blood-based marker for early knee osteoarthritis (OA).

More recent studies show the potential role that calprotectin might play in bone healing and fracture risk. Special attention is drawn to the modulation of the inflammatory response during bone healing, thereby indicating possible key players expressed during the process of healing, notably discussed being inflammatory cytokines and proteins, like calprotectin [4]. Lactoferrin (Lf) is found in highest concentration in human and mammalian milk, and in smaller amounts in other exocrine fluids (i.e. salivary secretions, semen, tears, gastrointestinal secretions, vaginal secretions) as well. Lf is also synthesized by the hematopoietic tissue of the bone marrow and is present within neutrophil granules [5–6]. It contributes to a variety of physiological processes *in vivo*. Consequently, lactoferrin was capable of decreasing oxidative stress, inflammation, and apoptosis processes, which are the basic pathways involved in the bone inflammatory disorders of different etiologies [6].

The **purpose** of the present study was to assess the diagnostic value of serum calprotectin and lactoferrin in the development of inflammatory response in patients with bone fracture.

MATERIALS AND METHODS

The total number of participants in this research was seventy subjects, forty individuals with bone fractures and thirty apparently healthy control group subjects. It was conducted at the Endocrine Center in Al-Sadr Medical City in Al-Najaf province, Iraq, from June 2023 to February 2024. It was prepared through a questionnaire tool for recording demographic information (age, gender) and type of fracture (open or closed fracture). A 10-ml blood sampling after fasting for 12 hours was done and kept in deep freeze (−20 °C) till laboratory measurements were applied and then assayed for calprotectin and lactoferrin by immunosorbent assay kits after separation of serum. Blood samples were taken within 24–28 hours after fracture. Strictly according to manufacturers' instructions (Calprotectin test, Nova Tec, Germany), this is a monoclonal antibody test coated with calibrator directed against polyclonal antibody against calprotectin. Optical density mean value was read in duplicates at 450 nm. The control curve was constructed at different concentrations of calprotectin. Data were analyzed using Statistical Package for the Social Sciences (SPSS) software, version 25. Analysis was done by descriptive statistics (percentage and frequency) and inferential statistics (t-test and Chi-squared test). Pearson Correlation Coefficient (r) is appropriate for measuring the relationship between quantitative variables.

RESULTS

The current study assessed the demographic characteristics of both patients and control groups. There was no significant variation (P > 0.05) in age and gender between patients and healthy groups (Table 1). On the other hand, 12 patients (30 %) had open fractures while 28 (70 %) had closed bone fractures (Fig. 1).

Table 1

Demographic characteristics of patients and control groups

Indicators		Patients (*No* = 40)		Control (*No* = 30)		Chi Square	*P* value (Sig.)
		Freq.	Percent	Freq.	Percent		
Age/Years	20–24	13	32.5	7	35.0	0.05	0.97 (NS)
	25–29	10	25.0	5	25.0		
	30–34	17	42.5	8	40.0		
Gender	Male	23	57.5	8	40.0	1.64	0.20 (NS)
	Female	17	42.5	12	60.0		

Notes: NS: Non-significant at *P* value > 0.05

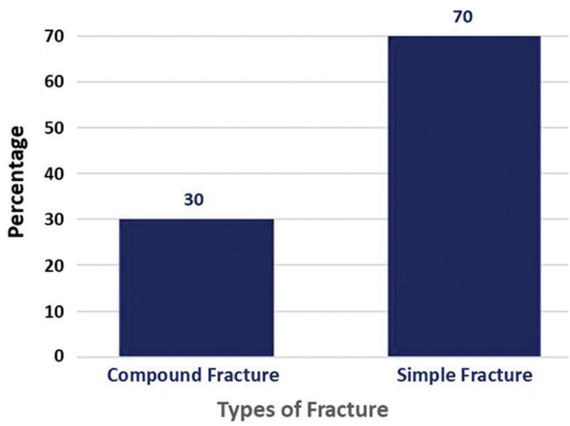

Fig. 1 Classification of patients according to the type of fracture

Serum levels of calprotectin and lactoferrin were evaluated in patients and control groups. The results exhibited a significant increase (*P* < 0.05 in calprotectin (μg/dl) in the patients compared to the healthy group (Table 2). The same table shows that there was no significant difference (*P* < 0.06) in lactoferrin (μg/dl) in the patients compared to the control group.

Table 2

Differences in calprotectin and lactoferrin between patients and healthy groups

Indicators	Patients (*No* = 40)		Control (*No* = 30)		Independent T Test	*P value (Sig.)*
	Mean	SD	Mean	SD		
Calprotectin, μg/dl	68.22	22.37	35.88	10.22	8.09	0.000 (HS)
Lactoferrin, μg/dl	10	25.0	5	25.0	1.93	0.06 (NS)

Notes: SD: Standard Deviation; HS: High Significant at *P* value < 0.01; NS: No-Significant at *P* value > 0.05

The inflammatory response in terms of calprotectin and lactoferrin between the patients with open and those with closed fractures was assessed. The results exhibited a significant increase (*P* < 0.05) in calprotectin (μg/dl) in patients with open fractures compared to those with closed fractures

(Table 3). The same table revealed that there was no significant difference ($P < 0.06$) in lactoferrin (µg/dl) in patients with open and closed fractures. The correlation test was achieved with the Pearson correlation coefficient (r) after assessing the normality of data. There was a high positive significant correlation ($P < 0.01$) between serum lactoferrin and calprotectin (r = 0.522), as shown in Figure 2.

Table 3

Differences in calprotectin and lactoferrin between patients with compound and simple fractures

Indicators	Compound Fracture (*No* = 12)		Simple Fracture (*No* = 28)		Independent T Test	*P value (Sig.)*
	Mean	SD	Mean	SD		
Calprotectin, µg/dl	70.41	6.33	66.03	5.13	2.05	0.05 (S)
Lactoferrin, µg/dl	9.78	4.55	8.01	1.29	1.32	0.21 (NS)

Notes: SD: Standard Deviation; NS: No-Significant at *P* value; S: Significant at *P* value < 0.05

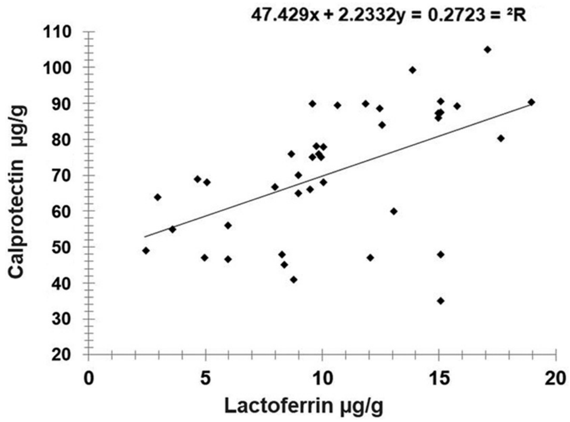

Fig. 2 Scatter plot and regression equation between calprotectin and lactoferrin

DISCUSSION

Calprotectin is made up of two proteins subunits bound to calcium ion (S100A8 & S100A9) from where calprotectin is derived. Calprotectin is classified as a potent proinflammatory marker that has been noted to be elevated in chronic inflammation such as irritable bowel syndrome (IBS), atherosclerotic lesions, different types of arthritis, and immunological rejection [5]. The present study, however, may only confirm an increase in calprotectin in patients with bone fractures.

Recently published studies indicate the potential new role of calprotectin in bone healing and fracture risk. It was noted that during modulation of the inflammatory response in bone healing process, the indicators of inflammatory cytokines and proteins are critical and the role played by calprotectin seems fundamental [4]. The same view is shared by a recent study that went even further to explain how aging and inflammation change behavior of stem cells and herefore impact bone healing hence the high levels of calprotectin could also be a reason for retarded bone repair [7]. It was recommended that inflammatory biomarkers, such as calprotectin, may be used as predictors for complications in the healing process in long bone fracture non-union, delayed union, mal-union. It can have an impact on making clinical decisions. In other words, this relationship therefore infers that monitoring the levels of calprotectin would show how the status of fracture healing is going on [8].

The particular mechanisms through which calprotectin may influence bone health are still under study, along with the studies on how mechanical loading and biological factors regulate bone remodeling [9]. In this sense, inflammatory biomarkers like calprotectin might modulate bone remodeling as indicated by the relatedness to some biochemical bone turnover markers [10].

One integration into the future may be the results from studies on genetic and clinical determinants of fracture risk. It is emphasized that fracture risk assessment is complex and may one day include inflammatory biomarkers, such as calprotectin. Integration such as this would enhance the model's precision in calculating an individual's probability of fracturing, which is of particular value in high prevalence populations with systemic inflammation [10].

In the present study, the levels of lactoferrin were not significantly different compared to the controls, though the *p*-value in question was at the borderline level (< 0.06). This may be because lactoferrin has been found to influence several cellular processes in relation to bone healing. Thus, it is underlined that coupling angiogenesis with osteogenesis during repair of bone fractures is crucial. This is an important step toward supplying the healing tissue with blood; where lactoferrin may have a role through effects on inflammatory processes and cellular differentiation. First of all, lactoferrin potentially affects this linkage because of the promotion of new types of floras or blood vessel growth shapes and bone [11]. Secondly, where one of the contributing factors is better understood, lactoferrin is set to play a role as well since macrophages are understood to contribute to bone healing by enhancing osteoblastic differentiation and playing a critical role in endochondral ossification. Such immunomodulatory effects by lactoferrin would reasonably enhance activity by macrophages to allow more effective bone regeneration. Indeed, lactoferrin may not act alone but may interact with other bio-molecules during bone healing [12–13]. For instance, materials that promote bone regeneration could be developed to work in synergy with the properties of lactoferrin for better healing [14].

A study on cell therapy of delayed unions leaves open the possibility that appropriate combination of lactoferrin with cellular therapies may also allow improvement to be obtained where nonunion fractures are found [15].

The other is bone healing under hypoxic conditions. Results from previous studies proved that hypoxic mesenchymal stem cell exosomes could drive the healing of fractures. There might be possible complicated interactions between lactoferrin and exosomal miR-126 transfer in future studies, especially to explicate how lactoferrin may enhance efficacy of stem cell therapies during fracture healing. Lactoferrin acts not only in antimicrobial protection but in provision of homeostasis related to intractable inflammation and iron metabolism — two pathways directly pertinent to situations of bone healing [16]. An informative review paper clearly described the structure and functions of lactoferrin that determine its important role in control over inflammation and maintenance of iron homeostasis, essential preconditions for optimal healing of fractures [17].

Previous studies indicated that patients suffering from conditions such as infections have high elastase levels, which degrade lactoferrin; hence the doses for individuals with severe conditions could be heightened. The present study revealed that there was a significant positive correlation between lactoferrin and calprotectin, several researchers have noted the positivity between lactoferrin and calprotectin in different inflammatory conditions. Thus, both markers showed a significant positive relationship with endoscopic scores among Crohn's patients (calprotectin, $p = 0.0001$; lactoferrin, $p = 0.038$), indicating their importance in evaluating disease activity [18].

Another study reported a high correlation between fecal levels of lactoferrin and calprotectin, with $r^2 = 0.74$; thus, the two biomarkers may act as complementary indicators of inflammation [19]. Lactoferrin and calprotectin were also valid to differentiate various disease states for mucosal healing independent of clinical symptoms in patients with ulcerative colitis by using fecal biomarkers [20]. This means these two biomarkers both have perspective as noninvasive indices in monitoring inflammatory activity.

CONCLUSION

It was concluded that high serum calprotectin and lactoferrin indicated a strong inflammatory status in patients with bone fractures. Patients with open fractures exhibited higher inflammatory response in terms of calprotectin compared to patients with closed fractures.

Conflict of interests *None.*

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Ethical approval *This case-control study was approved by the medical ethics committee at the Faculty of Medicine/Kufa University (Reference#: MEC-16 on June 21, 2022).*

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Impact of personalized alignment technique on implant components position in total knee arthroplasty

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Abstract

Introduction Due to substantial rates of dissatisfaction in patients with mechanical alignment in total knee replacement, surgeons began searching for alternative techniques to improve functional outcome. In the recent decade, kinematic alignment that is not based on the mechanical axis of the femur has become the most popular alternative to mechanical alignment. Kinematic alignment technique development has led to creation of a personalized alignment technique.

Purpose To compare postoperative implant positions in full-length standing lower-leg radiographs between kinematic alignment and mechanical alignment groups of patients.

Materials and methods A prospective, single-center, randomized, controlled study was performed in 139 patients with grade 3–4 knee osteoarthritis (Kellgren – Lawrence). We collected data from 76 cases of mechanical alignment (66 women and 10 men) and 83 cases of personalized alignment group (60 women and 23 men). There were no patients with significant post-traumatic or other deformities of the lower limb which can alter the results in the study. All measurements were done on digital full-length standing X-rays of the lower legs with special MediCAD software.

Results The positions of the implant components in mechanical and personalized alignments did not differ significantly in many parameters after operations, despite the fact that the alignment was based on completely different principles. There were no differences between the average values of the angles after operations with mechanical and anatomical axes of the femur in both study groups (the difference was 0.1° at $p = 0.595$). The only difference in the groups was the position of the tibial component in relation to the horizontal surface in the standing position: in personalized alignment, the angle was 0.9°, and in mechanical alignment it was 2.4° valgus ($p < 0.001$).

Discussion The absence of significant difference in the postoperative leg alignment and implant position except in the joint line orientation between the groups demonstrates possibility to achieve good leg alignment with both techniques. In the personalized alignment group, the joint line orientation in the coronal plane was found nearly parallel to the ground which can result in a more balanced weight distribution compared to mechanical alignment.

Conclusion In patients who receive total knee replacement with the personalized technique, the postoperative lower limb alignment was found within the safe boundaries of 3° from the mechanical axis while the joint line orientation in the coronal plane was significantly closer to be parallel with the ground compared with mechanical alignment group.

Keywords: total knee arthroplasty, personalized alignment, kinematic alignment, mechanical alignment, knee osteoarthrosis

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INTRODUCTION

In the last decade, the global orthopaedic community has shown increasing interest in alternative methods of lower limb alignment in total knee arthroplasty that replace the classical method of mechanical alignment [1, 2]. Some techniques have been proposed, in particular kinematic alignment [3, 4, 5], which demonstrate significant improvement in functional results [6–15].

Among the supporters of traditional mechanical alignment, there are many opponents of kinematic alignment. Their main argument is that limb deformities caused by the disease remain present after the surgery due to "incorrect position of the endoprosthesis components" [16–20], and that such installation of components will inevitably have a negative impact on the service life of the implant and increase the incidence of revision [21, 22].

Proponents of kinematic alignment, given the significant variability in patient anatomy, believe that attempts to achieve the same limb axes and joint line for all patients in mechanical alignment may significantly disorder the distribution of joint loads, which in turn may affect clinical outcome [23–27].

Purpose of the study: to compare the position of knee joint endoprosthesis components after total knee replacement with the use of mechanical and personalized alignment methods

MATERIALS AND METHODS

A total of 76 cases (66 women, 10 men) of the mechanical axis alignment method (group 1) and 83 cases (60 women, 23 men) of personalized alignment (group 2) were analyzed. The patients in the first group underwent surgery with the conventional techniques involving soft tissue release and external rotation of the femoral component. In the second group, the surgery was performed using the author's personalized alignment method based on the principle of kinematic alignment and described in detail in the Russian Federation patent for invention [27].

Inclusion criteria were age of 18 years and over, clinically and instrumentally confirmed gonarthrosis grade III–IV, patients' written informed consent to participate in the study.

Non-inclusion criteria were age under 18 years, absence of clinically and instrumentally confirmed diagnosis of gonarthrosis, presence of severe concomitant pathology that caused refusal of surgical treatment (uncompensated diabetes mellitus, acute cerebrovascular accident and acute myocardial infarction suffered less than 4 months prior to referral).

Exclusion criteria were patient's refusal to participate further in the study, change of residence (patient's move to another region of the Russian Federation), infectious complications that developed in the postoperative period and required repeated surgical intervention.

Before the operation and 3 months after it, the patients filled out the KOOS and Oxford questionnaires, and at the same time-points the range of motion in the joint was studied.

The position of the endoprosthesis components and the limb alignment parameters were studied on panoramic radiographs using the MediCAD program (Hectec GmbH, Germany). The following parameters were assessed in the frontal plane: HKA angle — the angle between the mechanical axis of the femur and the mechanical axis of the tibia, the angle between the joint line and the horizontal surface, the angle of inclination of the tibial component of the endoprosthesis to the mechanical axis of the tibia (90° — mMPTA) and the angle between the mechanical and anatomical axes of the femur (Fig. 1). It should be noted that the assessment of implant component position was carried out automatically using the MediCAD program, thus the influence of the researchers on the results was excluded.

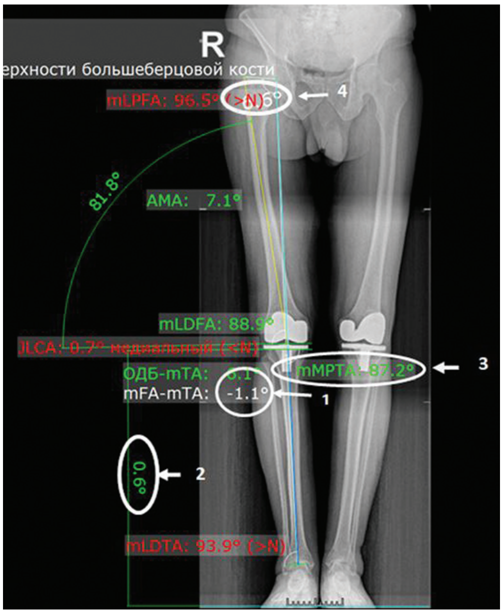

Fig. 1 Evaluation of total knee arthroplasty using the mediCAD program: 1) HKA angle between the mechanical axes of the femur and tibia; 2) angle between the line of the newly formed joint and the ground; 3) angle of deviation of the tibial component from the mechanical axis of the tibia; 4) angle between the mechanical and anatomical axes of the femur

Panoramic radiographs were taken at least 3 months after the surgery. When placing the patient on the platform, we abandoned the recommended distance of 30 cm between the feet, since for persons who are 150 cm and 190 cm tall, this is a completely different position in terms of comfort. The recommended distance is normal for a tall person, but for a short person, the legs are too wide apart, which is often impossible with very thick legs. Therefore, patients placed their feet on the platform in a comfortable for them position.

When assessing the initial condition before surgery, patients in both study groups had reliable differences only in age and average terms of follow-up examination after surgery. In all other parameters, patients in both groups were identical (Table 1).

Table 1

Patients' characteristics before the operation

Parameter	Group 1 Mechanical alignment	Group 2 Personalized alignment	*p*
BMI, Me [IQR]	32.30 [28.62; 34.92]	33.39 [27.70; 35.48]	0.701
Age (years), M (SD)	64 (8)	67 (8)	0.019*
Follow-up term (months), Me [IQR]	24 [4; 53]	7 [3; 11]	< 0.001*
KJ Oxford b/s, Me [IQR]	17.00 [12.00; 20.00]	17.00 [13.00; 22.00]	0.192
KOOS S b/s, Me [IQR]	36.00 [25.00; 46.00]	36.00 [25.00; 46.00]	0.638
Preoperative ROM (degrees), Me [IQR]	95 [90; 100]	95 [90; 105]	0.743

Operations with orientation to mechanical axes were performed according to the standard method. Joint balancing was performed by releasing soft tissues. During preoperative planning, the angle between the mechanical and anatomical axes of the femur was measured using special templates or by planning in the MediCAD program. The purpose of planning was to assess the general condition of the involved joint, the size of cartilage and bone tissue defects, and the condition of the ligamentous apparatus of the joint.

The Vicon motion capture system and the Neurocor stabilometric platform were used in the study. Statistical processing of the results was performed using the StatTech v. 4.1.7 software (StatTech LLC, Russia).

The study was approved by the Ethics Committee of City Clinical Hospital No 1. Before the study, each patient completed an informed consent for participation in the study and publication of its results.

RESULTS

Analyzing the results of the study, we first of all paid attention to the fact that the deviation of the mechanical axes of the femur and tibia of the involved limb did not differ between patients of the groups. The angles of inclination of the tibial component of the endoprosthesis in the mechanical and personalized alignment groups did not have statistically significant differences either (Table 2).

Table 2

Limb alignment and implant components position after the operation in the standing position

Parameter	Group 1 (mechanical alignment)	Group 2 (personalized alingment)	*p*
HKA (degrees), M (SD)	−2.3 (3.4)	−2.8 (3.2)	0.391
Actual Q angle (degrees), Me [IQR]	6.4 [5.9; 7.1]	6.5 [6.1; 7.1]	0.595
Horizontal angle (degrees), Me [IQR]	2.4 [0.6; 4.3]	0.9 [−0.3; 1.8]	< 0.001*
T varus (degrees), Me [IQR]	−0.5 [−2.2; 1.1]	−2.2 [−3.8; 1.7]	0.114

On postoperative radiographs, the angle between the mechanical and anatomical axes of the femur (Q angle) had very minor differences between the two groups of patients. In the first group of patients of the mechanical alignment method, the Q-angle was determined using a protractor or in the MediCad program during the preoperative planning process. In the second group of patients (personalized alignment), preoperative planning consisted of assessing the severity of wear of cartilage, subchondral bone, and the severity of osteophytes.

The relations of the lower limb axes were not evaluated. The difference in the mean values of the Q-angle between the groups was statistically not significant and was only 0.1°.

The most important thing in the position of the components in the studied groups was the significant difference in the angles of inclination of the joint line of the implant in relation to the horizontal line. The angle of inclination of the joint plane in the group with personalized alignment was significantly smaller than in the group of patients who underwent surgery with orientation to the mechanical axes (0.9° and 2.4°, respectively, $p < 0.001$) (Fig. 2).

A significant difference was that the permissible range of motion in the knee joint was significantly greater in the group of the personalized alignment method than in the group of mechanical alignment (Fig. 3).

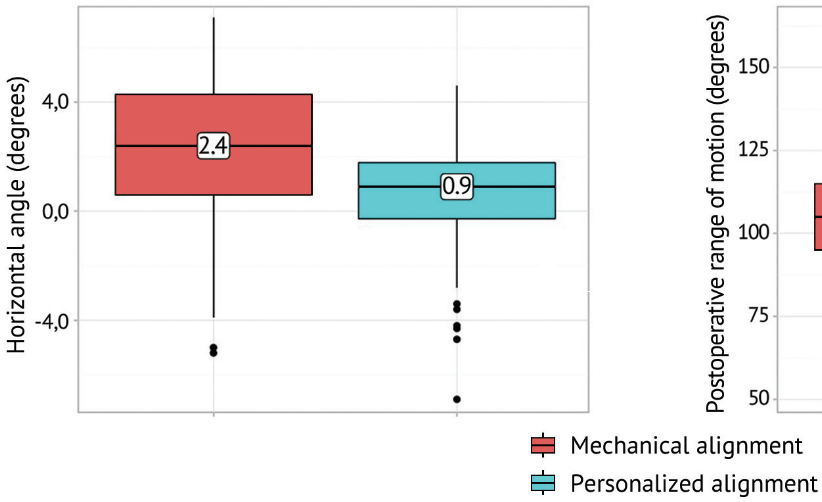

Fig. 2 Inclination of the joint line relative to the horizontal surface in a standing position

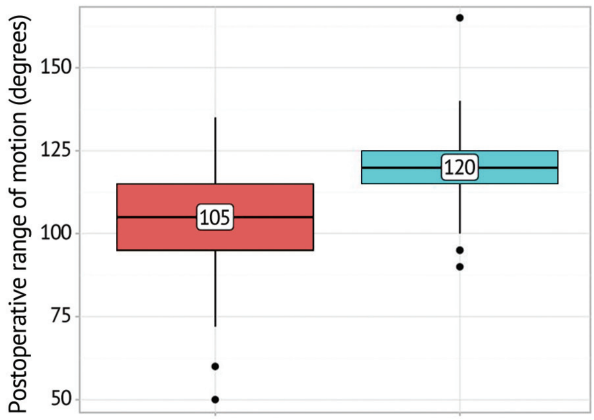

Fig. 3 Average range of motion at a time-point not earlier than 3 months after surgery

DISCUSSION

The positioning of the implant components in the two groups was carried out based on completely different principles. Despite this, a comparison of the postoperative position of the components in the mechanical and personalized alignment groups did not reveal significant differences. The mechanical axis of the femur determined before the operation in patients of the first group was the starting point from which the subsequent construction of the new joint was carried out. In personalized alignment, the joint wear severity and ligament balance were assessed before and during the operation. It should be emphasized that patients of both groups did not have statistical differences in all parameters, including the severity of the pathological process.

The absence of differences in the postoperative evaluation of the HKA demonstrates sufficient correction of the limb axis in personalized alignment. The postoperative limb axis is in the same range as in mechanical alignment. Similar results were obtained for the position of the tibial component in relation to the anatomical axis of the tibia: no significant difference was found between the groups.

Of particular interest was the fact that there was no difference in the angles between the mechanical and anatomical axes of the femur (the so-called Q-angle). In operations with orientation to the mechanical axis, this angle is the "cornerstone" and the first thing that is determined during preoperative planning. Everything can change during the operation, but only the Q-angle will remain unchanged. During preoperative planning for personalized alignment, we were not interested in the Q-angle; we did not determine it and, accordingly, did not take it into account in any way. However, the difference between the groups was 0.1° and was statistically not significant ($p = 0.595$). We did not find a complete, scientifically substantiated explanation. Thus, the data would have more differences in a significantly larger sample of patients. The mechanical axis of the femur determined during preoperative planning corresponded to the real axis of the limb in most patients and remained unchanged when the personalized alignment principle was used.

The only and most significant difference was the difference in the position of the tibial component and the line of the newly created joint in relation to the horizontal surface in the standing position. In mechanical alignment, the average angle of inclination of the joint line in the valgus position was 2.4°, and in personalized alignment it was 0.9° in valgus, that is with high statistical significance of the differences ($p < 0.001$). Similar data are described by other authors [28]. This result indicates that the line of the knee joint after total arthroplasty with a personalized alignment principle is reliably closer to the norm of 2–3° in varus than in performing an operation with orientation to mechanical axes, and does not lead to overload of the medial parts of the newly created joint [29].

CONCLUSION

It has been established that most parameters of implant components position in total knee arthroplasty do not depend on the principles of alignment, personalized or mechanical. The main difference is that in personalized alignment, the line of the reconstructed joint in the standing position reliably corresponds more to the line of the healthy joint, which may explain its better functional results after total knee arthroplasty that are presented in the literature.

Conflict of interest *Not declared.*

Funding source *The study was conducted within the framework of the Moscow Government Grant program.*

Ethical statement *the study was approved by the ethical board of City Clinical Hospital No 1.*

Informed consent *Before the start of the study, each patient completed an informed consent form for participation in the study and publication of the results.*

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Comparative analysis of the outcomes of high tibial osteotomy performed with different techniques

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Abstract

Introduction Opening- and closing wedge osteotomies are the two most commonly used variants of high tibial osteotomy in medial gonarthrosis associated with varus deformity.

Purpose Based on a retrospective analysis of the results of surgical treatment of patients with medial gonarthrosis associated with varus deformity of the proximal tibia, to evaluate functional and radiological outcomes of high tibial osteotomy performed with two different surgical techniques.

Material and methods The study included 37 patients (26 men and 11 women) aged 20 to 54 years (42.84 ± 9.1) with meadial gonarthrosis associated with varus deformity in the frontal plane. The first group included 23 patients with 25 operated limbs who underwent open wedge osteotomy (OWO), the second group included 14 patients who underwent closed wedge osteotomy (CWO).

Results Comparison of MPTA, LDTA, aPPTA and MAD in both groups after surgery did not show a statistically significant difference ($p > 0.05$), but in the closing wedge group, the recorded values had an extremely wide range. The results on the Lisholm-Tegner scale after surgery compared between the two groups showed a statistically significant difference ($p = 0.05$), this parameter showed that the opening-wedge osteotomy was more effective.

Discussion Opening wedge osteotomy is a more predictable surgical procedure compared to closing wedge osteotomy. In opening wedge osteotomy, there are significantly fewer cases with excessive or insufficient correction of reference angles and lines than after closing wedge osteotomy.

Conclusion Absence of specific surgical complications in the studied patients demonstrates the safety of both surgical techniques. The study showed an extremely wide range of MPTA and LDTA values in the closed wedge osteotomy group, which were beyond the preoperative planning. The CWO group had the highest number of patients who underwent hypercorrection of the mechanical limb axis, which was beyond the reference values. It is possible to use a small allograft or not to use it at all in OWO, which makes it a more manageable technology for correcting limb bone deformity.

Keywords: high tibial osteotomy, medial gonarthrosis, opening wedge osteotomy, closing wedge osteotomy

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INTRODUCTION

Osteoarthritis (OA) of the knee joint is a common and multifactorial disease that can lead to severe joint dysfunction due to cartilage wear, limb axis changes, and disorders in normal joint biomechanics [1]. In most OA patients, degenerative changes in the knee joint are associated with varus deformity, leading to overload of the medial compartment of the knee joint and terminal wear of the articular cartilage [2]. To eliminate the "mechanical" OA symptoms in the knee joint and, first of all, pain, various surgical techniques are used: corrective osteotomy of the proximal tibia (PT), total knee arthroplasty, unicompartmental knee arthroplasty, and arthroscopic surgery. Among them, corrective PT osteotomy is the method of choice in young and active patients with a high level of functional requirements [3, 4]. Corrective PT osteotomy allows the patient to get rid of pain, restore the impaired axis of the limb and delay the need for total knee arthroplasty [5].

The most commonly used methods for performing this operation in practice are closing wedge osteotomy (CWO) and opening wedge osteotomy (OWO). Excellent results have been reported using both methods, each with its own potential advantages and shortcomings [6, 7].

Purpose To evaluate functional and radiographic outcomes of high tibial osteotomy performed with two different surgical techniques for medial gonarthrosis associated with varus deformity of the proximal tibia.

MATERIALS AND METHODS

Study design: retrospective continuous cohort single-center study.

The study included patients who underwent corrective PT osteotomy in the period from 2021 to 2023 for medial gonarthrosis and associated varus deformity of the knee joint due to disordered reference angles of the proximal tibia, confirmed by clinical and radiographic findings.

Patient exclusion criteria were post-traumatic osteoarthritis, previous knee joint infections and systemic connective tissue diseases, aseptic osteonecrosis, absence of knee joint deformity in the frontal plane, varus deformity at the level of the knee joint due to the femur, age over 60 years, flexion contracture > 10°.

The study excluded patients who had knee joint radiographs taken in wrong positions in the postoperative period that did not allow assessment of reference angles and lines, or who did not have full lower-limb length radiographs.

All patients included in the study had anteroposterior full length radiographs of both lower limbs, and radiographs of the knee joint in two projections. For radiographic analysis, the medial proximal tibial angle (MPTA), lateral distal tibial angle (LDTA), and the degree of displacement of the mechanical axis of the limb (MAD) were measured. In plain radiographs of the knee joint in the lateral projection, the angle of inclination of the articular surface in the sagittal plane (aPPTA) was determined.

The study included 37 patients (26 (72.2 %) men and 11 (29.8 %) women), who underwent surgery on 39 knee joints. The average age of OWO patients was (43.04 ± 9.9) years and (42.5 ± 7.8) years of CWO patients.

The patients were divided into two groups according to the method of the surgical intervention. The first group included 23 patients (25 operated limbs, who underwent opening wedge osteotomy, the second group were 14 patients who underwent closing wedge osteotomy.

Preoperative planning was performed using the BoneNinja tablet multimedia application or the Weasys computer application using the Miniaci method.

Surgical technique Surgical interventions were performed under spinal anesthesia in both groups, using a pneumatic tourniquet on the affected limb. In the group of OWO patients, the surgical approach was performed through two skin incisions of 5 cm and 3 cm, placing the larger approach in an oblique direction coinciding with the course of the tendons of the pes anserinus muscles at a level of 4–5 cm from the edge of the articular surface of the tibia. The shorter approach was performed at the level of the lower third of the bone plate for its fixation with screws. According to the technique described by Lobenhoffer [8], multiplanar osteotomy of the proximal tibia and reduction of bone fragments were performed using special reduction gussets and expanders. The resulting gap was filled with a proportionate allograft from the head of the femur. Osteosynthesis was performed using a special proximal tibial medial bone plate fixed with screws with angular stability (special T-plate). In case of CWO, an anterolateral surgical approach to the proximal tibia was performed, a wedge osteotomy was performed in the frontal plane with removal of the bone wedge, the size of which was determined at the preoperative stage during radiographic planning of the osteotomy. To perform reduction from the same surgical approach, resection of the fibula was performed at the border of its upper and middle thirds. Osteoclasia was used to bring the bone fragments together and fix them with a lateral tibial plate fixed with screws with angular stability. In both techniques, the postoperative wounds were sutured tightly, without wound drainage.

Postoperative care The rehabilitation of patients in both groups included unloading of the limb for 6 weeks after surgery with early function. From the day of surgery, patients were verticalized and began to recover the impaired range of motion in the knee joint. Plaster or other immobilization of the limb was not used. Regardless of the knee radiographic findings, patients after surgery began to increase the axial load from postoperative week 6 to 8, bringing it to full weight-bearing within another 4–8 weeks.

Assessment of results In the postoperative period, patients filled out the Lysholm-Tegner questionnaire [9] remotely in Google forms, starting from the first year after the operation.

Statistical analysis Based on the initial data of the patients included in the study, Microsoft Excel spreadsheets were created. For statistical processing of the obtained data, we used the Past ver. 4.15 program. All data were checked for compliance with the normal (Gaussian) distribution using the Shapiro – Wilk and Kolmogorov – Smirnov criteria. Data that did not correlate with the normal distribution were examined using nonparametric statistics methods. Samples were compared using the Mann – Whitney and Kruskal – Wallis criteria.

Limitations of the study Significant limitations of the study were its retrospective nature, small sample size, assessment of joint function using the specialized Lysholm – Tegner scale only in the postoperative period, and the performance of surgical interventions by different surgeons, which could affect such parameters as the duration of the operation, its reproducibility, and a number of others. Moreover, the most important limitation of all so-called “industrial”, or standardized types of osteotomies, is that the correction of the deformity is performed beyond its apex, so an undesirable change in adjacent reference angles is a natural consequence of violating osteotomy rules [10], what is also confirmed by our study.

RESULTS

Comparison of MPTA before surgery in both groups revealed that the values were almost equal, whereas after surgery, despite the absence of a statistically significant difference ($p > 0.05$), in the group with a closing wedge the values were in an extremely wide range (Table 1). This effect was equally representative for LDTA (Table 2).

Table 1

MPTA (°) values

Statistical parameters	MPTA (before surgery)		MPTA (after surgery)	
	Opening wedge	Closing wedge	Opening wedge	Closing wedge
P value	0.5488		0.4719	
Mean	87.32	86.307	91.72	90.96
Median	87.1	86.25	91.55	90.55
Max	99.7	91.9	98.7	99.2
Min	81.3	80.1	84.6	82
Stand. dev.	3	3.3	3.5	4.5

Table 2

LDTA (°) values

Statistical parameters	LDTA (before surgery)		LDTA (after surgery)	
	Opening wedge	Closing wedge	Opening wedge	Closing wedge
P value	0.0825		0.837	
Mean	88.79	91.035	92.04	91.675
Median	89.4	91.1	92.05	91.05
Max	95.5	96.1	97.4	99.4
Min	81.5	82	85.7	83.9
Stand. dev.	2.7	3.7	2.9	4.4

As stated above, the change in LDTA being an adjacent reference angle of the operated limb is explained by the peculiarity of all variants of standardized osteotomies of the femur or tibia, which are performed not at the level of the deformity apex (which is often at the level of the knee joint), but outside it, thus adapting to the requirements of the implant used during the operation. This effect requires further study, especially for assessing the function of the ankle joint after surgical interventions.

Having compared the angle of inclination of the articular surface in the sagittal plane (aPPTA) after surgery, a higher variability of the indicators was found for osteotomy with an opening wedge (Table 3). Evaluation of this parameter is extremely important since the inclination of the articular surface in the sagittal plane, often referred to in foreign orthopedic literature as a slope, is of great importance for correct functioning of the anterior cruciate ligament and has a significant impact on the sagittal stability of the knee joint.

Table 3

Values of aPPTA (°)

Statistical parameters	aPPTA (before surgery)		aPPTA (after surgery)	
	Opening wedge	Closing wedge	Opening wedge	Closing wedge
P value	0.3126		0.314	
Mean	79.21	80.44	77.25	78.88
Median	77.4	79.6	76.85	79.5
Max	90.2	88.3	87.7	83.7
Min	74.1	76.2	68.1	73.4
Stand. dev.	4.1	3.8	6.6	3.7

The parameter of displacement of the mechanical axis of the limb (MAD) did not show a significant difference ($p > 0.05$) in the results obtained when comparing the two groups after surgery. In both study groups, translation of the limb axis from the varus to the valgus was detected. However, in the closing wedge osteotomy group, this parameter changed in an extremely wide range with a low degree of repeatability from operation to operation (Table 4).

Table 4

MAD Values

Statistical parameters	MAD (mm)	
	Opening wedge	Closing wedge
P value	0.1221	
Mean	27.535	38.8
Median	26.45	35.95
Max	56.3	71.4
Min	11.1	16.1
Stand. dev.	10.9	18.9

At the same time, despite similar radiographic results which did not show significant differences in their analysis, the data of the Lysholm – Tegner questionnaire after the operation showed a statistically significant difference ($p = 0.05$) between the two groups. It was revealed in assessing this parameter, that the most effective was the osteotomy operation with an opening wedge after which the patients showed better functional postoperative results (Table 5).

Table 5

Data from the Lysholm – Tegner questionnaire

Statistical parameters	Lisholm scores	
	Opening wedge	Closing wedge
P value	0.054	
Mean	85.5	55.8
Median	89.5	50.5
Max	100	95
Min	50	39
Stand. dev.	15.4	20.7

In addition to filling out a validated questionnaire, patients answered three additional questions in the postoperative period:

— Are you satisfied with the surgical intervention performed?

— If you had to decide again about the need for this operation, would you agree to have it performed?

— Have you “forgotten” about the operation performed and are you able to live a full life without physical limitations associated with the operated knee joint?

If in OWO group, the "forgotten knee" effect was reported in almost 70 % of patients, in the CWO group this effect was reported by only 17 % of patients (Table 6). The obtained results do not allow us to draw unambiguous conclusions, since a valid and tested tool is required to evaluate such a complex parameter as "function of the operated joint", and the three separate questions we formulated are not such. The use of questionnaires developed for knee arthroplasty, such as FJS 12, or the new ones adapted for reconstructive surgery would allow us to more accurately answer questions about patient satisfaction after corrective osteotomy in the planned scientific studies.

Table 6

Rating of answers to additional questions

Questions	Opening wedge, %		Closing wedge, %	
	yes	no	yes	no
Are you satisfied with the surfery?	89	11	67	33
Would you repeat it if required?	89	11	71	29
Did you forget about the surgery?	65	35	17	83

Complications The results of our study show no specific perioperative complications (damage to the peroneal nerve, intraoperative fractures of the proximal tibia, osteotomy nonunion, septic complications, or others [11–14, 33]) detected in the patients, what may be explained by the small sample. We assessed the change in reference angles and lines beyond the reference values, but it was not considered as a complication in the course of this study. In the future, we plan to study the correlation between the precision of intraoperative correction of the mechanical limb axis and other reference angles and lines and the functional treatment results.

DISCUSSION

Corrective osteotomy of the proximal tibia is a valuable surgical method for bone deformity correction, normalization of reference lines and angles of the limb segment, and unloading the damaged part of the joint. One of the debatable points in discussing the operation of tibial osteotomy is the choice between the most common in practice surgical techniques. This means what the place is to intersect the bone and then fix it for subsequent consolidation. It is important to understand here that the choice of the osteotomy option with which the bone deformity will be corrected is not as important as compliance with general orthopedic rules. In particular, the goal of osteotomy can be considered achieved not only in case of subjective improvement of the patient's condition, but also provided that adequate values of the limb axis and reference angles and lines are restored. "Industrial" osteotomy of the proximal tibia, that is, an operation focused primarily on the used internal fixator in the vast majority of cases violates the so-called "rules of osteotomy" [10]. In simple terms, they can be formulated as follows: osteotomy must be performed at the deformity apex. Otherwise, restoration of reference angles and lines will require translation of bone fragments. All surgical variants of osteotomy of this segment (opening wedge, closing wedge, combination of opening and closing ones, and hinged osteotomy) are a compromise between these rules and the requirements of the implant used to fix the bone [32].

The choice of a particular surgical technique in the patients included in this study depended on the surgeons' preferences and was determined mainly by the traditions at the clinical department. Ideal candidates for surgery were physically active patients with arthrosis of the medial compartment of the knee joint with its varus deformity without terminal wear of the articular cartilage. The physiological age of the patients was no more than 60–65 years.

At the present stage of corrective osteotomies technologies at the knee joint there is a search in the scientific community for expansion of possibilities of this type of operations and analysis of unsatisfactory results of treatment associated with the choice of one or another surgical technique. Kuwashimo et al. conducted a study of 31 patients and 40 operated knee joints. The work compared the influence of the type of osteotomy on the rotational profile of the tibia. After analysing computed tomography findings, the authors came to the conclusion that in the group of patients who underwent CWO, excessive external rotation of the distal fragment of the tibia was observed, while in the group of patients with OWO no significant rotational changes were observed [15]. Similar results are presented in other scientific publications [16, 17]. This is obvious, since the integrity of the lateral cortical layer of the tibia and fibula is not violated during OWO, thus providing axial stabilization.

Of particular interest is the comparison of methods for changing the length of the limbs [18]. Thus, the conclusion of the meta-analysis by O-Sung et al. is that the average change in leg length before and after surgery with OWO was 6.96 mm. The average change between preoperative and postoperative leg length in CWO is 1.95 mm. Thus, the change in the length of the lower limbs after OWO is greater than after CWO. At the same time, 70 % of patients after OWO had a subjective feeling of discrepancy in the length of the lower limbs, whereas after CWO only 20 % noticed a discrepancy in length. A feeling of discomfort was felt in 37 % after OWO, and in 7 % of patients with CWO [19].

One of the observations obtained in the course of our study is that the change in MPTA, LDTA and MAD after surgery has an extremely wide range with a low degree of repeatability in closing-wedge osteotomy. Similar data were obtained by Hao et al. in a meta-analysis of studies comparing two methods of performing corrective PT osteotomy. Having analyzed the radiographic results, the authors concluded that there were significantly fewer cases of over- and undercorrection in opening-wedge osteotomy than in CWO patients [20].

Of interest is the influence of the type of surgical technique on the angle of inclination of the proximal tibia in the sagittal plane (aPPTA). Schubert et al. analyzed the results of surgical treatment of 279 knee joints, of which 179 joints were operated on using opening wedge osteotomy and 89 with a closing wedge. When comparing the parameters before and after surgerythere were virtually no changes in the parameters in the OWO group, with a minimal tendency of increase in the slope. However, in the CWO group, the surgery led to a significant decrease in the proximal tibial slope. The authors associate the decrease in the slope in CWO with the fact that after osteotomy, less bone tissue is resected in the dorsal direction than in the anterolateral direction. As a result, the osteotomy gap narrows in the dorsal direction [21]. Ji et al. reported the results of a study that included 440 knee joints, of which 50 with CWO and 390 with OWO. When comparing the tibial slope before and after surgery, there were no changes in the OWO group, while in the CWO group, a significant decrease in the proximal tibial slope was observed after surgery [22].

Our study of functional results established that patients who underwent OWO received a statistically significant improvement in the function of the operated joint according to the Lysholm – Tegner scale compared to patients who underwent closing-wedge osteotomy ($p < 0.05$). Scientific publications show no statistically significant difference in the functional results between the methods of proximal tibial osteotomy [23–30]. The authors associate the difference in the functional results of surgical treatment of patients revealed in the present study performed at the Vreden NMIC for TO with the small sample of patients. Some patients were excluded from the evaluation according to the relevant criteria. A more objective evaluation of the results requires a prospective study on larger samples.

The CWO group had a larger number of patients who underwent hypercorrection of the mechanical axis of the limb during surgical treatment, beyond the reference values. According to the authors, this may be due to the fact that in CWO it is important to reduce the proximal and distal fragments after wedge removal. Moreover, it is necessary to consider such a parameter as insufficient precision when performing filing associated with an oscillatory saw (excessive blade thickness, uneven oscillation, "beating" of the blade). This leads to the fact that after removal of a large wedge, hypercorrection of the mechanical axis of the limb occurs.

High variability of the parameters revealed in the course of the present study shows the need for a more thorough analysis of the surgical technique used in the clinic of our Center in order to make both methods as effective and safe as possible. Also, the question what was the reason for the significantly higher level of functional treatment results revealed in the course of the study in the OWO group requires further study, and how to make this parameter as stable as possible for patients of the studied profile.

Each of the variants of the PT osteotomies has its advantages and shortcomings. Further high-quality scientific studies using large samples of patients and including the method of controlled transosseous osteosynthesis in the comparative analysis would allow formulating a consensus on what to consider the method of choice and what approaches to surgical treatment of patients of the studied profile should be considered the most rational.

CONCLUSION

Corrective osteotomy of the proximal tibia is a current and effective method of surgical treatment of monocompartmental knee OA combined with frontal deformity. The absence of specific surgical complications in the patients studied demonstrates the safety of both surgical techniques assessed in this study.

Our study showed an extremely wide range of MPTA and LDTA values in the CWO group, which were beyond the preoperative planning. This group also had a greater number of patients who had hypercorrection of the mechanical axis of the limb during surgical treatment which was beyond the reference values. Thus, the surgeon has no right to make a mistake in performing this technique.

On the contrary, in OWO performance, there is always the possibility of using a smaller allograft or not using it at all. This circumstance makes OWO a more manageable technology for correcting limb bone deformity. In the OWO group, there is low repeatability of the sagittal inclination of the articular surface of the tibia from operation to operation.

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Original article
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Possible application of glassy carbon composite scaffolds in bone tissue engineering

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Annotation

Introduction Bone defect management remains one of the challenging problems of regenerative medicine, for the solution of which the most promising trend is the use of tissue-engineered implants based on composite scaffolds that stimulate osteogenesis. One of the main tasks of tissue engineering is the development of a scaffold that mimics three-dimensional architecture for osteogenic progenitor cells inside the scaffold, with the possibility of cell interaction with appropriate chemical and physical stimuli of natural bone.

The **purpose** of the work is to evaluate the possibility of using composite scaffolds based on glassy carbon in tissue engineering.

Materials and methods This study describes a reproducible method of obtaining three-dimensional porous glass-carbon-based scaffolds with surfaces modified with pyrocarbon (CF-C) and pyrocarbon and hydroxyapatite (CF-C-HAP) and investigates the porosity, strength characteristics, cytotoxicity, and osteoinductivity of the composite scaffolds obtained. Osteogenic differentiation of cultured human mesenchymal stem cells (MSCs) was evaluated on CF-C and CF-C-HAP scaffolds using common osteogenic markers such as: alkaline phosphatase (ALP) activity, alizarin red staining and quantitative real-time PCR (qPCR).

Results *In vitro* studies showed the biocompatibility of the developed scaffolds. The ability of CF-C-HAP to induce MSC differentiation in osteogenic direction and to produce calcium-containing matrix was established.

Discussion The scaffolds based on glassy carbon foam with pyrocarbon and hydroxyapatite coatings have a three-dimensional structure with open porosity, along with the strength comparable to the strength of the replaced tissue, and imitate the structure of trabecular bone. However, the strength of glassy carbon foam without coating is characterized by low compressive strength. All the studied materials demonstrated adhesive and proliferative activity of MSCs, high cell adhesion and absence of cytotoxicity. Determination of the mRNA expression level by real-time PCR showed that after 14 days, cells cultured on CS-C-HAP showed expression of the VDR, BMP7, IGFR1, SPP1 genes, what demonstrates osteogenic potential. The results of our studies on phosphatase activity and alizarin red staining demonstrated that the CF-C-HAP scaffold stimulates osteoblast differentiation *in vitro* in the osteogenic direction, as well as intracellular mineralization processes.

Conclusion Composite CF-C-HAP scaffolds based on glassy carbon foam support cell proliferation and differentiation and may be promising for use in bone tissue engineering.

Keywords: scaffold, glassy carbon, hydroxyapatite, osteogenesis, mesenchymal stromal cells, bone tissue engineering

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INTRODUCTION

Bone is a hard vascularized human organ that performs protective and mechanical support functions. Moreover, bone tissue can be attributed to as a part of the endocrine system: osteocalcin is secreted mainly by osteoblasts and in a decarboxylated form is able to bind to its own receptor on pancreatic beta cells and Leydig cells [1]; FGF23 (fibroblast growth factor 23) is synthesized by osteocytes and is the main regulator of phosphorus-calcium metabolism [1]. Bone tissue has good regenerative properties and is able to restore its structure without fibrous scar tissue. However, in the case of crush injury or aggravating factors, such as old age and/or concomitant somatic diseases, a deviation of bone tissue regeneration from organotypic towards substitution (formation of fibrous and cartilaginous tissue) is possible [2]. In critical size bone defects, independent recovery becomes impossible and surgical intervention is required. Extensive bone tissue defects can be caused by various factors: trauma, tumor and infectious processes, surgical interventions (resection of pathological areas). Besides, the increase in the geriatric population also contributes to the growth of the number of musculoskeletal system diseases.

Traditional approaches to the treatment of critical-size defects include the use of auto- and allografts [3, 4]. Autografts are considered the "gold standard" due to their good osteoinductivity, osteoconductivity, and osseointegration, which promote tissue formation at the defect site [5, 6]. However, the use of autografts has a number of significant disadvantages, such as an increase in the volume of surgical intervention, a limited volume of donor tissue, and an increased risk of postoperative complications (infection, bleeding, and damage to the neurovascular system of the donor site). The disadvantages of allografts include low osteoinductivity, the risk of transmitting infectious diseases from the recipient to the donor, the possibility of developing a histoincompatibility reaction and chronic inflammation, as well as violation of ethical and religious principles [7–9].

In recent years, tissue engineering has been considered a promising alternative to auto- and allografts in the treatment of bone tissue diseases and injuries [10, 11]. The concept of tissue engineering includes three main units: cells, scaffolds, and osteoinductive growth factors [12, 13].

Due to their bioinertness, porous carbon-based materials may be candidates for use as scaffolds. Scaffolds based on hydroxyapatite/porous carbon composite have been reported to promote MG-63 adhesion and proliferation [14]. However, despite this, the use of porous carbon materials as scaffolds is limited due to their low strength properties (the compressive strength of Duacel® carbon foam is 0.47 MPa). Since implantable scaffolds are subjected to various mechanical loads, including compression, tension, torsion, and shear [1], it is extremely important to create a material that is able to withstand the load during the regeneration process.

The **purpose** the work is to evaluate the possibility of using composite scaffolds based on glassy carbon in tissue engineering.

MATERIALS AND METHODS

Composite scaffolds Commercially available phenol-formaldehyde resin powder of the SFP-012A2 brand (Metadinea LLC) was used as a carbon precursor. The phenol-formaldehyde resin powder was dissolved in ethyl alcohol to obtain a solution with a concentration of 30 wt. % for subsequent impregnation of polymer templates (Regicell® PPI 80). The samples were impregnated by immersing them in an alcohol solution of phenol-formaldehyde resin at a temperature of 35–40 °C with treatment in an ultrasonic bath for 30 min, after which the samples were extracted and excess impregnation solution was removed from them by squeezing. The impregnated samples were dried using forced convection for 15 min at a temperature of 70 °C and then dried in a drying cabinet at temperatures of 70, 90, 120 °C. Curing was carried out at a temperature of 150 °C for 4 hours. Pyrolysis of foam precursors was carried out in a nitrogen atmosphere at a temperature of (1000 ± 50) °C, with a temperature rise rate of 2.5 °C/min and isothermal holding for 30 minutes. As a result of pyrolysis, glassy carbon foam replicating the precursor polymer was obtained. Then the process of pyrolytic carbon deposition on the surface of glassy carbon foam was carried out using the CVI method. Methane (purity 99.9 %, JSC MGPZ, Russia) was used as a precursor gas, the process temperature was (1050 ± 50) °C, the process duration was 20 hours.

Hydroxyapatite coating To grant the material osteoinductive properties, its surface was modified with hydroxyapatite. The operations described below were performed.

A porous carbon scaffold. pyrocarbon coated, with geometric dimensions of 10 × 10 × 20 mm was degreased and cleaned from mechanical impurities by boiling in ethyl alcohol, after which it was washed with distilled water to a neutral pH. The cleaned scaffold was immersed in an electrolyte solution with a component concentration providing a Ca/P ratio of 1.67, the pH was maintained at 3–5, the deposition time was 25 min at a temperature of 40 °C under constant stirring with a magnetic stirrer. A sample of pyrocarbon-coated carbon scaffold, acting as a cathode, was placed in the center of a spiral platinum anode. A Matrix MPS-3020 current source (China) was used for electrochemical deposition. After completion of the electrolytic deposition, the sample was removed and dried in air to constant weight, after which the electrolyte residues were removed by washing in distilled water to neutral pH of the washing water. The washed sample was dried at a temperature of 140 °C to constant weight.

The samples were labeled as follows: CF (carbon foam), C (carbon coating), HAP (hydroxyapatite).

Density and porosity The volumetric density of the samples was calculated as the ratio of mass to volume; the volume was determined by measuring the geometric dimensions of the sample using a digital caliper. Pycnometry using helium was carried out to establish the true density of the carbon "skeleton" on the AccuPyc II 1340 device [13].

Porosity Ƥ (%) and pore volume V_P (cm^3/g):

$$Ƥ = \left(1 - \frac{\rho_b}{\rho_s}\right) \times 100\ \% \quad (1)$$

$$V_P = \frac{1}{\rho_b} - \frac{1}{\rho_s} \quad (2)$$

where ρ_b — volumetric density; g/cm^3; ρ_s — true density, g/cm^3.

Compressive strength The mechanical properties of the scaffolds were studied at room temperature on a universal testing machine manufactured by Zwick/Roell (Germany) under a constant speed of movement of the active crosshead of 0.5 mm/min.

To conduct the tests to determine the compressive strength, parallelepiped-shaped samples sized 10 × 10 × 20 mm were used.

When preparing (cutting) the samples, treatment of the loading surfaces was assessed. The ends of the samples were made plane-parallel to each other to avoid skewing during loading. Otherwise, destruction could occur at the ends of the sample, and the ultimate strength would be significantly lower than the actual one. To minimize the effect of skewing, the tests were carried out using a special floating support (Fig. 1). During the test, the loading diagram was recorded in the coordinates "Load-Deformation", the ultimate strength σ_{comp} was calculated using the formula:

$$\sigma_{comp} = P_{max}/bh \quad (3)$$

where: P_{max} — maximum load, H; b — sample width, mm; h — sample thickness, mm.

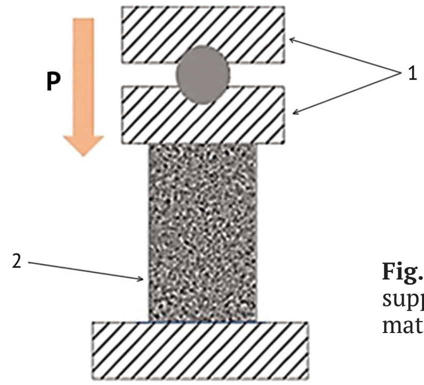


Fig. 1 Loading diagram: 1) floating support; 2) a sample of carbon porous material

To obtain statistically reliable data, the average value of at least five different measurements was obtained and the standard deviation was calculated.

Cell culture The study was performed using a primary culture of human dental pulp mesenchymal stromal cells (DPSCs) which phenotype (CD44+CD54+, CD90+, CD105+, CD34–, CD45–, HLA–DR–, CD31–, CD133–) is consistent with MSCs. The primary culture of human multipotent mesenchymal stromal cells was isolated from the third molar rudiment extracted for orthodontic reasons (DPSCs, Dental Pulp Stem Cells) of a healthy 16-year-old patient. The aseptically extracted tooth rudiment was crushed with scissors to a size of 1–2 mm^3 and dissociated with a solution of 0.25 % trypsin — 0.02 % EDTA (ethylenediaminetetraacetic acid) (PanEco, Russia) for 30 min at 37 °C. The isolated cells were centrifuged for 3 min at 200 g and placed in DMEM/F-12 (Dulbecco's modified Eagles medium, PanEco) culture medium at a 1:1 ratio with the addition of 10 % fetal bovine serum (FBS), transferred to 25 cm^2 flasks and cultured in an atmosphere of 5 % CO_2 at 37 °C in DMEM (PanEco) medium containing 10 % FBS (HyClone), 100 units/ml penicillin/streptomycin and the addition of 2 mM L-glutamine. Upon reaching a subconfluent state, the cells were treated with 0.25 % trypsin-EDTA solution and transferred to 75 cm2 flasks, cultivation was carried out in DMEM / F-12 medium 10 % FBS, 100 units / ml penicillin / streptomycin and the addition of 2 mM L-glutamine in a ratio of 1: 1 (Life technologies, USA) at 37 °C in an atmosphere of 5 % CO_2. As they grew and reached a subconfluent state, the cells were treated with 0.25 % trypsin-EDTA solution and passaged into new flasks in a ratio of 1: 2. Cells at passage 3 were used for the studies.

Citotoxicity The cell viability was studied using the MTT test, which is based on the restoration of a colorless tetrazolium salt (3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide, MTT) by mitochondrial and cytoplasmic dehydrogenases of living metabolically active cells with the formation of blue crystals of formazan, soluble in dimethyl sulfoxide.

After 2 days from the introduction of the extracts of the materials, the culture medium was removed and 100 µl of a 0.5 mg/ml MTT solution in DMEM/F12 culture medium without serum were added to each well. After incubation for 3 hours at 37 °C in a humidified atmosphere of 5 % CO_2, the liquid was removed, 100 µl of dimethyl sulfoxide (DMSO) were added and, shaking the plates at room temperature for 10 min, the formed formazan salts were dissolved. The amount of reduced formazan was determined by the optical density of the solutions on a model 680 photometer (BIO-RAD, USA) at a wavelength of 540 nm. Statistical analysis of the obtained results was performed using the nonparametric Mann – Whitney U-test. The standard deviation from the mean value was taken as an error, differences according to the Mann – Whitney U-test at $p < 0.05$ were taken as reliable.

Viability, adhesive, proliferative and differentiating activity of human MSCs To study the viability, adhesive, proliferative and differentiating activity of human MSCs, the cells were seeded on the surface of the samples at a density of 40 thousand/cm^2 and cultured for 14 days, while the volume of the medium was 0.5 ml/well. The medium was changed every 3–4 days. Differentiating activity of the cells was assessed by determining the degree of calcification and detecting the activity of alkaline phosphatase in the cells. To determine the viability of the cells, the fluorescent staining method with a mixture of SYTO 9 dyes, propidium iodide and Hoechst 33342 was used. The fluorescent dye SYTO 9 in the study mode λ_{exc} = 450–490 nm, λ_{emiss} = 515–565 nm stained DNA and RNA of living and dead cells in green color. The intercalating reagent propidium iodide in the study mode λ_{exc} = 546 nm, λ_{emiss} = 575–640 nm stained the nuclei of dead cells red. The fluorescent dye Hoechst 33342 in the study mode λ_{exc} = 355 nm, λ_{emiss} = 460 nm stained the DNA of living and dead cells blue. Microphotography of the cells was taken on an Axiovert 200 microscope (Carl Zeiss, Germany).

The degree of calcification was determined by staining calcium phosphate deposits with alizarin red (pH = 4.1). For this purpose, after the end of cultivation, the cells were washed with 0.01 M phosphate buffer (pH = 7.4) and fixed for 20 min. in 3.7 % buffered formaldehyde solution. After removing the fixative and washing with deionized water, the cells were stained with 2 % alizarin red solution for 5 min to detect the formation of mineralized matrix. Cell morphology and the amount of calcifications were assessed using an Axiovert 200 microscope (Carl Zeiss, Germany). Alkaline phosphatase activity was determined using a reagent kit (Alkaline phosphatase kit, Sigma 86-R) according to the manufacturer's instructions. The cells were fixed for 30 sec in citrate-acetone-formaldehyde fixative, washed with deionized water and stained for 15 min with a buffered solution containing naphthol-AS-phosphate, fast red violet (chromogenic substrate used to determine alkaline phosphatase activity). The wells were washed with deionized water and counterstained with hematoxylin solution for 2 min. After washing three times with deionized water, the samples were air-dried. Cell morphology and staining were assessed using an Axiovert 200 microscope (Carl Zeiss, Germany).

Upon completion of the cultivation, the samples were prepared for examination by scanning electron microscopy (SEM). The samples were washed in 0.1 M phosphate-buffered saline (pH 7.4) and fixed for 12 hours at 5 °C in 2.5 % buffered glutaraldehyde. After fixation, the samples were washed with water and dehydrated at 4°C sequentially in a battery of aqueous ethanol solutions of ascending concentrations (50 %, 75 %, 80 %, 90 %) and in absolute ethanol at the final stage. At each stage, the samples were immersed twice for 5 min in the appropriate ethyl alcohol solution. To remove alcohol, the samples were transferred to hexamethyldisilazane (HMDS) for 30 min, and were air-dried thereafter. The microstructure of the samples was studied using a scanning electron microscope with a Tescan Vega II field emission source (TESCAN, Czech Republic) in secondary electrons (SE type detector) at an accelerating voltage of 20 kV.

The phenotypic expression profile of the cultured cells was assessed by real-time PCR on day 14. The expression of 22 marker genes reflecting osteogenic differentiation processes was studied. The analyzed genes were selected from the database http://www.sabiosciences.com/ for PCR profiling of various biological processes (Table 1).

The gene transcription level was normalized by the average expression levels of the house-keeping genes β-actin and rplp0 (ribosomal protein, large, P0). Gene-specific primers were selected using the Primer Express 3 (Applied Biosystems, USA) (Table 1). The “Isolation of full-length poly (A) mRNA on magnetic particles” kit (Silex, Russia) was used to isolate total matrix RNA from the cells. The resulting mRNA was used to synthesize complementary DNA using the “Synthesis of the first strand of cDNA (oligo (dT) 15)” kit (Eurogen, Russia). cDNA was used as a template for real-time PCR, which was performed on a CFX 96 device (BioRad, USA) using a kit from Eurogen containing the intercalating dye SybrGreen. For this, the reaction mixture was defrosted and thoroughly mixed. The reaction components were mixed in the following sequence (per 25 µl reaction): qPCRmix-HS SYBR — 5 µl, PCR primer 1 — 0.3 µM, PCR primer 2 — 0.3 µM, cDNA template — 1 ng per reaction and sterile water — up to 25 µl. The concentration of primers in the optimization reactions was 0.05 pmol/µl, the concentration of Mg2+ ions was from 1.5 mM, the enzyme concentration was from 0.2 units per 20 µl reaction. The length of the primers was on average 24 nucleotides. Annealing temperature was 60 °C, the length of the amplified fragment was 94–100 nucleotide pairs.

Table 1

Genes which expression was assessed in the study

Abbrivation	Genes name	NCBI Reference Sequence
ALPL	alkaline phosphatase, liver/bone/kidney	NM_000478.4
BGLAP	osteocalcin (bone gamma-carboxyglutamate (gla) protein)	NM_199173.4
BMP1	bone morphogenetic protein 1	NM_006129.4
BMPR1A	bone morphogenetic protein receptor, type IA	NM_004329.2
COL1A1	collagen, type I, alpha 1	NM_000088.3
COL3A1	collagen, type III, alpha 1	NM_000090.3
EGFR	epidermal growth factor receptor	NM_005228.3
FGF-2	fibroblast growth factor 2 (basic)	NM_002006.4
FGFR1	fibroblast growth factor receptor 1	NM_015850.3
IGF1	insulin-like growth factor 1 (somatomedin C)	NM_000618.3
IGFR1	insulin-like growth factor 1 receptor	NM_000875.3
IGF2	insulin-like growth factor 2	NM_000612
RUNX2	runt-related transcription factor 2	NM_004348.3
SMAD2	SMAD family member 2	NM_005901.5
SMAD4	SMAD family member 4	NM_005359.5
SMAD5	SMAD family member 5	NM_005903.6
SPP1	osteopontin-1 (secreted phosphoprotein 1)	NM_000582.2
TGFBR1	transforming growth factor, beta receptor 1	NM_004612.2
TNF	tumor necrosis factor	NM_000594.3
VDR	vitamin D (1,25-dihydroxyvitamin D3) receptor	NM_000376.2
BMP7	bone morphogenetic protein 7	NM_001719.2
TWIST1	twist family bHLH transcription factor 1	NM_000474.3
RPLP0	ribosomal protein, large, P0	NM_001002.3
ACTIN	beta-actin	XM_006715764.1

The reaction was carried out according to the following mode: 1 cycle 95 °C — 5 min; 2–40 cycles 95 °C — 30 sec, 60 °C — 40 sec; 1 cycle (dissociation stage) 95 °C — 15 sec, 60 °C — 1 min, 95 °C — 15 sec. To determine the specificity of the reaction, the amplification products were checked by electrophoresis in 2 % agarose. The specificity of the reaction was also determined from the temperature dissociation curves of the amplicons using the CFX Manager 2.0 program (BioRad, USA). The analysis of data obtained using real-time PCR was performed using the threshold fluorescence method ΔΔC(T), using the web resource for PCR data analysis Qiagen (http://www.qiagen.com); the construction of heat maps of gene expression was performed using the Genesis program (https://genome.tugraz.at/genesisclient/genesisclient_description.shtml).

The obtained expression data were analyzed using the threshold fluorescence method ΔC(T):

$$\Delta C(T)gene = C(T)gene - C(T)\ house\ keeping,$$

where C(T)house keeping is threshold fluorescence house keeping gene.

The difference between gene expression in the experiment and the control was calculated using the method ΔΔC(T):

$$\Delta\Delta C(T)gene = \Delta C(T)gene\ experiment - \Delta C(T)gene\ control.$$

The relative level of gene expression was calculated using the formula:

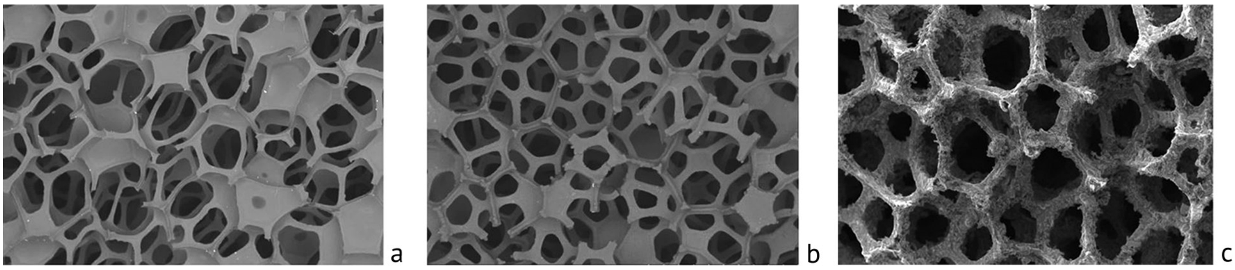
$$Rel.\ Exper. = 2\Delta\Delta C(T)gene.$$

The online services http://www.qiagen.com/, the Mayday-2.14 program (Center for Bioinformatics Tübingen, Germany) and the Genesis program (Sturn et al., 2002) were used to analyze the data array. The sample without the reverse transcription stage served as a control. Only those results were considered for which changes in the gene expression level were observed at $p < 0.05$.

Statistical processing of the results was performed using the Origin 8.1 program, the standard deviation from the mean was taken as an error; differences according to the Mann – Whitney U-test at $p < 0.05$ were taken as reliable.

RESULTS

Figure 2 and Figure 3 show SEM photographs of carbon scaffolds with and without different types of surface modification in comparison with spongy bone. All the studied samples had a cellular structure consisting of cells communicating with each other, morphologically similar to spongy bone. The size of macropores is in the range from 150 to 200 μm.



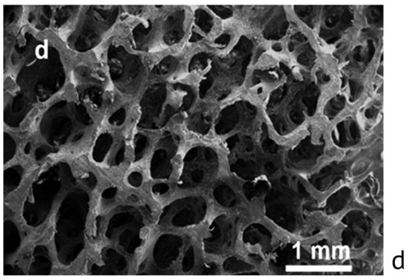
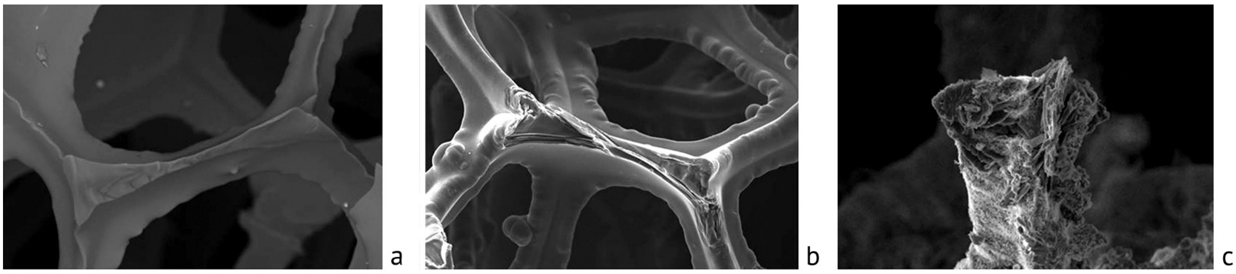


Fig. 2 SEM photo of the microstructure: *a* carbon scaffold; *b* carbon scaffold with pyrocarbon coating; *c* carbon scaffold with pyrocarbon coating modified with hydroxyapatite; *d* trabecular bone [15]. Magnification ×50



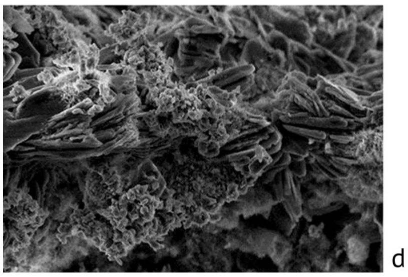


Fig. 3 SEM photo of the surface of scaffolds based on: *a* glassy carbon foam (magnification ×400); *b* glassy carbon foam with a pyrocarbon coating (magnification ×300); *c* glassy carbon foam with a pyrocarbon coating modified with hydroxyapatite (magnification ×500); *d* glassy carbon foam with a pyrocarbon coating modified with hydroxyapatite (magnification ×850)

In terms of their mechanical characteristics, scaffolds used in tissue engineering should be comparable to the characteristics of the bone tissue that should be replaced (Fig. 4).

As can be seen in the presented diagram, the compressive strength of the modified scaffolds was ~ 3 MPa, which is within the range of values for trabecular bone (2 ~ 10 MPa) [16]. The porosity of the studied samples was in the range from 89 to 96 %.

Based on the obtained data, the samples that showed the best results in the physical and mechanical tests, CF-C and CF-C-HAP, were selected for *in vitro* studies.

The study of the metabolic activity of human MSCs showed the absence of toxic effects on the cells of extracts from all the studied materials (Fig. 5).

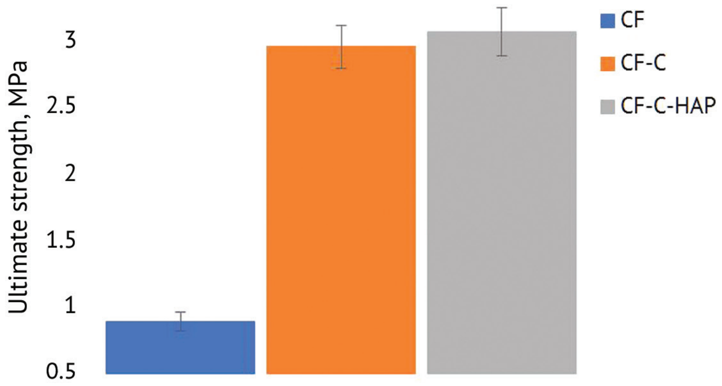


Fig. 4 Compressive strength of carbon scaffolds according to the type of surface modification

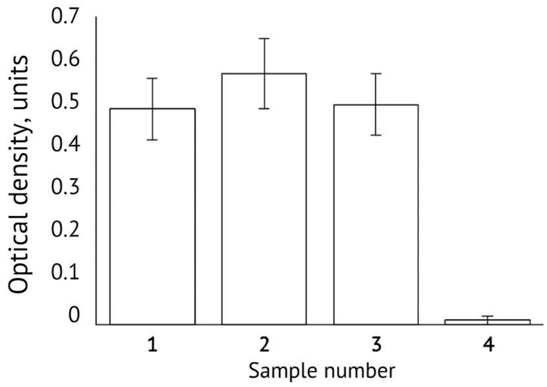


Fig. 5 Metabolic activity of human MSCs based on the results of the MTT test during 48 h incubation with three-day extracts from the studied materials: 1) CF-C; 2) CF-C-HAP; 3) negative control (DMEM/F12 medium); 4) positive control (DMEM/F12 medium + 10 % DMSO)

The results of the study on the viability, adhesive and proliferative activity of human MSCs during cultivation on the surface of carbon scaffolds, carried out using fluorescence microscopy methods, are shown in Figure 6.

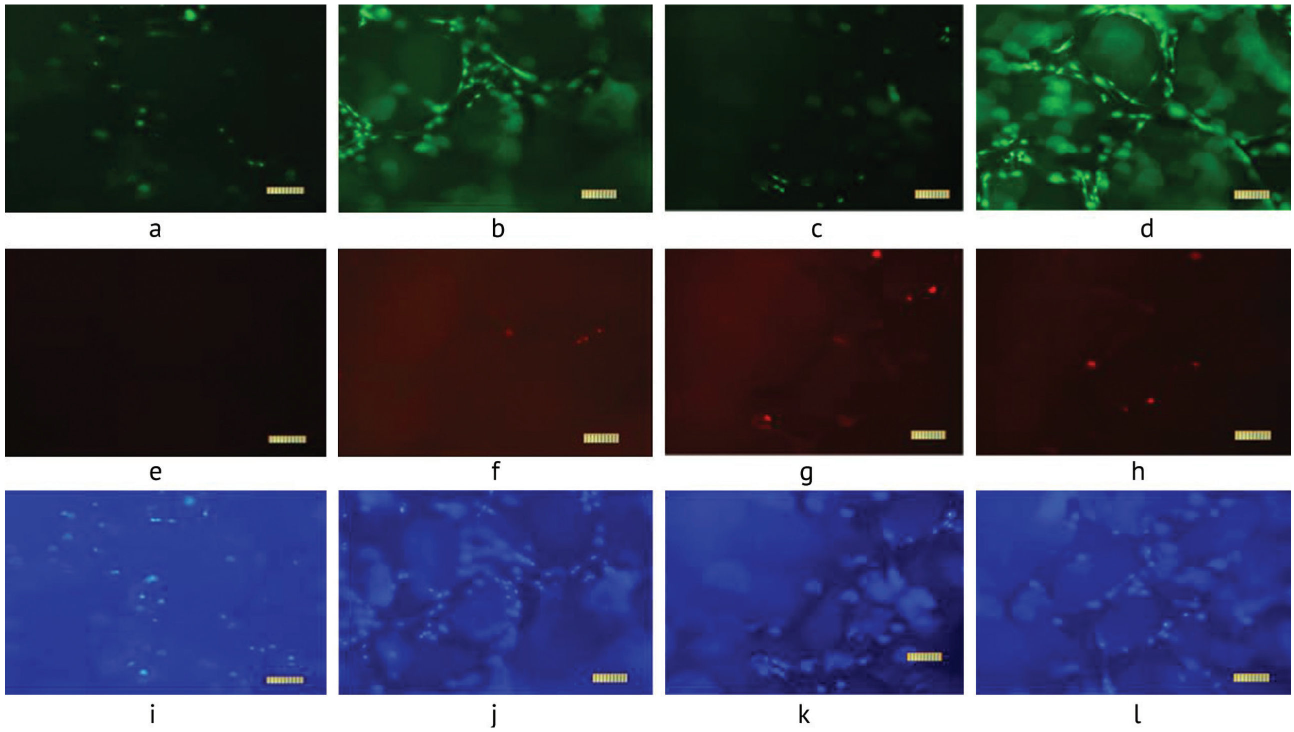


Fig. 6 External human MSCs during cultivation on the surface of CF-C and CF-C-HAP on the seventh (*a, e, i; c, g, k*) and fourteenth (*b, f, j; d, h, l*) days after seeding. Staining SYTO 9 (*a, b, c, d*); PI (*e, f, g, h*); Hoechst 33342 (*i, j, k, l*). Scale bar 100 µm

The differential fluorescent staining method is based on monitoring viable cells depending on the integrity of their membrane. The SYTO 9 dye stains all cells in the culture (green staining), while the disruption of the membrane integrity ensures its permeability for the selective DNA dye propidium iodide (red staining of the nucleus). Hoechst 33342 is a cell permeator (blue staining), staining the DNA of living and dead cells [17].

For control, fluorescent microscopy was performed on cells cultured on a cover glass (Fig. 7).

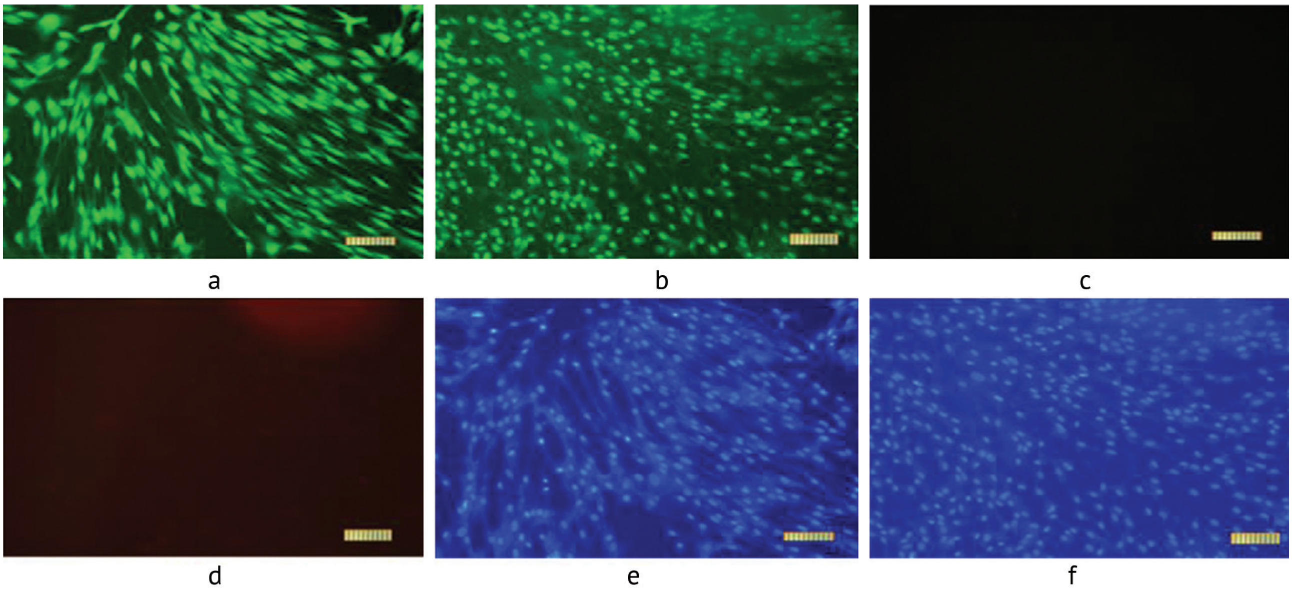


Fig. 7 Appearance of human MSCs during cultivation on the surface of a cover glass (control) on the seventh (*a, c, e*) and fourteenth (*b, d, f*) days after seeding. Staining SYTO 9 (*a, b*); PI (*c, d*); Hoechst 33342 (*e, f*). Scale 100 μm

Also, using SEM, the morphology of the cells was analyzed after culturing for 14 days (Fig. 8).

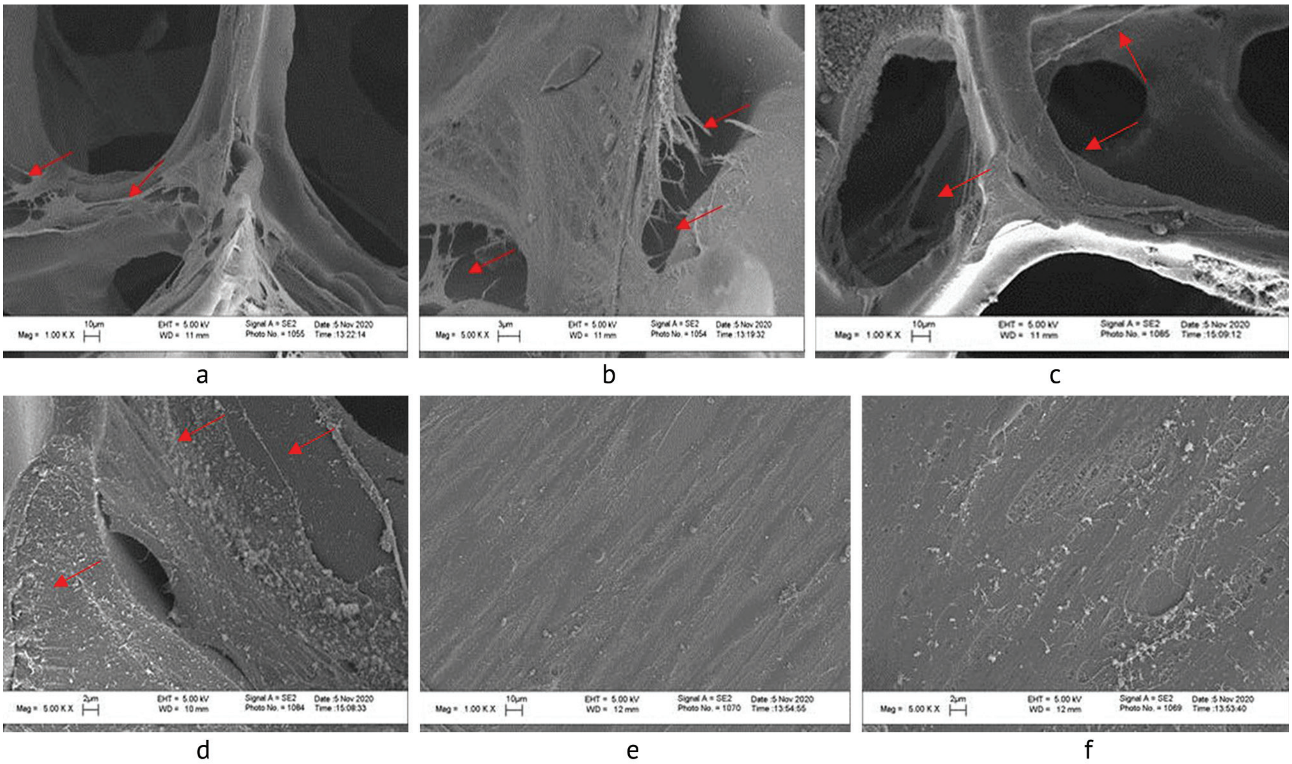


Fig. 8 The appearance of human MSCs cultivated on the surface of: scaffolds based on CF-C (*a* magnification 1000, *b* magnification 5000), CF-C-HAP (*c* magnification ×1000, *d* magnification ×5000) and a cover glass (*e* magnification ×1000, *f* magnification ×5000) on the 14th day after seeding.

Determination of mRNA expression level using real-time PCR Human MSCs cultured on coverslips in DMEM/F12 medium supplemented with 10 % FBS, 100 U/ml penicillin/streptomycin were used as a control.

Comparison of the materials with different surface modifications showed that predominantly similar expression patterns of the studied genes were observed in the cultured cells (Fig. 9, Table 2).

In general, when compared with the control samples, a decrease in the transcriptional activity of all the studied genes was noted, but an increased content of SPP1, VDR and BMP7 gene transcripts was found in B1 samples and in the cells.

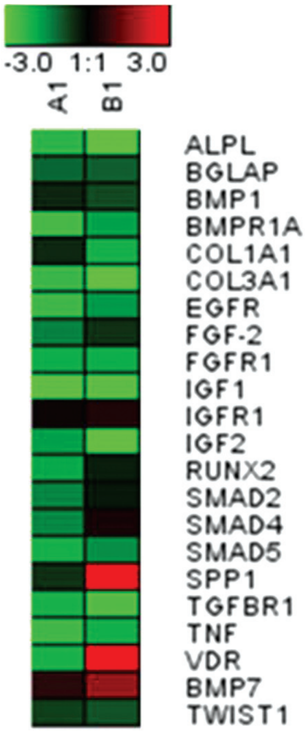


Fig. 9 Gene expression patterns in the cells growing on the samples A1 (CF-C), B1 (CF-C-HAP) in the form of heat maps. In the diagrams: black color - the expression level is comparable to the control; color grading from black to green reflects the degree of inhibition of gene expression, gradations from black to red reflect the level of stimulation relative to the control

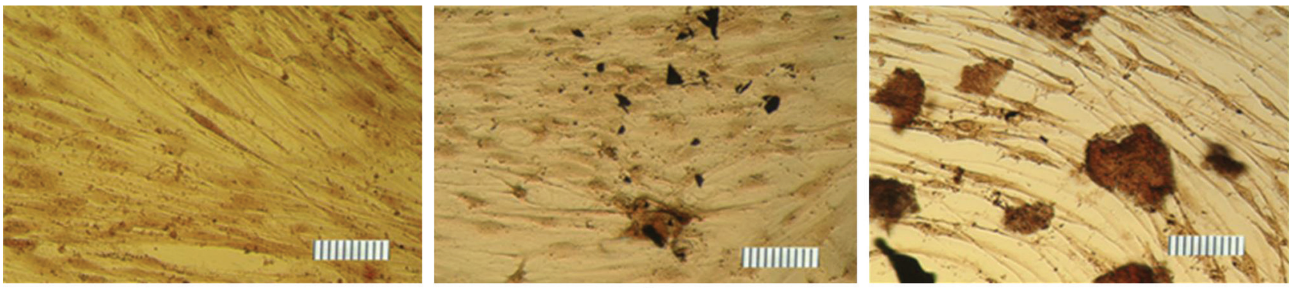
Table 2

Gene expression change parameter data from analyzed samples expressed as Log2

Genes	A1	B1
ALPL	−2.28	−3.80
BGLAP	−1.11	−0.76
BMP1	−0.47	−1.21
BMPR1A	−2.57	−1.14
COL1A1	−0.49	−2.50
COL3A1	−2.40	−3.33
EGFR	−2.47	−1.79
FGF-2	−1.40	1.10
FGFR1	−1.95	−1.85
IGF1	−2.90	−1.60
IGFR1	1.14	1.77
IGF2	−1.75	−2.17
RUNX2	−1.85	−0.81
SMAD2	−1.44	−0.59
SMAD4	−1.46	−0.65
SMAD5	−2.05	−1.87
SPP1	−0.58	46.21
TGFBR1	−2.08	−2.23
TNF	−2.49	−1.88
VDR	−2.09	17.51
BMP7	1.44	1.62
TWIST1	−0.73	−0.95

Osteoinductive potential of porous carbon-based matrices The initial stages of osteogenic differentiation of MSCs were analyzed using the Alkaline Phosphatase Kit (Sigma-Aldrich, USA), assessing the histochemical detection of alkaline phosphatase activity in the cells. Alkaline phosphatase, an ectoenzyme secreted by mature osteoblasts, is an early phenotypic marker of MSCs osteogenic differentiation [18–20]. Alkaline phosphatase activity is usually noted *in vitro* on the seventh day after the onset of osteoinduction and is visualized by staining on the 14th day.

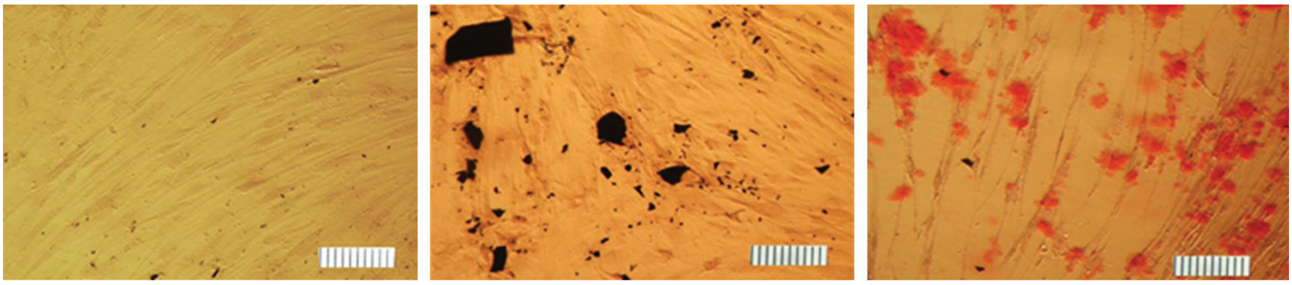
To assess the effect of scaffolds on osteogenic differentiation, cells were cultured on the surface of a cover glass, CF-C, CF-C-HAP (Fig. 10).



a b c

Fig. 10 Alkaline phosphatase activity of human MSCs cultured for 14 days on the surface of material samples: cover glass (*a*), CF-C (*b*); CF-C-HAP (*c*). DMEM/F-12 medium. Scale 100 μm

One of the quantitative methods for determining mineralization during osteogenic differentiation is staining with alizarin red. The appearance of MSCs cultured for 14 days is shown in Fig. 11.



a b c

Fig. 11 Appearance of MSCs cultured for 14 days in DMEM/F-12 medium (*a*) and in the presence of CS material samples (*b*); CS-HAP (*c*). Alizarin red staining. Scale bar 100 μm

DISCUSSION

One of the main tasks of tissue engineering is the development of a scaffold that imitates the three-dimensional architecture for osteogenic progenitor cells inside the scaffold that are able to interact with the corresponding chemical and physical stimuli of the natural bone [21]. Despite a significant research conducted in this area, the requirements for the design of scaffolds for tissue engineering have not been fully formulated. However, a number of key structural characteristics are identified that determine the possibility of intercellular interactions inside the scaffold. It is known that pore size, the degree of canal interconnectivity, as well as overall porosity play a decisive role in regulating the morphology and behavior of various cell types [1, 22–25]. Porosity and pore size make a significant contribution to the ability of the scaffold to maintain cell adhesion, which, in turn, has an impact on the cell population density in the scaffold volume, as well as on their distribution and migration [24, 26]. The pore sizes required by different cell types vary significantly, but on average, a pore size range of 100–500 μm is acceptable for efficient cell growth, migration, nutrient penetration, and waste removal. Increasing the pore size of the scaffold reduces the surface area, limits cell adhesion, and prevents the formation of protein-cell bridges. Moreover, the mechanical properties of the scaffold are impaired by increased empty spaces, which is another critical parameter in the design [17, 22]. For scaffolds intended for bone tissue regeneration, a pore size in the range of 150–400 μm is optimal for stimulating osteogenesis and vascularization deep into the tissue-engineered construct [22, 27].

In this study, we propose a technically simple and inexpensive method for obtaining scaffolds that imitate the structure of human trabecular bone tissue. Glassy carbon foam was chosen as the base for the composite scaffold. Glassy carbon foam based on a polyurethane template is a three-dimensional structure with a pore size of 150–200 μm, open porosity, mainly consisting of carbon. The pores in this range facilitate the infiltration of cells involved in proliferation, migration, and vascularization *in vivo* [27].

Due to the cellular structure and bioinertness, glassy carbon foams are suitable for use as scaffolds in tissue engineering [28, 29]. The most important characteristics of the material for use as scaffolds are porosity, strength, lack of toxicity, along with osteoinductivity and osteoconductivity [22, 30]. The scaffold material should have the strength comparable to the strength of the replaced tissue. Since glassy carbon foams are brittle materials, their strength characteristics are assessed by the compressive strength [28]. The compressive strength and elastic modulus of glassy carbon foams depend primarily on such parameters as volumetric density and porosity. It is extremely important to maintain high open porosity of scaffolds, since this favors cell adhesion and proliferation [27, 31]. One of the ways to improve strength characteristics is surface modification by applying various coatings. Pyrocarbon deposition allowed increasing the compressive strength to ~3 MPa, while maintaining the overall porosity at 93 %. The high porosity of the scaffold due to the large surface area ensures greater interaction with the extracellular matrix [32], which in turn promotes bone tissue ingrowth and vascularization [32]. Moreover, constant contact of the scaffold with the extracellular matrix over time leads to pore occlusion. Therefore, high porosity of the scaffold ensures sufficient permeability for the transport of nutrients and biomolecules [32].

To improve the osteoinductive properties of the scaffold, the surface was additionally modified with hydroxyapatite [27, 33]. SEM studies showed that the resulting coating is formed on both the external and internal surfaces of the scaffold, is homogeneous, and consists predominantly of lamellar hydroxyapatite crystals. The application of the hydroxyapatite coating resulted in a slight increase in strength characteristics, which is consistent with the results obtained in the work of Rahman et al [27].

The study of the metabolic activity of human MSCs showed the absence of toxic effects on the cells of extracts from all the studied materials. At the same time, a slight increase in the optical density of the solution to which the extract from CF-C-HAP was added was noted (Fig. 5). It may indicate the presence of water-soluble factors stimulating cell activity. However, statistical analysis of the results of the study of the metabolic activity of DPSC cells that was carried out using the nonparametric Mann-Whitney U criterion did not show significant differences with the control when the cells were exposed to extracts from all materials. Thus, it can be concluded that all the materials studied by us did not exhibit cytotoxicity and that there were no water-soluble components that affected the viability of human MSCs.

Studies of MSCs viability, adhesion and proliferative activity showed that at all experiment observation periods for CF-C and CF-C-HAP, adherent cells were detected, and the dynamics of their density increased during the observation periods. On the 14th day after incubation, a dense arrangement of cells was observed both on the surface and inside the three-dimensional scaffolds (Fig. 6).

SEM analysis of cell attachment and morphology showed that the cells actively proliferated on the surface of scaffolds modified with both pyrocarbon and hydroxyapatite. Modification of the surface of carbon scaffolds leads to the appearance of roughness (Fig. 2 b, c), which, in turn, is one of the factors stimulating osteogenesis [34].

The cells formed a dense monolayer growing through pores within the three-dimensional carbon scaffold. The cells were elongated with a flat surface and have extensive filopodia (Fig. 8 a, b), indicating strong cell adhesion and growth.

Determination of the mRNA expression level using the real-time PCR method showed (Table 2) that the cells cultured on CS-C-HAP showed gene expression after 14 days. VDR encodes the vitamin D3 receptor, which regulates the activity of mineral metabolism genes and controls calcium and phosphorus homeostasis [35, 36]. BMP7 is a stimulator of osteoblast differentiation, which is necessary for the differentiation of preosteoblasts into mature osteoblasts [37]. IGFR1 is an important regulator of bone tissue homeostasis, which probably stimulates the replication and differentiation of osteoblasts [38, 39], and also increases the expression of type I collagen in osteoblasts and reduces the transcription of matrix metalloproteinase (MMP)-13 [40], which destroys collagen fibers and bones [41]. SPP1 is a glycoprotein involved in osteogenesis [42–44], enhances differentiation and proliferation of osteoblasts [42, 44, 45], and modulates both bone formation and resorption due to the attachment of osteoclasts to the mineralized bone matrix [45]. Based on the data on the increase in the expression of genes associated with osteogenesis, it can be concluded that the developed materials have osteogenic potential.

Osteogenesis is the process of new bone formation that involves calcification of the pre-bone matrix and differentiation of osteoblasts, the precursors of bone tissue, into mature osteocytes. Matrix mineralization or calcification in osteoinduced MSCs can be detected by ALP activity and alizarin red staining. After 14 days of induction, a small number of ALP-positive cells were observed on the CF-C surface. Cells cultured on the CF-C-HAP surface (Fig. 10 c) showed higher ALP activity compared to Figure 10 a and 10 b. Alizarin red staining of the cultured cells showed that spontaneous osteogenic differentiation was absent in the control (Fig. 11 a). Staining of the MSC culture in the presence of CF-C gave a negative result similar to the control, indicating the absence of mineralization and differentiation in the osteogenic direction (Fig. 11 b). In the presence of CF-C-HAP (Fig. 11 c), cell clusters shaped as osteoblast nodules and deposits of extracellular matrix were observed, revealed histochemically by staining with alizarin red as calcifications, indicating its ability to induce MSC differentiation in the osteogenic direction and produce calcium-containing matrix.

The results of our studies on phosphatase activity and alizarin red staining showed that the CF-C-HAP scaffold stimulates osteoblast differentiation *in vitro* in the osteogenic direction, along with intracellular mineralization processes in osteoblasts.

CONCLUSION

Carbon scaffolds based on glassy carbon foam with a hydroxyapatite-modified surface have high porosity, developed surface, and reproduce the architecture of trabecular bone tissue. Application of a pyrolytic carbon-based coating helps to increase the strength characteristics and reduces the hydrophobicity of the carbon scaffold. Modification with hydroxyapatite significantly increases the roughness of the material, which has a positive effect on adhesion and cell attachment. All carbon scaffolds studied in the work showed no cytotoxicity.

It was found that scaffolds modified with hydroxyapatite possess osteoinductivity, are capable of inducing MSC differentiation in the osteogenic direction, producing a calcium-containing matrix and increasing the expression of genes associated with osteogenesis.

The material thus developed is promising for use in tissue engineering.

Conflict of interests *The authors declare no conflict of interest.*

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Histomorphometric characteristics of the metaepiphyseal plate of the distal femur of lambs during the period of their intensive growth

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Abstract

Introduction Growth zone injuries are quite common and account for 15–30 % of all skeletal bone injuries in children. Complications occur in 2–14 % of patients. An adequate experimental animal model is needed to develop new methods for treating growth zone injuries.

The purpose of the work is to identify patterns in the dynamics of histomorphometric characteristics of the metaepiphyseal cartilage of the distal femur of lambs during the period of their intensive growth.

Materials and methods The metaepiphyseal cartilage of the distal femur of 12 lambs (aged 3.5 and 5.5 months, 5 males and 7 females) previously participating in an experiment on the effect of osteosynthesis pins on the structural reorganization of the metaepiphyseal cartilage was studied. Histological, immunohistochemical, and histomorphometric studies were performed.

Results The zonal structure of the metaepiphyseal plate along with an increased proportion of PAS-positive structures in the outer layer of the border zone and in the calcified cartilage zone were determined. Masson staining revealed fuchsinophilic areas of the border zone matrix in the metaepiphyseal cartilage of animals aged 5.5 months, as well as an increase in the proportion of fuchsinophilic areas of the calcified cartilage zone compared to animals aged 3.5 months, which indicated increased mineralization. CD34 expression at 3.5 months was detected in the outer layer of the border zone, at 5.5 months the depth of vascular invasion increased, but did not reach the proliferating cartilage zone. A decrease in the thickness of the metaepiphyseal cartilage at the age of 5.5 months by an average of 18.2 % is due to a decrease in the thickness of the border zone by 1.9 times, while the thickness of the proliferating cartilage zone increased by 1.2 times.

Discussion The changes observed in the main substance of the metaepiphyseal cartilage indicated that the processes of matrix calcification are more intense in lambs by the age of 5.5 months. The depth of vascular penetration from the diaphysis is more pronounced than from the epiphysis. Fractures in the growth zone during the period of intensive growth can be caused by the predominance of the border zone and by the proliferating cartilage zone.

Conclusion Histomorphometric changes in the metaepiphyseal plate of the distal femur of lambs during the period of their intensive growth were characterized by a decrease in its thickness due to a marked decrease in the thickness of the reserve zone, while the thickness of the proliferating cartilage statistically significantly increased. The depth of vascular invasion in the border zone increased, but did not reach the proliferating cartilage zone, changes in the tinctorial characteristics of the ground substance indicated the activation of matrix calcification processes from the subchondral bone of the epiphysis and endomorphic ossification from the diaphysis.

Keywords: lambs, metaepiphyseal cartilage, histology, immunohistochemistry, histomorphometry

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INTRODUCTION

The growth zone (physis, metaepiphyseal plate, metaepiphyseal cartilage) is hyaline cartilage located between the epiphysis and metaphysis of tubular bones and is responsible for their longitudinal growth [1]. According to statistics, growth zone injuries are quite common and account for 15–30 % of all skeletal bone injuries in children; complications occur in 2–14 % of patients [2, 3]. Distal femur fractures are the most common in children, with Salter–Harris type II fractures dominating [4, 5].

Currently, there is an urgent need to develop effective methods of treating children with growth plate injuries that not only prevent the formation of "bone bridges" but also create conditions for complete regeneration of hyaline cartilage and normal bone growth [6, 7].

Experimental studies aimed at developing new methods for treating children with growth zone injuries and correcting pathological conditions associated with impaired function are relevant. An adequate animal model is needed to study the healing of metaepiphyseal plate damage. In preclinical studies, small mammals such as mice, rats, and rabbits are used as experimental models [8, 9, 10, 11, 12, 13]. Rodent models are not suitable for extrapolating experimental data to humans not only because rodent growth zones do not close during maturation, but also because of differences in their histological structure, blood supply, cell cycle, and growth time. Also, small animal models cannot simulate the biomechanical conditions of human skeletal loads [14, 15]. According to a number of authors, dogs and sheep are the most suitable experimental animals for studying the metaepiphyseal plate. Sheep are more similar to humans in terms of weight and bone size, and the long bones of their limbs are subject to similar loads. Moreover, their growth zone closes with age, and young sheep have plexiform bone structures similar to those of children during periods of rapid growth [15, 16, 17, 18]. Despite the availability of extensive information on the growth and development of animals, many phenomena of this biological process remain unexplored to date. In the available literature, we did not find data on structural changes in the metaepiphyseal plate of lambs during their growth. To determine the differences in the qualitative and quantitative characteristics of the metaepiphyseal cartilage from the norm, there is a need to compare them with similar characteristics of the metaepiphyseal cartilage of intact animals.

The **purpose** of the work was to identify patterns in the changes of histomorphometric characteristics of the metaepiphyseal cartilage of the distal femur of lambs during the period of their intensive growth.

MATERIALS AND METHODS

The object of study was the metaepiphyseal plate of the distal femur of the contralateral limb in 12 lambs (5 males, 7 females), which had previously participated in an experiment on the effect of osteosynthesis pins on the structural reorganization of the metaepiphyseal cartilage [19], at the age of 3.5 and 5.5 months (body weight — (21.92 ± 0.85) and (28.92 ± 2.4) kg, respectively). This is the period of rapid growth of the long bones in lambs. From 7 months of age, the growth rate decreases, while the muscle mass accumulates [20].

The animals were euthanized after premedication with a solution of 1 % diphenhydramine (0.02 mg/kg) and 2 % rometar (1 mg/kg), and a lethal dose of barbiturates. The animals were kept in the experimental conditions in accordance with the following regulatory documents: GOST R 33044-2014; PS SanPiN 3.3686-21; GOST 33215-2014; GOST 34088-2017.

For microscopic study, fragments of the distal articular end of the femur were cut out; next, the samples were fixed in a 10 % solution of neutral formalin for 48 hours. Decalcification was carried out in a mixture of hydrochloric and formic acid solutions (1:1), washed in water, dehydrated in alcohols, and embedded in paraffin using a standard method.

To obtain reliable information on the qualitative and quantitative characteristics of the metaepiphyseal cartilage, its zonal structure was considered, and paraffin sections of adequate orientation and thickness were used [21, 22]. Longitudinal serial sections along the femur axis (5.00 μm) were produced on an HM 450 microtome (Thermo Scientific, USA), which were stained with Alcian blue pH 2.5 and PAS-Reaction, using the three-color method according to Masson.

The immunohistochemical reaction was performed using the angiogenesis marker CD34 (CD34 [EP373Y]) (Abcam, UK) and the peroxidase detection system with diaminobenzidine with the micropolymer ab236469 (Rabbit specific HRP/DAB Detection IHC Detection Kit-Micropolymer, Abcam, UK). All stages of the immunohistochemical reaction were performed according to the protocol of the manufacturer for antibodies. Sections were counterstained with hematoxylin.

Histomorphometric examination and digitalization were performed on an AxioScope.A1 microscope with an AxioCam digital camera (Carl Zeiss MicroImaging GmbH, Germany) using the Zenblue image analysis program (Carl Zeiss MicroImaging GmbH, Germany).

The thickness of the metaepiphyseal cartilage (h, mm) was measured as the distance between its upper and lower borders with an interval of about 20 μm; 20 measurements were taken for each case. The thickness of the metaepiphyseal cartilage zones (h, μm) and their percentage ratio were determined. The boundary between the border zone and the proliferating cartilage zone was considered to be the point of appearance of the first flattened chondrocyte in the column; the boundary between the proliferating cartilage zone and the vesicular cartilage zone was considered to be the point of appearance of the first rounded chondrocyte; the boundary between the vesicular cartilage zone and the calcified cartilage zone was considered to be the point of appearance of areas of resorbable matrix [23]. The percentage of each zone was determined as a portion of the total thickness of the metaepiphyseal cartilage equal to 100 %.

Quantitative data were analyzed using descriptive statistics. The distribution pattern of data was assessed using the Kolmogorov test; the measure of central tendency was presented as a median and quartiles (Me (p25–p75)). Hypotheses about differences in the compared groups were tested using the Mann–Whitney test; differences were considered significant at $p < 0.05$ (AtteStat software, version 9.3.1).

RESULTS

On histotopograms, the metaepiphyseal plate of the distal part of the femur of lambs was visualized as a slightly sinous line. Light-optical study of paraffin sections showed that the metaepiphyseal cartilage had a zonal structure. Four zones were clearly distinguished: the border or reserve zone at the epiphyseal bone; the zone of proliferating or colum cartilage; the zone of vesicular (dying) cartilage; the zone of calcified (calcifying) cartilage (Fig. 1).

In the border zone, chondrocytes were located by one, rarely in the form of two-membered isogenic groups. In all other zones, a colum arrangement of cartilaginous cells was observed;

in the proliferative zone, chondrocytes were flattened, in the zone of vesicular cartilage they were enlarged in size, rounded in shape; and in the zone of calcified cartilage, the majority of cells showed signs of destruction (Fig. 1).

According to the tinctorial characteristics of the ground substance of the border zone, two layers were distinguished: outer and inner. The outer layer, when stained with alcian blue, was as follows: PAS is close to the bone, PAS is positive (the PAS reaction at the age of 5.5 months was more intense than at the age of 3.5 months), and the inner layer was stained with alcian blue pH 2.5 in blue (Fig. 1).

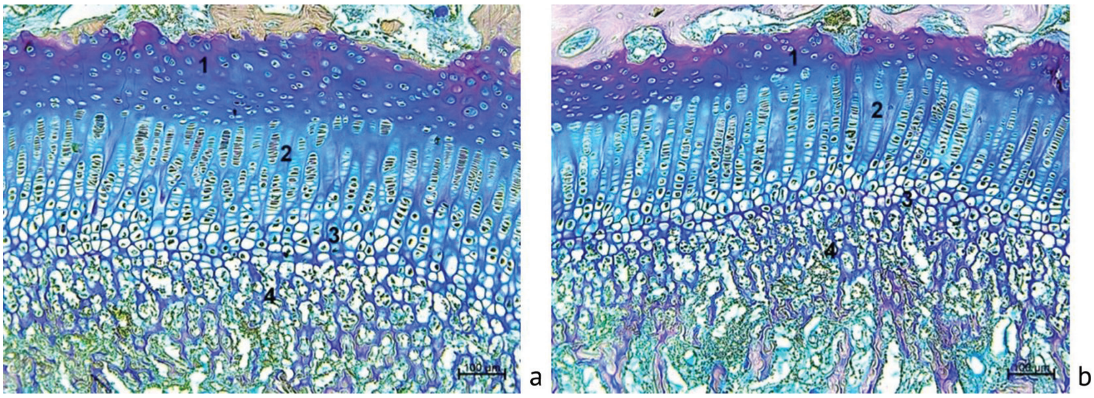

Fig. 1 Metaepiphyseal cartilage of the distal femur of a lamb: *a* age 3.5 months; *b* age 5.5 months. Border (reserve) zone (1), zone of proliferating cartilage (2); zone of vesicular cartilage (3); zone of calcified cartilage (4). Paraffin section, stained with Alcian blue pH 2.5 and PAS reaction. Magnification ×100

When stained using the three-color Masson method, the intercellular substance of the border zone in animals aged 3.5 months was stained blue, while at the age of 5.5 months there were extensive areas of the intercellular substance stained red, indicating calcification of the matrix (Fig. 2 a, c).

The intercellular substance of the zones of proliferating and vesicular (mature) cartilage with alcian blue: PAS was stained in an intense blue color, which indicates a high content of sulfated glycosaminoglycans. In the zone of calcifying cartilage, the matrix was partially resorbed, at the age of 5.5 months it was more PAS-positive (Fig. 1 b). When stained according to Masson, the red color prevailed (Fig. 2 d). Cartilaginous islands were located in the direction of the longitudinal axis of the bone and were the basis for appositional bone growth (Fig. 2 b, d).

Blood vessels feeding the metaepiphyseal cartilage were located both from the epiphysis and metaphysis sides (Fig. 3). In animals aged 3.5 months, the vessels from the epiphyseal subchondral bone side were in contact with the border zone and penetrated into it to a small depth (Fig. 2 a). Positive immunohistochemical staining for CD34 was recorded in the epiphyseal vessels at the border with the border zone (Fig. 3 a). During growth, the depth of vessel penetration increased; at the age of 5.5 months, vascular invasion was observed up to the border with the proliferating cartilage zone (Fig. 2 c; 3, c). CD34 expression from the metaphysis side was more pronounced than from the epiphysis side (Fig. 3 b, d).

The results of morphometric studies showed that the thickness of the metaepiphyseal cartilage of lambs during the period of their intensive growth from 3.5 to 5.5 months decreased by an average of 18.2 % and amounted to 0.66 (0.57–0.64) and 0.54 (0.46–0.59) mm, respectively. The decrease in the thickness of the metaepiphyseal cartilage at the age of 5.5 months is due to a significant decrease in the thickness of the border zone by 1.9 times, while the thickness of the proliferating cartilage zone increased by 1.2 times (Fig. 4, Table 1).

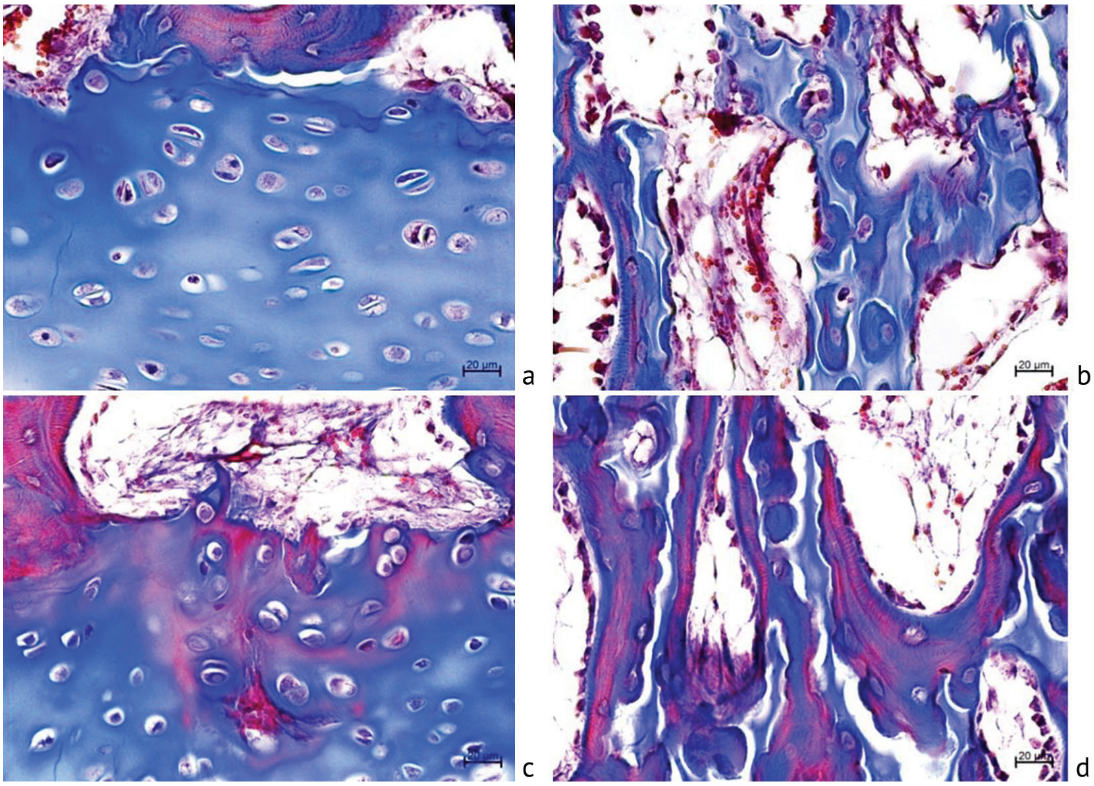

Fig. 2 Metaepiphyseal cartilage of the distal femur of a lamb: *a, b* age 3.5 months; *c, d* age 5.5 months. Border zone (*a, c*), deep penetration of vessels, presence of a mineralization front, formation of bone tissue (*c*). Zone of calcified cartilage (*b, d*). Pronounced mineralization of the matrix, osteoblasts on the surface of the calcified cartilage produce bone matrix (*d*). Paraffin section, stained with the three-color Masson method. Magnification ×400

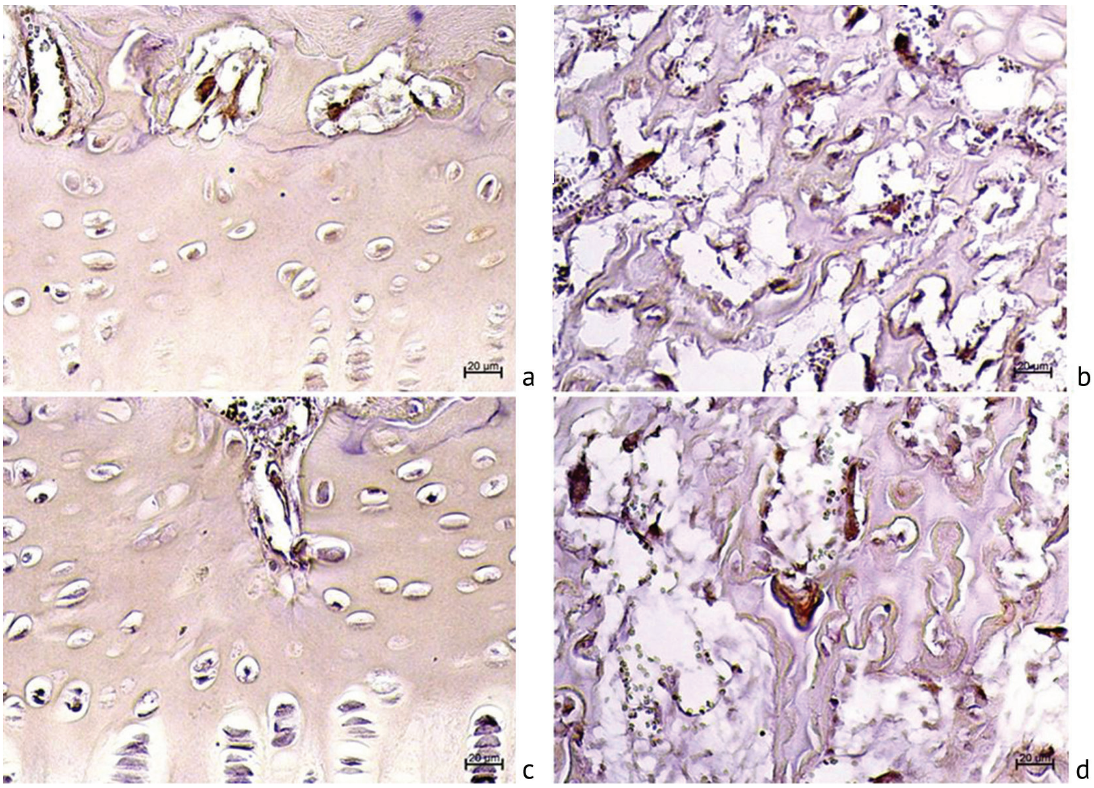

Fig. 3 Paraffin sections of metaepiphyseal cartilage of the distal femur of lambs: *a, b* age 3.5 months; *c, d* age 5.5 months. Positive immunohistochemical staining for CD34 in the epiphyseal vessels at the border with the border zone (*a*) and in the depth of the border zone (*c*). CD34 expression in the endothelium of the microcirculatory bed vessels from the diaphysis side (*b, d*). Magnification ×400

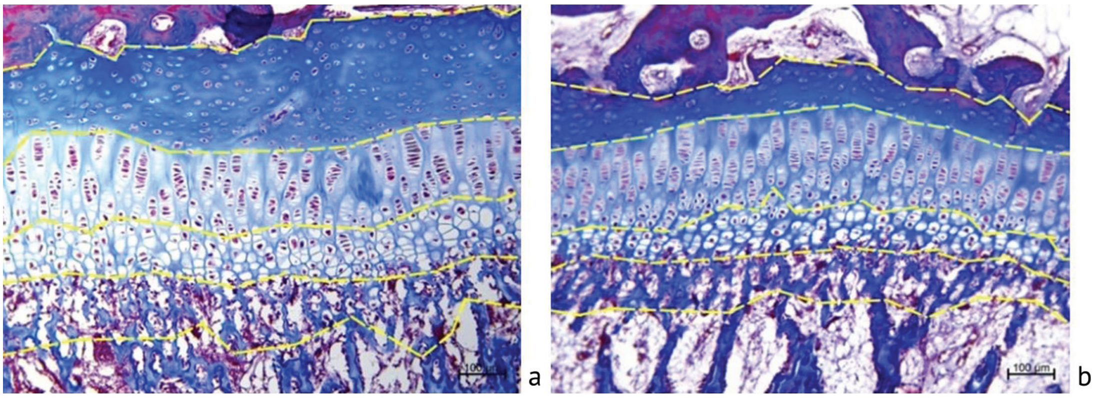

Fig. 4 Metaepiphyseal cartilage of the distal part of the femur of a lamb: *a* age 3.5 months; *b* age 5.5 months. The boundaries of the metaepiphyseal cartilage zones are indicated by yellow dotted lines. Paraffin section, stained with the three-color method according to Masson. Magnification ×100

Table 1

Thickness of metaepiphyseal cartilage zones of the distal femur in lambs

Zones of metaepiphyseal cartilage	Thickness (h, μm)		p
	3.5 months	5.5 months	
Border	238.45 (214.29–252.18)	124.76 (107.17–132.62)	0.0001
Proliferating cartilage	195.47 (185.18–198.64)	235.74 (217.37–249.27)	0.0001
Vesicular cartilage	125.49 (107.38–134.99)	128.57 (116.35–138.92)	0.4223
Calcified cartilage	106.16 (92.44–128.28)	116.31 (93.41–120.84)	0.5222

Note: Mann–Whitney test was used; the differences were statistically significant at $p < 0.05$.

The percentage ratio of zones of metaepiphyseal cartilage of the distal femur in lambs is presented in the diagram (Fig. 5). At the age of 5.5 months, a pronounced decrease in the proportion of the reserve zone and an increase in the proportion of the zone of proliferating chondrocytes were recorded.

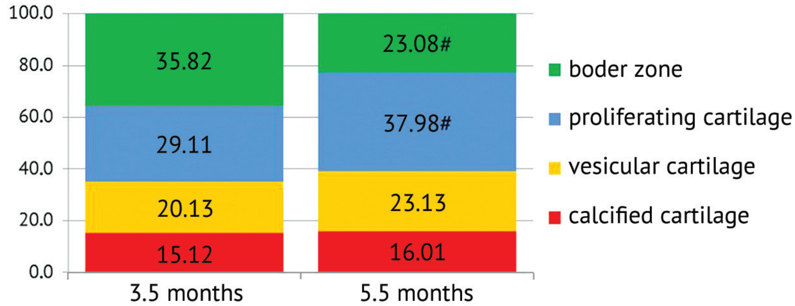

Fig. 5 Diagram of the percentage ratio of zones of metaepiphyseal cartilage of the distal femur in lambs: # statistically significant differences between the age of 3.5 and 5.5 months at $p < 0.05$.

DISCUSSION

The growth plate (physis) is formed by hyaline cartilage and is the weakest structure in the child's skeleton; it is often the site of injury or fracture. Treatment of children with fractures in the growth plate is a complex problem, since the consequences of such an injury can lead to growth impairment [24]. Experimental models of growing sheep are few in orthopaedic studies [19, 25], and data on sex differences in structural reorganization of the physis of lambs are absent.

It is known that growth rates are gender specific. According to a number of authors, a growth spurt in girls is registered at the age of 11–12 years while in boys 1.5–2 years later. Complete closure of growth zones occurs in girls by 16 years, in boys by 18 years [26, 27].

Metaepiphyseal cartilage is characterized by pronounced organ specificity, due to its topography and provisional function [23]. There is no unanimity among researchers in the classification of metaepiphyseal cartilage zones. Today, there are several classifications that distinguish from three to six zones, all of which are based on the functional activity of cartilage cells and the degree of their differentiation [23, 28, 29].

The results of our study demonstrate for the first time the features of structural reorganization of the metaepiphyseal cartilage of the distal femur during the period of intensive growth in lambs. At the age of 3.5 and 5.5 months, the zonal structure of the metaepiphyseal plate is clearly defined with the allocation of a border or reserve zone, a zone of proliferating chondrocytes, a zone of vesicular cartilage or hypertrophied chondrocytes and a zone of calcified cartilage.

The functional unity of bone and cartilage determines the normal development and functioning of the main units of the skeleton. At the present stage, the contact of the subchondral epiphyseal bone and the border zone of the metaepiphyseal cartilage, its formation and structure, are poorly studied, in contrast to the interface between articular cartilage and subchondral bone [29].

In all the cases, an increase in the PAS reaction was noted in the intercellular substance of the outer layer of the border zone when stained with alcian blue-PAS. It is the outer layer that is close in color to the subchondral epiphyseal bone; an increase in the proportion of PAS-positive structures was also seen in the calcified cartilage zone. A high content of glycosaminoglycans was noted by staining with alcian blue-PAS in the border zone, the zone of proliferating and hypertrophied chondrocytes.

The three-color Masson method differentiates mineralized and demineralized structures; mineralized structures exhibit affinity for acid fuchsin and are stained red [30]. Masson staining revealed fuchsinophilic areas of the matrix of the border zone in the metaepiphyseal cartilage of animals aged 5.5 months, as well as an increase in the proportion of fuchsinophilic areas of the calcified cartilage zone compared to the animals aged 3.5 months. It confirmed increased mineralization.

The changes observed in the tinctorial characteristics of the ground substance of the metaepiphyseal cartilage indicate that the processes of matrix calcification from the side of the subchondral bone of the epiphysis and the processes of endophysial ossification from the side of the diaphysis are more intensive in lambs by the age of 5.5 months. It is known that the nutrition of the metaepiphyseal cartilage is produced by diffusion from both sides, from the vessels of the epiphyseal and diaphyseal bones, but the invasion of vessels from the side of the diaphysis is more pronounced [23, 31].

The immunohistochemical study of paraffin sections of metaepiphyseal cartilage detected CD34 expression in 3.5-month-old lambs in the outer layer of the border zone; vessels penetrated from the subchondral bone of the epiphysis into the border zone to a small depth; at 5.5 months, the depth of vascular invasion in the border zone increased, but did not reach the zone of proliferating cartilage. The depth of vessel penetration from the diaphysis was more pronounced than from the epiphysis.

Metaphyseal plate fractures are the prevailing injury in young children (7–11 years), whereas in children over 12 years of age, ligament ruptures associated with low-energy trauma and muscle damage with high-energy trauma are observed more [2, 31].

Celarek et al. in an experimental model of fractures in the growth zone in sheep of different ages found that the fracture ran parallel to the growth zone at the age of 1.5 months, but at the age of 3.5–7 months, in the region of the metaepiphyseal plate through the zone of proliferating cartilage [25].

According to our data, during the period of intensive growth of lambs from 3.5 to 5.5 months, the thickness of the metaepiphyseal cartilage was reduced by an average of 18.2 %, due to a significant decrease (1.9 times) in the thickness of the reserve zone. At the age of 5.5 months, a statistically significant increase in the thickness of the proliferating chondrocyte zone (1.3 times) was revealed relative to the age of 3.5 months. In lambs aged 3.5–5.5 months, the proportion of the border zone and the proliferating cartilage zone was more than 50 % of the total thickness of the metaepiphyseal cartilage. These zones are characterized by the prevalence of the cell component and a low portion of intercellular substance [23, 32], which may indicate their vulnerability and inability to withstand high mechanical loads.

Limitation of this work was a small sample; a study with a larger number of growing animals of different ages would allow us to study gender patterns of structural reorganization of the metaepiphyseal cartilage, expand the statistical analysis, and thus to identify differences in the ratios of metaepiphyseal cartilage zones.

CONCLUSION

Histomorphometric changes in the metaepiphyseal plate of the distal femur of lambs during the period of their intensive growth were characterized by a decrease in its thickness due to a marked decrease in the thickness of the reserve zone, while a statistically significant increase in the thickness of the proliferating cartilage zone was revealed. In the animals aged 5.5 months, the depth of vascular invasion in the border zone increased, but did not reach the proliferating cartilage zone; changes in the tinctorial characteristics of the ground substance indicated activation of matrix calcification processes from the subchondral bone of the epiphysis and endophysis ossification processes from the diaphysis. The new data obtained on the dynamics of histomorphometric characteristics of the metaepiphyseal cartilage of the distal femur of lambs during the period of their intensive growth are the basis for experimental studies of pathological conditions of the growth zone and methods for their correction.

Conflict of interest Not declared

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The authors bear full responsibility for submitting the final version of the manuscript to be published.

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Results of limb reconstruction surgery using a telescopic titanium rod: early findings

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Abstract

Introduction Pediatric limb reconstruction associated with impaired osteogenesis and fragile bone suggests the use of combined techniques with telescopic intramedullary rods left in situ.

The **objective** was to test the hypothesis that transphyseal telescopic rods applied simultaneously with an external fixation device for pediatric femur or tibia lengthening associated with weak and brittle bone in Ollier disease and osteogenesis imperfecta does not lead to the rod blocking during fixation, does not prevent distraction bone regeneration, lengthening and deformity correction.

Material and methods The study involved four male patients with Ollier disease and a female patient with osteogenesis imperfecta who underwent limb lengthening and/or deformity correction using a combined technique. Ilizarov apparatus was used as an external fixator, and a telescopic titanium rod was placed simultaneously with external fixator. With the bone consolidated, the Ilizarov apparatus was removed and the telescopic rod left in place.

Results The length gain and deformity correction intended were achieved in all patients. No loss of fixation of the threaded rod was observed in the femur and tibia epiphyses, or greater trochanter apophysis during distraction. There was no blocking of the rod telescopes during distraction. The external fixation index was 11.6 days/cm for polysegmental lengthening, 22.6 days/cm to 28.8 days/cm with monosegmental femoral lengthening.

Discussion Limb lengthening with a telescopic rod has the advantages of additional reinforcement through the segment with no risk of intramedullary construct migration as compared with combined lengthening techniques using flexible intramedullary nailing. There were no problems with formation of the distraction regenerate and longer period of external fixation, which can be seen with other techniques.

Conclusion Outcomes in this series indicated the possibility of limb lengthening and simultaneous osteosynthesis using external fixator and a telescopic titanium rod in patients with pathological osteogenesis. No loss of fixation of the threaded parts of the intramedullary rod, no blocking of the sliding parts of the rod were observed during limb lengthening.

Keywords: lengthening, Ollier disease, osteogenesis imperfecta, telescopic rod, external fixation

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INTRODUCTION

Treatment of diseases accompanied by a weak and brittle bone (Ollier disease, osteogenesis imperfecta, polyostotic fibrous dysplasia, metabolic osteopathies) can be associated with secondary deformities, pathological fractures, limb length inequalities, which is an indication for combined surgical solutions employed with an intramedullary telescopic rod as a key element [1–5]. A telescopic rod left in situ for many years can reduce the risk of recurrent skeletal deformities and fractures [6, 7]. Prophylactic nailing technologies applied concomitantly with external fixation have been reported [2, 8–10]. Lengthening over a rigid nail and the external fixator or a fully implantable electromagnetic intramedullary devices can be used for patients with congenital skeletal pathologies or Ollier disease to avoid the risk of fractures after removal of the external fixator and reduce the rehabilitation period [11–13]. The use of intramedullary devices may be limited by the presence of growth plates and a relatively small diaphyseal diameter [12, 14–16]. In addition to that, an electromagnetic rod staying inside the bone for a long period of time can cause concern [17].

Schiedel et al. [8] and Grill et al. [9] offered “lengthening then rodding” suggesting prophylactic nailing of the elongated bone at the time of removal of the external fixation device by introducing a rigid or elastic rod. However, the authors admit there is a significant risk of a fracture within a short period of time between removal of the device and introduction of an intramedullary fixator, a risk of infection due to the presence of bacteria in the pin tract [8, 9]. Our experience shows certain advantages of nailing the elongated bone during limb reconstruction with the flexible nail and the external fixator applied concomitantly at the beginning of treatment [18, 19]. Flexible nails introduced through the metaphyses does not provide reinforcement of the newly formed bone areas in the long-term period as the growth zones function in children [2].

In pediatric orthopedics, transphyseal telescopic rods inserted for deformity correction and fixed in the proximal and distal epiphyses (or apophysis of the greater trochanter), provide bone reinforcement along the entire length with the inner part of the rod sliding in the outer part as the child grows [3, 6, 20– 22]. Telescopic rods have advantages over transphyseal elastic reinforcement in terms of maintaining position of the construct and fewer re-operations [23].

The **objective** was to test the hypothesis that transphyseal telescopic rods applied simultaneously with an external fixation device for pediatric femur or tibia lengthening associated with weak and brittle bone in Ollier disease and osteogenesis imperfecta does not lead to the rod blocking during fixation, does not prevent distraction bone regeneration, lengthening and deformity correction.

MATERIAL AND METHODS

Our study is based on a retrospective small series of five patients: four femoral lengthenings and one case of bisegmental limb lengthening (femur and tibia) performed between March 2022 and November 2024 (Table 1). The mean age of the patients was (6.0 ± 1.9) years. Four patients with Ollier disease were males; a female patient was diagnosed with osteogenesis imperfecta. Previously, one patient had undergone tibial lengthening. The patients and their parents reported preoperatively progressive deterioration in motor abilities, leg length inequality and bone deformities. Patients had a history of two to four pathological fractures.

An intramedullary telescopic titanium rod was used (RU No. RZN 2017/5875 dated July 10, 2017, included in the set of implants for pediatric orthopedics “OrthoKid” according to TU 9437-001-73747729-2014).

Table 1

Patient data, type of operation performed

Patient	Diagnosis	Age, years	Aspects of osteotomy and telescopic rodding	External fixation device, surgical procedure performed
S.	Osteogenesis imperfecta, type I	5	Double percutaneous osteotomy of the femur to correct varus and derotate the bone with the proximal osteotomy, to lengthen at the distal femur, 4.2 mm antegrade rodding	Ilizarov apparatus
L.	Ollier disease	4	Distal wedge correction osteotomy of the femur, 5.5 mm antegrade rodding	Ilizarov apparatus, concomitant tibial lengthening over intramedullary flexible rods
R.	Ollier disease	11	Distal wedge correction osteotomy of the femur, 5.5 mm retrograde telescopic rodding	Ilizarov apparatus, removal of antecedent flexible rods
K.	Ollier disease	6	Concomitant lengthening of the femur and tibia, 5.5 mm retrograde rodding of the femur, 5.5 mm antegrade rodding of the tibia	Ilizarov apparatus
N.	Ollier disease	6	Femur lengthening, retrograde rodding, acute correction of the varus deformity	Ilizarov apparatus

The surgical lengthening technique with a telescopic rod consisted of several stages.

A subperiosteal osteotomy was performed in patients with Ollier disease (Fig. 1), if needed, after removal of antecedent implant (two patients) and wedge osteotomy produced for deformity correction.

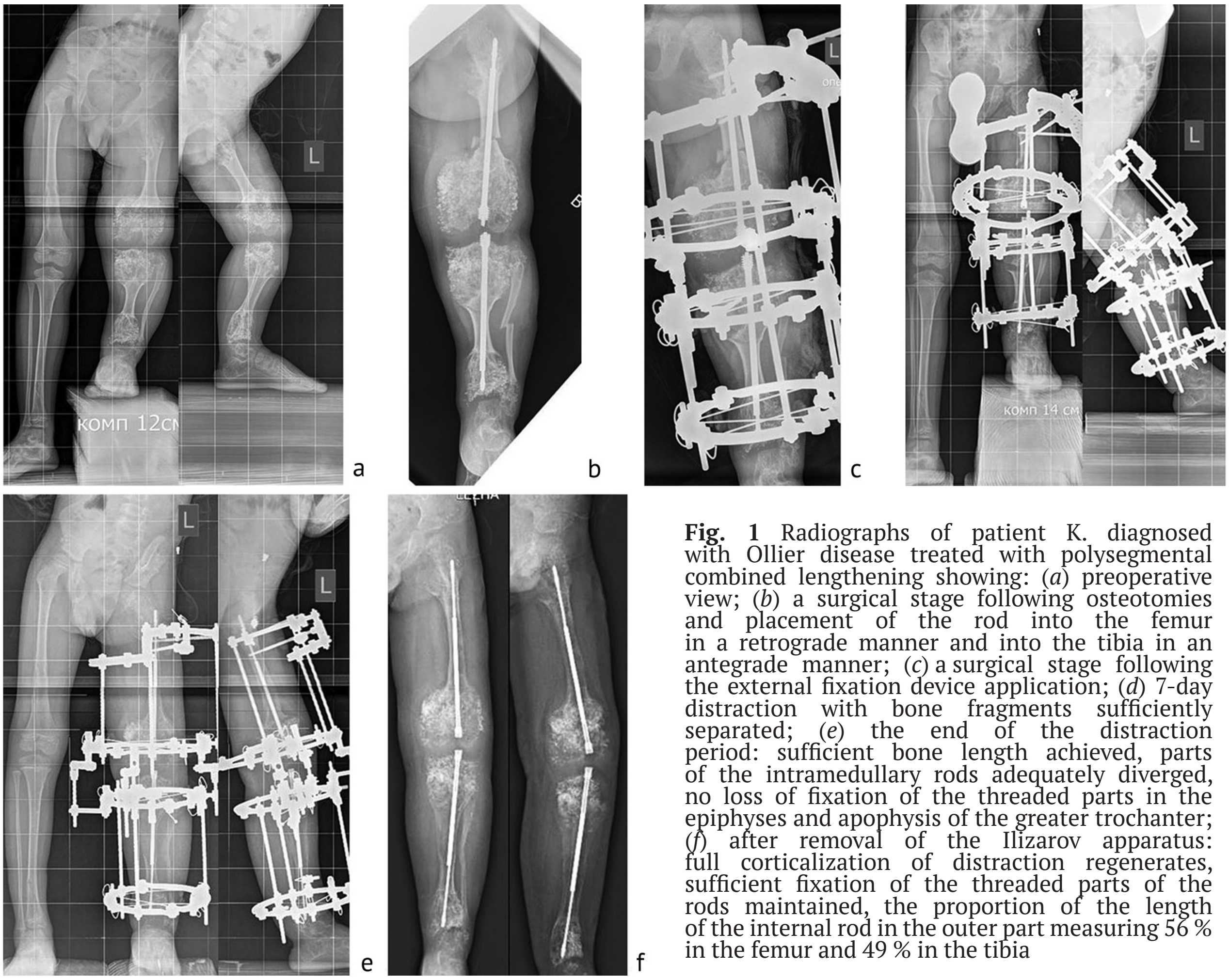
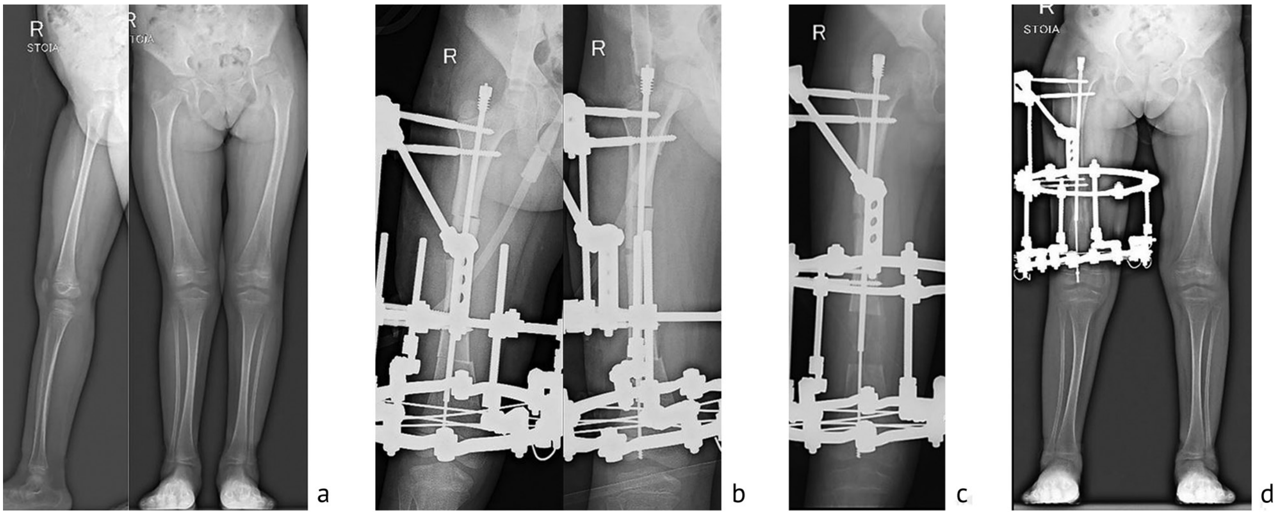


Fig. 1 Radiographs of patient K. diagnosed with Ollier disease treated with polysegmental combined lengthening showing: (*a*) preoperative view; (*b*) a surgical stage following osteotomies and placement of the rod into the femur in a retrograde manner and into the tibia in an antegrade manner; (*c*) a surgical stage following the external fixation device application; (*d*) 7-day distraction with bone fragments sufficiently separated; (*e*) the end of the distraction period: sufficient bone length achieved, parts of the intramedullary rods adequately diverged, no loss of fixation of the threaded parts in the epiphyses and apophysis of the greater trochanter; (*f*) after removal of the Ilizarov apparatus: full corticalization of distraction regenerates, sufficient fixation of the threaded parts of the rods maintained, the proportion of the length of the internal rod in the outer part measuring 56 % in the femur and 49 % in the tibia

The osteotomy level and the magnitude of one-stage correction were determined preoperatively based on the deformity characteristics. Reaming of the canal was performed in the patients with Ollier disease using a guide wire. The wires were inserted in an antegrade manner (through the greater trochanter) in two cases and in a retrograde way (parapatellar approach) in two cases. The inner part of the telescopic rod was placed to the opposite metaphysis after drilling and removing the guide wire without fixation of the threaded portion to the epiphysis/apophysis. The outer (hollow) part of the telescopic rod was shortened, if needed, inserted into the canal, the threaded portion screwed into the distal epiphysis of the femur in the intercondylar space (with retrograde insertion of the rod) and into the greater trochanter so that the thread did not extend beyond the growth site into the metaphyses. Then the inner part of the rod was screwed into the opposite epiphysis/apophysis using a T-shaped handle avoiding the thread being in the metaphysis. Retrograde insertion of the rod was performed in cases of large chondromatous lesions located predominantly in the distal femur. The outer diameter of the diaphyseal part of the inserted rod was 4.2 mm in one case (patient with osteogenesis imperfecta) and 5.5 mm in the remaining cases. The Ilizarov apparatus was mounted at the final stage of the operation to be followed by distraction along the vector being parallel to the intramedullary telescopic rod.

Surgical lengthening of the femur in a female patient with osteogenesis imperfecta suggested percutaneous osteotomy and initial fixation of the threaded external part of the rod as recommended by Birke et al. [3] (Fig. 2). Varus deformity was corrected with percutaneous osteotomy at this level (proximal osteotomy) and a telescopic rod introduced without drilling out the medullary canal. Derotation was produced by twisting maneuver using the Ilizarov rings with the rod in place.



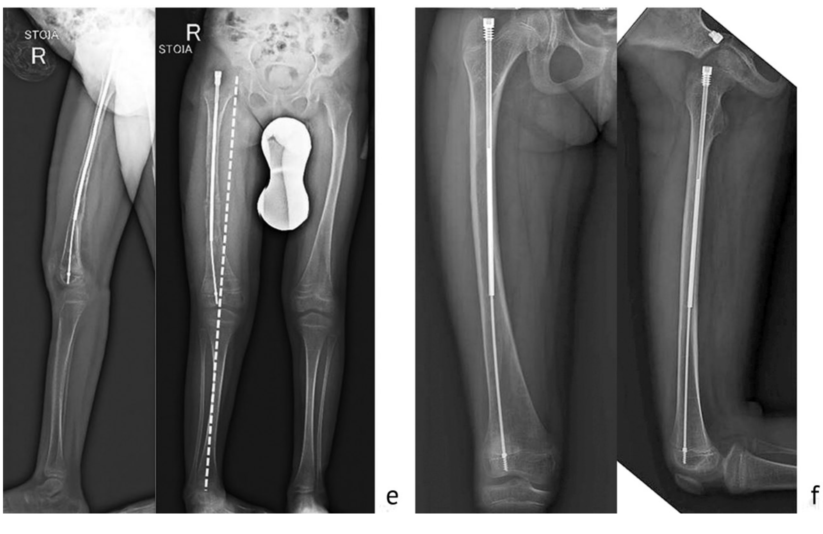


Fig. 2 Radiographs of patient S. diagnosed with osteogenesis imperfecta showing: (*a*) preoperative view; (*b*) intraoperative view of double osteotomy of the femur; (*c*) the end of distraction with the intramedullary rod lengthened without loss of fixation of the threaded ends; (*d*) normal radiological anatomy of the operated lower limb seen prior to removal of the Ilizarov apparatus; (*e*) realigned anatomical axis of the limb with the center of the knee joint maintained at 3 months of removed external fixation device; (*f*) well realigned elongated segment maintained at 21.5 years with no loss of fixation of the threaded parts with the rod moving apart safely)

Patients were encouraged to get verticalized and ambulate using walkers or crutches at 2–3 postoperative days. The latency period was five days with distraction performed at a rate of 1.5 mm/day for 6–7 days prior to the first radiography. An increased rate of distraction was initiated to provide reliable separation of bone fragments in the presence of a telescopic rod and to avoid premature bone consolidation. With adequate interfragmentary diastasis established with the first radiographic control, the distraction rate was reduced to 1 mm/day. Variation in the distraction rate during the lengthening process relied on the intensity of bone regeneration. With evident signs of bone fusion the external fixation device was removed. The study received a favourable opinion from the relevant research ethics committee of the Ilizarov Center (Abstract of minutes № 1 (76) dtd 29.11.2024). Written informed consent was obtained from each subject or the subject's parent/legally acceptable representative for surgery and publication of the findings without identification.

RESULTS

The bone length and correction pre-planned were achieved in the patients. A plaster splint or a circular plaster cast was used for 3 to 4 weeks after removal of the device, when patients returned to walking with a gradually increasing weight-bearing. The results of elongation with a telescopic rod are presented in Table 2. No complications specific to telescopic intramedullary osteosynthesis (loss of fixation of the threaded parts in the epiphyses and apophysis, migration of the rod into the knee joint, bending and blocking of the rod preventing telescoping) were observed during the distraction phase as most critical from the point of view of the requirements for the position of the intramedullary rod. Sliding of the intramedullary rod was not blocked by external fixation components including wires and half-pins during the distraction period. A superficial infection was observed at a pin site in one case and was treated locally. Another patient experienced premature consolidation of the fibula, which required re-osteotomy and additional wire placement.

Table 2

Results of bone lengthening with telescopic rod

<table>
<tr><th rowspan="2">Patient</th><th colspan="2">Length gain</th><th rowspan="2">External fixation length, days</th><th rowspan="2">IEX; days/cm</th><th rowspan="2">Proportion of the length of the inner rod in the outer part, %</th><th rowspan="2">Complications</th></tr>
<tr><th>abs., cm</th><th>%</th></tr>
<tr><td>S.</td><td>4.2</td><td>16.7</td><td>120</td><td>61.8</td><td>28.8</td><td>None</td></tr>
<tr><td>L.</td><td>5.8</td><td>35.7</td><td>131</td><td>43.9</td><td>22.6</td><td>Superficial infection</td></tr>
<tr><td>R.</td><td>4.0</td><td>15.4</td><td>97</td><td>69.9</td><td>24.3</td><td>None</td></tr>
<tr><td>K.</td><td>12</td><td></td><td rowspan="3">139</td><td></td><td rowspan="3">11.6</td><td rowspan="3">Premature consolidation of the fibula, re-osteotomy</td></tr>
<tr><td>femur</td><td>6</td><td>32.6</td><td>56</td></tr>
<tr><td>tibia</td><td>6</td><td>33.1</td><td>49</td></tr>
<tr><td>N.</td><td>5.5</td><td>30.2</td><td>134</td><td>62.5</td><td>23.5</td><td>None</td></tr>
</table>

DISCUSSION

In pediatric reconstructive orthopedics of the limbs, intramedullary osteosynthesis including telescopic rodding left in situ is essential for deformity correction in patients with systemic diseases (osteogenesis imperfecta, X-linked hypophosphatemia, polyostotic fibrous dysplasia, etc.) to prevent or reduce the risk of pathological fractures and recurrent deformities [2–7]. Consecutive implementation of lengthening and intramedullary nailing at the time of dismantling the external fixation device can be associated with a fracture of the lengthened bone at the time of surgery or infection [8, 9]. Simultaneous introduction of intramedullary components (flexible rods) and external osteosynthesis helps to avoid the adverse events [10, 25]. However, the combined method confers an increased risk of rod migration in the bone due to weak rod locking and off the bone compromising soft tissues so that the intramedullary rod is to be removed [26]. Introduction of elastic rods suggests channels in the metaphyses to prevent nailing throughout the bone, and transphyseal insertion prevents the central location of the rods relative to the plane of growth plates, which could potentially lead to angulation [23, 27]. Finally, flexible rods telescoping in the medullary canal can be associated with blocking effect during growth and the loss of bone reinforcement at a long term [23].

Transphyseal telescopic rodding is likely to be more reliable than transphyseal telescopic rods inserted from both bone ends in terms of less complication rate and a longer reinforcement effect as demonstrated in recent literature on the correction of limb deformities in children with osteogenesis imperfecta [20, 23, 24]. From this point of view we consider combined use of transphyseal telescopic rodding and external osteosynthesis for limb lengthening in children with genetic diseases and poor bone quality is associated with lower risk of complications, with intramedullary fixator left in situ.

The sample size was too small to draw meaningful conclusions about the efficacy of the method. However, we can discuss other aspects in addition to proved possibility of performing this type of combined osteosynthesis. Telescopic rods used for patients with osteogenesis imperfecta may be predisposed to loss of fixation of the threaded parts, bending of the rod, blocking and absence of telescoping [3, 5, 28–30]. Holmes et al. emphasize that the distal fixation is to be perfectly centered in the epiphysis to improve survival of osteosynthesis and the time before revision [29]. Rod bending is often the fundamental cause of rod failure during developmental growth of the segment and the loss of fixation of threaded parts [29, 31–33]. An additional osteotomy aimed at the limb realignment is important for telescopic system functioning at a long term [7, 33]. We performed careful planning of deformity correction and their implementation to avoid rod bending and blocking during distraction with the telescoping rate being extremely high. A gradual correction of angular deformity should be avoided in preoperative planning with use of telescopic rods during distraction to prevent rod bending and blocking the sliding parts.

To avoid protrusion of the threaded part of the inner rod into the knee or ankle joint during installation of the telescopic fixator, we remain committed to the recommendations of Birke et al. [3], tightening the threads of the inner part of the rod only after screwing the threads of the outer part into the corresponding epiphysis (apophysis). We observed no protrusion of the rod into the joint, no loss of fixation of the threaded parts, no blocked sliding of the internal part in the external portion with lengthening of six segments.

Many authors report isolated use of intramedullary telescopic rods in the deformity correction being accompanied by secondary rotational and longitudinal bone displacement [3, 4, 34, 35]. Cho et al. [4], Franzone et al. [36] report the use of short locking plates for monocortical fixation to avoid the displacements [4, 36]. The approach resulted in bone union achieved in 85.3 % of cases; peri-implant fractures, refractures at screw sites occurred in 18.9 % of cases [37]. In this scenario, external fixation used to correct the deformity and lengthen the limb helps prevent secondary angular and rotational displacements and peri-implant fractures. No delayed bone consolidation was observed in our series.

The external fixation index was the lowest for polysegmental lengthening (11.6 d/cm) and ranged from 22.6 days/cm to 28.8 days/cm for monofocal femoral lengthening. These results are comparable to the results of lengthening in children in whom osteogenesis was stimulated with elastic nails placed in the metaphyses [19, 26, 38]. No other complications that would affect the outcome of treatment were encountered in our series. Premature consolidation of the fibula was the only adverse event requiring unintended intervention with re-osteotomy to continue lengthening.

Telescopic rodding used for limb lengthening is an advanced technique, which is technically challenging to provide the distal fixation to be perfectly centered in the epiphysis, angular deformities to be corrected acutely, limb lengthening to be strictly parallel to the axis of the telescopic rod. This approach prevents gradual correction of angular deformities to avoid rod bending and prevent absence of telescoping in the future. The small sample size, the heterogeneity (two nosologies) are obvious limitations of the study. We plan to expand the sample to 30 or more patients to obtain evidence-based results that would justify the expected duration of treatment and risks of complications. The long-term follow-up period will be increased to two years or more to determine the feasibility of telescoping intramedullary nails.

CONCLUSION

The case series demonstrated the possibility of long bone lengthening in patients with Ollier disease and mild forms of osteogenesis imperfecta with concomitant use of an external fixation device and a transphyseal titanium telescopic rod. The study of the six segment elongations showed that the “accelerated” telescopic rodding during distraction was not associated with failure of sliding and the loss of the required fixation of the threaded parts in the epiphyses. No delay in the formation and maturation of the distraction regenerate was detected in the series.

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Ethical Approval *The study received a favourable opinion from the relevant research ethics committee of the Ilizarov Center (Abstract of minutes № 1 (76) dtd 29.11.2024).*

Informed consent *Written informed consent was obtained from each subject or the subject's parent/legally acceptable representative for surgery and publication of the findings without identification.*

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Clinical case
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First experience with the use of a partially bioresorbable bone substitution material in a patient with 34-year old chronic osteomyelitis of the tibia

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Abstract

Introduction The most common approach to the treatment of osteomyelitic cavities (Cierny – Mader type III) is a two-stage approach proposed by Masquelet, the main shortcoming of which is the need to perform a second surgical intervention which results in a longer rehabilitation period, increased economic costs and additional emotional distress of the patient. In electronic databases, we found 17 publications devoted to the use of partially bioresorbable materials for filling in uncomplicated bone defects. The experience of treatment of chronic osteomyelitis (Cierny – Mader type III) using such materials has not been described.

Purpose Demonstration of the first use of a partially bioresorbable osteosubstituting material in a one-stage treatment of a patient with a long-term osteomyelitic process after failures of conventional surgical treatment methods.

Materials and methods We present a case of a 54-year old patient with a diagnosis of chronic post-traumatic osteomyelitis of the right leg, fistulous form, associated with contracture of the right ankle joint, 2-cm shortening of the right lower limb. A one-stage treatment technique was used using a partially bioresorbable osteosubstituting material for the first time in combination with antibacterial drugs, preselected in accordance with the patient's microbial cultures.

Results The study evaluated the use of a partially bioresorbable material impregnated with antibacterial drugs in the treatment of a patient with osteomyelitic cavity Cierny – Mader type III that achieved stable arrest of purulent and inflammatory process.

Discussion The mandatory two-stage Masquelet approach increases the surgical aggression, requires collection of an autologous bone graft, thus the risk of possible complications becomes higher. The obvious advantages of bioresorbable materials impregnated with antibacterial drugs to fill in bone defects are: no need to collect an autograft, a reduction in the number of surgical interventions to one, the possibility of gradual natural degradation of the implant from the patient's body due to bioresorption. Conclusion The study demonstrates the potential use of partially bioresorbable materials in a one-stage technology for treating patients with Cierny – Mader type III osteomyelitic cavities.

Keywords: chronic osteomyelitis, osteomyelitis cavity, one-stage surgical treatment of osteomyelitis

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INTRODUCTION

Chronic osteomyelitis is a social, sanitary-medical and economic problem of modern healthcare worldwide and accounts for up to 10 % of all pathologies of the musculoskeletal system. Treatment of osteomyelitis in most cases is labor-intensive, long-term, multi-stage, and is accompanied by frequent relapses [1, 2].

The surgical community is guided by the classification proposed by Cierny – Mader for choosing the technique of surgical intervention, according to which cystic forms of osteomyelitis belong to anatomical type III [3].

The most common treatment option for osteomyelitic cavities, reported in the literature, is the two-stage Masquelet method (induced membrane technique) [4–9]. An integral part of this method is the performance of a repeated operation: removal of the antibacterial spacer made of polymethyl methacrylate and its replacement with an osteosubstituting graft, which can lead to slow healing of fibrously altered integumentary tissues, prolongation of the rehabilitation period, increased economic costs and additional emotional stress [1, 2, 6, 8, 10].

The use of partially bioresorbable materials impregnated with antibacterial drugs in the treatment of patients with traumatological and orthopaedic profiles is poorly covered in the literature. The eLIBRARY.RU and PubMed databases contain 17 publications devoted to the use of partially bioresorbable materials in the management of uncomplicated bone defects. Treating patients with chronic Cierny – Mader type III osteomyelitis with the use of such materials has not been described yet.

Our case of using bioresorbable bone cement demonstrates the potential prospects for further study of the compatibility of bioresorbable materials and antibacterial drugs, the timing and effective impact on microflora.

Purpose Demonstration of the first use of a partially bioresorbable osteosubstituting material in a one-stage treatment of a patient with a long-term osteomyelitic process after failures of conventional surgical treatment methods.

MATERIALS AND METHODS

A 54-year-old male patient referred to the clinic of bone and joint infection of the Ilizarov National Medical Research Center of Traumatology and Orthopaedics in 2022 with complaints of a long-term functioning fistula in the middle third of the leg with exudate, and impaired weight-bearing of the right lower limb.

In the preoperative period, along with collecting anamnesis and clinical examination, the patient underwent radiography of the affected limb in two projections, analysis of the microbial cultures of the wound discharge.

At admission to the clinic, the patient's general condition was satisfactory; his body temperature was 36.6 °C. Breathing was vesicular, no wheezing. Respiratory rate was 16 per 1 min. Heart sounds were clear, rhythmic, blood pressure was 120/80 mm Hg, pulse was 72 beats per 1 min. There were no signs of pathology from other internal organs and systems.

Case history The patient sustained an open comminuted fracture of the bones of the lower third of the tibia with displacement, complicated compartment syndrome and an extensive wound defect in a car accident 34 years ago. Due to the injury and the complications that developed, the patient underwent multiple surgeries: plastic surgery of the wound defect; BIOS; bone plating; osteosynthesis according to Ilizarov. The treatment resulted in consolidation of the fracture but the osteomyelitic process was not arrested.

The patient moved without using additional support means or other orthopedic devices, limping on the right lower limb. The right lower limb was shortened by 2 cm due to the tibia. The skin on the anterior surface of the right tibia was cicatricially altered tissues with functioning fistula tracts in the middle third (Fig. 1 a) and purulent exudate. The function of adjacent joints was not impaired.

The microbial culture test showed growth of *Staphylococcus aureus* (10/4 CFU/ml. MSSA) in the exudate.

Radiologically, varus-recurvation deformity of 10/15° was revealed with signs of osteosclerosis in the area of the cavity defect at the level of the upper and middle thirds of the metadiaphyseal zone, irregular in shape and with clear contours (Fig. 1 b).

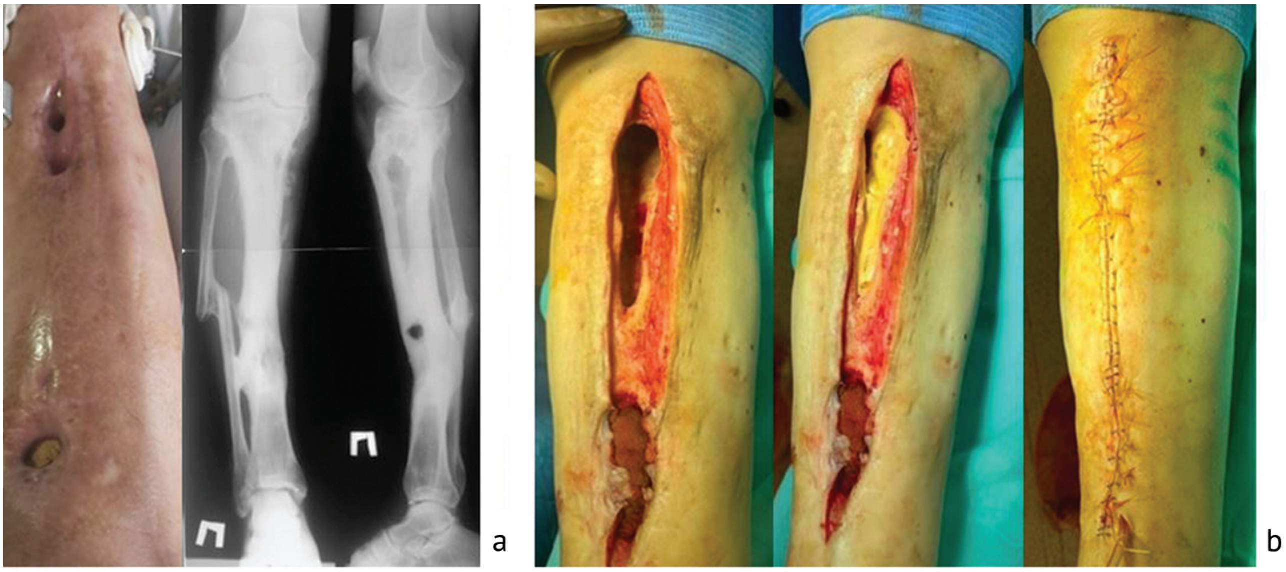

Fig. 1 Photo of the limb and radiographs of the lower leg with adjacent joints in 2 projections: *a* upon admission; *b* during surgery; *c* 12 months after surgery

The study was conducted in accordance with the ethical standards and norms of the legislation of the Russian Federation. The patient gave informed consent to participate in the study and publish the data.

Based on the obtained clinical and radiological findigs, the patient underwent surgical intervention (Fig. 1 c), during which, after contrasting the fistula tracts with the introduction of a brilliant green solution with hemostasis due to the application of a hemostatic tourniquet at the level of the lower third of the thigh, a longitudinal dissection of the skin was performed, simultaneously excising the fistula tracts along the anterior surface of the tibia. After exposing the osteomyelitic cavity, a radical sequester necrectomy was performed with subsequent lavage of the bone wound with a pulsating stream of antiseptic solution in a volume of 5 liters. Then, a partially bioresorbable spacer based on polyurethane foam impregnated with antibacterial drugs which were pre-selected in accordance with the patient's microbial culture test was implanted.

Due to the properties of the material (it increases in volume during low-temperature polymerization which lasts for 20 minutes), it was possible to fill all the free areas of the bone cavity, provide hemotamponade of the bone wound and create an increased concentration of the antibacterial drug in the osteomyelitic focus. At the end of the surgical intervention, the surgical wound was hermetically sutured; a temporary drainage system was installed.

In the postoperative period, etiotropic antibacterial therapy (Ceftazidime 2.0 per day, for 20 days), drug correction of homeostasis parameters, in accordance with the traditional treatment regimen for patients with chronic osteomyelitis, local wound care were carried out.

RESULTS

The postoperative period was satisfactory; on the 14th day the sutures were removed from the postoperative wound, and 20 days later the patient was discharged for outpatient examination by a surgeon at the place of residence.

At follow-up control 12 months after the treatment the achieved result was preserved (Fig. 1 c); the patient walks with a full weight on the operated limb, without the use of additional support means, there is no relapse of the purulent inflammatory process.

DISCUSSION

According to available literature, a bioinert polymer (polymethyl methacrylate) is mostly used for treating patients with cavitary chronic osteomyelitis (Cierny – Mader type III). There are two options of the intervention: one-stage and two-stage. The one-stage treatment approach involves implantation of an antibacterial carrier without its subsequent removal in case of arrest of the purulent process. It is necessary to note the complications arising from the use of such tactics are: osteolysis of the paraimplant zone, pain, relapse of the purulent inflammatory process with the formation of biofilms on the spacer. The two-stage treatment technology involves implantation of an antibacterial carrier for a short period (up to 2–4 months) with its subsequent removal and filling of the formed defect with auto-, allo-, xenografts, biodegradable materials. In this case, the spacer, due to the reaction to a foreign body (spacer), prevents the growth of fibrous tissue in the area of the bone defect and induces the development of the surrounding pseudo-synovial membrane (Masquelet effect) [11–19].

The properties of partially bioresorbable osteosubstituting materials described in the literature [20–23] and identified by us during the study are as follows: filling the entire space of the bone defect due to expansion during the polymerization period, maintaining the supporting function of the affected segment due to adhesion to surrounding tissues, and the possibility of using heat-stable antibacterial drugs.

Further study of the compatibility of bioresorbable material and antibacterial drugs with an analysis of the timing and effectiveness of the impact on laboratory microflora would be perspective.

CONCLUSION

Our clinical case demonstrates the successful use of a partially bioresorbable osteosubstitution material as a spacer in one-stage treatment of a patient with chronic long-term Cierny – Mader type III osteomyelitis.

Conflict of interest *The authors declare no conflict of interest.*

Funding *Not declared.*

Ethical review The study was conducted in accordance with ethical standards and the legislation of the Russian Federation.

Informed consent *The patient gave informed consent to participate in the study and publish the data.*

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Clinical case
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Management of a total defect of the talus with a customized 3D-implant made of porous titanium for Charcot neuroosteoarthropathy in a patient with neurosyphilis: a case report

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Abstract

Introduction Neuropathic arthropathy, or Charcot arthropathy, is characterized by rapid progressive bone destruction due to impaired nociceptive and proprioceptive innervation of the affected limb. In recent years, there have been publications on the use of 3D modeling and 3D printing of porous titanium implants for filling large bone defects in the foot, but we found only two descriptions of clinical cases of 3D porous titanium implants in patients with Charcot arthropathy.

The **aim** of the work is to demonstrate and analyze the results of performing resection calcaneotibial arthrodesis with defect plasty using a customized 3D implant made of porous titanium in a patient with manifestation of Charcot arthropathy as a complication of tertiary syphilis.

Materials and methods A 50-year-old woman, with a history of syphilis for 26 years, noted the signs of inflammation in the ankle joint during increased loading two months after total knee arthroplasty on the left joint. The examination revealed total destruction of the talus. The diagnosis was Charcot neuroosteoarthropathy of the foot, active stage. After 2.5 months of unloading, based on the results of a CT study of the left ankle joint and 3D modeling, a 3D porous titanium customized implant was fabricated; resection calcaneotibial arthrodesis with autograft harvesting from the tibial canal and plastic surgery of the defect with a 3D implant and fixation with the Ilizarov apparatus were performed. Five months after the operation, consolidation was determined based on the results of control radiographs, and the Ilizarov apparatus was dismantled.

Discussion The proposed method of surgical treatment for total destruction of the talus and the resulting defect-diastasis allows for reconstructive intervention with immediate compensation of shortening, regardless of the shape and size of the defect, to avoid secondary shortening of the limb while maintaining its ability to support, thereby preventing the occurrence of secondary overload changes in the adjacent joints.

Conclusion The initial results in this clinical case seem encouraging, but additional research is required to clarify the indications and patient selection criteria for this treatment method.

Keywords: Charcot arthropathy, total defect of the talus, 3D porous titanium customized implant, resection calcaneotibial arthrodesis

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INTRODUCTION

Neuropathic arthropathy, or Charcot arthropathy, is characterized by rapid progression of bone destruction due to severe impairment of nociceptive and proprioceptive innervation of the affected limb. In 1868, Jean-Martin Charcot identified the relationship between spinal cord damage (tabes dorsalis), a form of tertiary neurosyphilis that may develop months to decades after the initial infection of the patient, and a specific foot deformity based on aseptic destruction of its osseo-articular apparatus and/or ankle joint [1]. Currently, Charcot arthropathy is most often found in patients with diabetes mellitus [2]. There are known cases of Charcot arthropathy developing with other lesions of the peripheral and central nervous system, while in the contemporary society and current healthcare, syphilitic etiology of arthropathy is quite rare [3].

Charcot's neuroosteoarthropathy results in necrosis and pathological destruction of the ankle joint bone tissue, including the talus, and therefore ankle joint arthroplasty is unacceptable in this case [4]. Moreover, movements and loads in the affected area is a trigger that exacerbates the pathological process. Therefore, one of the main components of management is the exclusion of the load on the affected segment and immobilization, achieved with conservative treatment using polymer customized unloading TCC (Total Contact Cast) or various orthoses. Surgical treatment uses various options of joint arthrodesis [5, 6].

The issue of total defects of the talus in reconstructive surgery has always been challenging. The search for materials for filling extensive defects led to its plastic surgery with implants made of porous titanium or nickel-titanium [7–10], implants of various shapes were used, both with cavities for integrating a heterotopic autograft and without them.

Since 2015, due to the development of 3D modeling and 3D printing from porous titanium, publications have appeared on the implementation of this technology in the field of foot surgery. The use of customized dodecahedral implants marked a new direction in the management of defects of the hind foot [11, 12]. However, despite the growing number of publications on this topic, we found only two descriptions of clinical cases in the literature on the use of 3D porous titanium implants in patients with Charcot arthropathy [13, 14]. A search in the electronic platform PubMed (with keywords: neuropathic arthropathy; syphilis) showed that over the past 15 years, only 10 cases were published on the Charcot arthropathy of various joints developed as a complication of tertiary syphilis. However, based on the analysis of published clinical cases and literature reviews, it can be assumed that the most common localization of arthropathy in tertiary syphilis is the knee joint [3, 15].

Purpose The aim of the work is to demonstrate and analyze the results of performing resection calcaneotibial arthrodesis with defect plastic surgery using a customized 3D implant made of porous titanium in a patient with manifestation of Charcot arthropathy as a complication of tertiary syphilis.

MATERIALS AND METHODS

This is a case of a 50-year-old woman without diabetes mellitus, with BMI of 22 kg/m2, history of syphilis diagnosed for the first time in 1997 that was treated with a course of penicillin and a repeated course of antibiotic therapy in 2008. She did not receive specific therapy lately. The tests findings: from 03/31/2016: RMP 4+, RPGA 4+, ELISA + 10.9; from 08/11/2016: RMP 2+, RPGA 4+, ELISA 10.9; from 03/23/2020: RMP +1, RPGA 4+, ELISA 13.3. She was registered with the dermatovenereology dispensary at her place of residence. Control analysis from 09/21/2023: Syphilis RPR (+) in titer 1:2.

Two months before the admission, total arthroplasty of the left knee joint was performed due to grade 3 arthrosis. During rehabilitation when she increased the duration of walking with crutches and load on the left lower limb, she noted the appearance of edema, minor local hyperthermia and hyperemia in the area of the left ankle joint and foot. There was no pain during passive and active movements. She denied injuries. A CT scan of the left ankle joint was performed on an outpatient basis and revealed a pathological fracture and destruction of the talus with its fragmentation and displacement of fragments.

Based on the examination results, the patient was consulted at the Center for Foot and Diabetic Foot Surgery of the Yudin City Clinical Hospital and hospitalized. At admission, the foot and lower leg were swollen, there was moderate hyperemia in the area of the left ankle joint (Fig. 1). According to laboratory tests, the erythrocyte sedimentation rate (ESR according to Panchenkov) was elevated (42 mm/h); the number of leukocytes in the general blood test was 7.6 × 109/l; the level of C-reactive protein was 6.52 mg/l. Radiography revealed destruction of the subtalar joint corresponding to Eichenholtz stage 2 [16–18]. Magnetic resonance imaging confirmed the extent of the lesion, and also revealed edema of the bone marrow of the navicular bone and tibia and signs of synovitis of the associated joints (Fig. 2).

Fig. 1 Appearance of the limb at first examination; tight edema and foot hyperemia of the foot, ankle and tibia

Fig. 2 Radiograph and MRI of the ankle joint and foot upon admission: *a* the radiograph shows unclear edges of osteodestruction and cloud-like foci of osteoproliferation; *b* MRI in fat-suppression mode shows pronounced bone marrow edema of the talus, navicular, tibial head and calcaneus, destruction of the talus, calcaneus and, to a lesser extent, navicular bone

The diagnosis was established: Charcot's neuroosteoarthropathy of the left foot with damage to the ankle and subtalar joints, Eichenholtz stage 2, varus deformity [19].

After examination, a posterior plaster immobilizing cast was applied from the toes to the upper third of the shin, and walking without weight-bearing on the left leg with crutches was allowed. The patient was followed up on an outpatient basis at the Yudin City Clinical Hospital.

After 2.5 months of limb immobilization with a plaster cast and unloading with additional support means, the patient was hospitalized at the Yudin City Clinical Hospital. Based on the results of a CT scan of the left ankle joint, 3D model of a customized implant was done to fill in the bone defect. A patient-specific 3D implant made of porous titanium was manufactured based on the 3D model (Fig. 3).

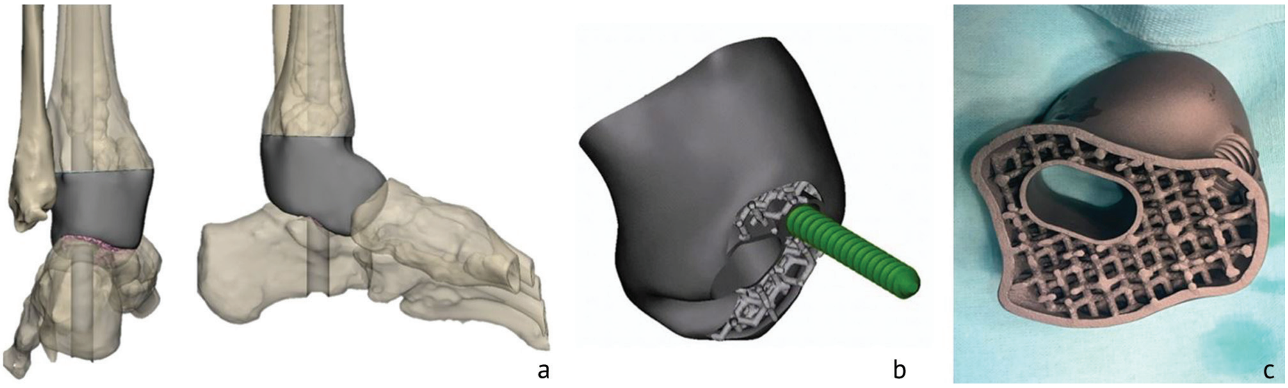

Fig. 3 Diagram of implant position in the ankle joint (*a*); 3D-model (*b*) and view of the fabricated implant (*c*)

Intraoperatively, destruction of the talus in the left foot was detected, its fragments, articular surfaces of the calcaneus and tibia were removed. Then, using the RIA (Reamer Irrigator Aspirator) system, an autograft was taken from the tibial canal using a retrograde approach (Fig. 4). After bringing the foot into normocorrection, plastic surgery of the defect thus formed after removal of the talus was performed using a custom-made 3D implant made of porous titanium with preliminary integration of the bone autograft into the intertrabecular space and fixation with the Ilizarov apparatus [7, 19].

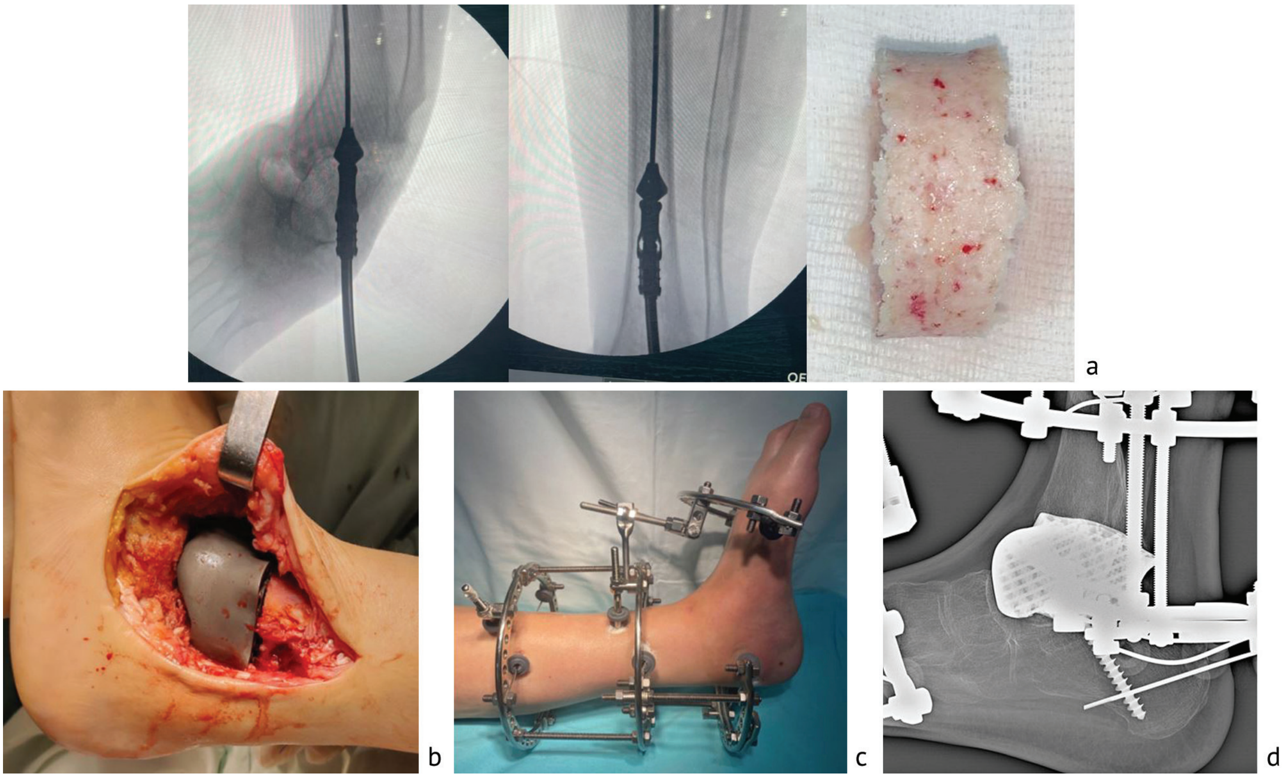

Fig. 4 Stages of surgical intervention: using the RIA system, an autograft was taken from the tibial canal (*a*); placement of the 3D porous titanium customized implant (*b*); fixation with the Ilizarov apparatus, the final appearance of the foot and ankle joint after surgery (*c*); X-ray of the foot and ankle joint after surgery (*d*)

She was discharged on the 12th day and was followed on an outpatient basis; the sutures were removed after 6 weeks. Staged supporting 1-mm compression in the Ilizarov fixator was performed monthly. Five months after the operation, the results of checking radiographs and computed tomography revealed restructuring of the bone graft in the intertrabecular spaces of the implant; lysis phenomena and instability of the implant were not detected.

The Ilizarov apparatus was dismantled as planned (Fig. 5). Subsequently, the left ankle joint was unloaded for 6 months using an individual polymer unloading bandage. The patient was activated using additional support means with a dosed load on the operated lower limb up to 20 % of the weight, followed by a gradual increase to full weight-bearing.

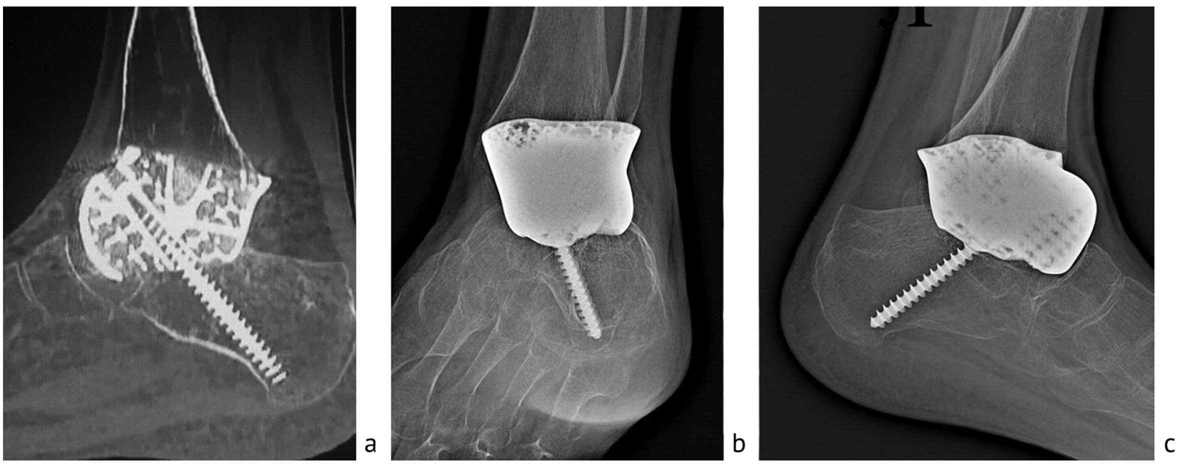

Fig. 5 Treatment results: CT image after dismantling the Ilizarov fixator shows signs of bone remodeling (*a*); X-rays of the ankle joint (*b*) and foot (*c*) six months after surgery

RESULTS

At the follow-up after 10 months, no clinical or radiographic signs of early instability of the endoprosthesis components and 3D porous titanium implant were observed (Fig. 6). The patient walked without the use of additional support means in orthopaedic diabetic shoes with individual orthopaedic insoles.

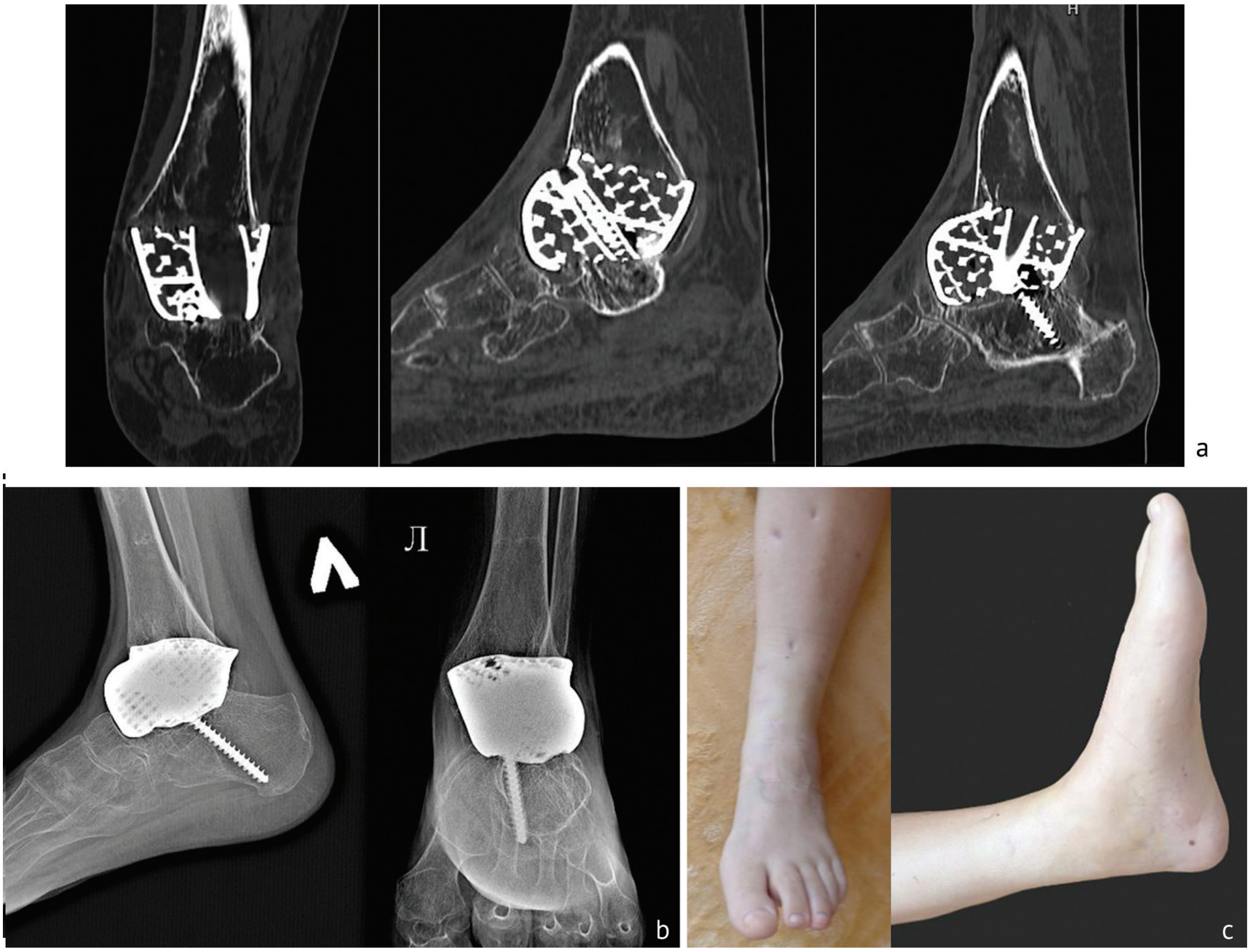

Fig. 6 CT-scans (a); radiographs (b) and photos of the foot (c) at 10-month follow-up after Ilizarov fixator removal

DISCUSSION

This clinical case demonstrates the need for a thorough anamnesis and preoperative examination to verify concomitant diseases and associated possible complications.

Conservative methods still prevail in the treatment of diabetic neuroosteoarthropathy, but cannot be applied to patients with complete or partial disorder of the supporting function of the foot, which, in turn, significantly increases the urgency of orthopedic reconstruction [20].

This method of surgical treatment is used in total destruction of the talus and the resulting defect-diastasis due to resection for calcaneotibial arthrodesis. The method allows for one-stage reconstructive intervention and precise compensation of shortening, regardless of the shape and size of the defect, avoiding secondary shortening of the limb while maintaining its support ability, thereby preventing the occurrence of secondary overload changes in the adjacent joints. However, one of the key tasks of orthopaedic treatment of patients with Charcot's neuroosteoarthropathy is to reduce the risk of high amputation and maintain the patient's motor activity. Stabilization of the foot with an external fixator is a factor that contributes to subsidence of the process and, as a result, has a positive effect on the completeness of the arthrodesis performed. It should also be noted that the treatment result largely depends on the patient's compliance and adherence to treatment, as well as his/her adherence to prescriptions and recommendations [21].

To clarify the indications for this treatment method and patient selection criteria, it is necessary to have a group of patients and conduct additional studies.

CONCLUSION

The results of performing resection calcaneotibial arthrodesis associated with defect plasty using a 3D porous titanium customized implant, presented in a patient with manifestation of Charcot arthropathy as a complication of tertiary syphilis, are encouraging. Given the person-specific approach, this method appears to be a promising treatment concept that allows restoring the weight-bearing capacity of the lower limb without shortening.

Conflict of interests *None declared.*

Source of funding *None declared.*

Informed consent *The patient gave written informed consent for the study to be conducted and for the results to be published.*

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Clinical case
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Effective combination of arthroscopic and minimally invasive surgery for chronic posterolateral elbow instability

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Abstract

Introduction Trauma and extreme physical activity may result in common patterns of forearm dislocation, which account for 10 to 25 % of all elbow injuries in the adult population. Good long-term results of eliminating joint dislocation with the use of conservative treatment have been much described, but 8 % of patients experience symptoms of chronic instability. We present a case of successful arthroscopic treatment of ligamentous stabilizers of the elbow joint using an effective combination of implants for its posterolateral instability. We found no publications on such an experience in the Russian literature.

The **purpose** of the work is to present a clinical case of an effective combination of arthroscopic and minimally invasive surgery methods for reconstruction of the ligamentous apparatus in chronic posterolateral instability of the elbow joint.

Material and methods Patient N., 31 years old, suffered chronic posterolateral rotational instability of the left elbow joint after dislocation of the forearm bones for more than 10 years. The operative technique was based on the principles of minimally invasive reconstructive plastic surgery and meets the objectives of gentle treatment of soft tissues, allowing visualization of the lesion and avoiding the contact with neuro-vascular structures. Baseline clinical tests (O'Driscoll, Regan/Lapner, Pollock), questionnaires (VAS, DASH, MEPS, SF-36), and MRI, 1.5 Tesla MRI scans of dynamic stabilizer disruption are reflected. Evaluation was performed at two control points (45 and 180 days).

Results The assessment was carried out at two control points. First follow-up (45 days): flexion/extension 50/175º, pronation/supination 90/90º, VAS 2, DASH 24.2, MEPS 80 points, respectively. Second follow-up (180 days): VAS 1, DASH 9.2, MEPS 95 points, comparative ranges of motion corresponded to a healthy joint. An MRI study confirmed the progress of the autotenograft and tendon ligamentization in the area of reinsertion, the absence of inflammatory changes and no heterotopic ossification.

Discussion Improvements in elbow surgery and technical progress are focused on minimally invasive interventions, while arthroscopy of the elbow joint is still technically difficult due to a limited space. And yet, this is an effective treatment method, as a result of which specialists can avoid a wide range of complications (14.7 %), and patients start rehabilitation faster and, as a result, recover faster than with open surgical approaches with a higher percentage of risks (52 %).

Conclusion The combination of the above techniques avoids conflict with neurovascular structures, provides visual control of the implantation of anchors and, as a result, reduces the overall risk of complications in the treatment of a rare group of patients with instability of the elbow joint.

Keywords: elbow joint, arthroscopic treatment, dislocation of the forearm bones, sports medicine, posterolateral elbow instability, collateral ligaments

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INTRODUCTION

The elbow joint consists of a complex of bone and ligament stabilizers that provide both mechanical and dynamic limitation of dislocation of the forearm bones. Due to injuries and extreme physical exertion, classical patterns of dislocation may occur that account for 10–25 % of all elbow joint injuries in the adult population, while the incidence rate is 7 cases per 100,000 people a year. A quarter of the conditions are accompanied by a fracture of the bone structures that make up the elbow joint, in 60 % of cases the non-dominant extremity is involved [1–4].

Falls on an extended elbow joint resulting from low-energy injuries are the most common mechanism of forearm bone dislocation (56.5 %) in everyday life activities and extremely rare in sport activities (4 %) [1, 4]. Such dislocations at the age of 10–19 years are more common in men (53 % to 47 % in women) and are frequently combined with shoulder or wrist injuries (10–15 %) [5]. It is reported that 6 out of 58 (10 %) forearm bone dislocations in children require open surgery. Interposition of the medial epicondyle of the humerus by intra-articular fragments is the most common cause of reduction difficulties [5, 6]. The effectiveness of therapeutic measures is determined by knowledge of the anatomy and biomechanics of the joint, as well as by the vectors of force that preceded the primary dislocation.

There are three primary static stabilizers of the elbow joint: the humeroulnar joint, the anterior portion of the medial ulnar collateral ligament (MUCL), and the lateral collateral ligament complex (LCLC). Secondary stabilizers include the humeroradial joint, the tendons of the flexor and extensor muscle groups of the wrist (m. flexor carpi radialis et ulnaris, m. extensor capri radialis longus et brevis, etc.), and the capsule. The muscles that cross the elbow joint (m. pronator teres, m. brachialis, m. anconeus, etc.) are dynamic stabilizers. The LCLC provides varus stability of the elbow joint and includes the annular ligament, fibers of the accessory lateral collateral ligament, the lateral ulnar collateral ligament (LUCL) and the radial collateral ligament (RCL). The antagonist of the lateral collateral ligament complex is the MUCL that consists of the anterior oblique, posterior and transverse portions (Cooper's ligament) [7].

Currently, three types of post-traumatic instability of the elbow joint have been identified, associated with the mechanism of injury and disruption of the anatomical structures [8]:

— posterolateral rotational instability (PLRI) develops after damage to the LCLC due to a fall on an outstretched arm and is the most common (80%);

— valgus instability (VI) is caused by injury to the MUCL due to a cyclic traction mechanism, often found in athletes who regularly throw a ball;

— posteromedial varus instability (PMVI) is typical for elbow injuries accompanied by damage to the ligament associated with a fracture in the ulna.

In diagnostic terms, post-traumatic instability of the elbow joint can be determined by instrumental methods of visual diagnostics and with the help of provocative tests. The O'Driscoll dynamic valgus stress test is 100 % sensitive and 75 % specific for injuries of the medial stabilizing complex in VI, as well as the lateral pivot-shift test, suitable for PLRI. Regan et Lapner presented a push-up and chair-stand load test with a sensitivity of 87.5 % (100 % with sequential use of both tests) for identifying PLRI [9]. The Pollock gravity stress test is the most sensitive and specific for PMVI [1, 3]. It is important to know that some tests can be performed only after the implementation of conduction or general anesthesia in patients, otherwise the sensitivity will not exceed 38% and will be hampered by pain syndrome.

CT has a sensitivity of 71–86% and a specificity of 91% and is routinely used to evaluate the disruption of the architec-ture of the bone stabilizers in the forearm fracture-dislocation model. In the context of chronic post-traumatic elbow instability, provocation of the coronoid process is best seen in VI [1, 3]. MRI allows evaluation of the structures of soft tissue stabilizers, including the LCLC/LUCL/MUCL, and visualization of the osteochondral fragments of the trochlea humeri or fossa olecrani [3, 6, 10]. Magnetic resonance imaging has a sensitivity of 57–79% in detecting VI and is 100% specific for damage to the ligamentous apparatus structures [1]. Radiography of the elbow joint in standard views does not have a high degree of specificity for this nosology, which can be increased by using an image intersifier for dynamic radiography [1]. The method allows vizualizing avulsion fractures, intra-articular chondral bodies or heterotopic osteophytes of the ulnar processes, which are indirect signs of post-traumatic instability of the elbow joint.

In academic terms, the classifications of Albert (1881), Gui (1957) and Morrey (1996) are of interest; however, according to some authors, the most relevant in practical terms are the classifications of O'Driscoll (2000) and SICSeG (Italian Society of Shoulder and Elbow Surgery, 2015) [11]. The O'Driscoll classification defines the complexity of the dislocation of the forearm bones and post-traumatic instability of the elbow joint according to the criteria: time, involved joints, direction, severity, concomitant fractures. The SICSeG classification divides the pathology into types: A (acute) and B (chronic, with bone / bone and soft tissue injury).

Good long-term results of forearm bone dislocation correction after conservative treatment have been described; however, the outcome was poor in 10 % of patients, of which 2 % require surgical intervention, and approximately 8 % experience symptoms of post-traumatic instability of the elbow joint [8, 12].

Improvements in surgical techniques and technical progress have focused on minimally invasive interventions, while elbow arthroscopy is still technically challenging due to limited space and proximity of neurovascular structures. However, it is an effective treatment method that allows avoiding a wide range of complications: iatrogenic neuropathy (3.4%), superficial and deep wound infection (2.0% and 0.7%, respectively), wound healing complications (1.5%), joint contracture and instability (4.5% and 2.6%), and the need for revision surgery (4.1%). Patients are be able to begin rehabilitation and, as a result, recover faster than with open surgical approaches (overall complication rate is 52%; tunnel and contusion neuropathy of the ulnar and median nerves, pseudarthrosis of the ulnar or coronoid process, heterotopic ossifications) [13–18]. There have been no comprehensive studies of the consequences of forearm bone dislocations on a big sample of patients and with a large volume of data. Therefore, even a single episode is of academic interest.

Purpose The aim of the work is to present a clinical case of an effective combination of arthroscopic and minimally invasive surgery methods for reconstruction of the ligamentous apparatus in chronic posterolateral instability of the elbow joint.

MATERIALS AND METHODS

Patient H., 31 years old, a former professional snowboarder, came to an outpatient appointment with a trauma orthopaedist at the Novosibirsk Tsivyan Research Institute of Traumatology and Orthopaedics on November 3, 2023, complaining of pain, posterolateral instability of the left elbow joint, acoustic elements ("clicks"), transient blocks, and muscle weakness of the limb. History: primary organized sports injury (2006): fall on a straightened left upper limb while performing a sports element in a half-pipe.

Emergency medical care was provided to the patient outside the Russian Federation within 24 hours. Radiography of the left elbow joint was taken in two projections and the diagnosis was: acute complicated posterior dislocation of the bones of the left forearm with damage to the ulnar collateral and medial collateral ligaments of the elbow joint, non-tension hemarthrosis. Manual reduction was performed under local anesthesia with Sol. Novocaini 0.5 % 40 ml. There were no complications such as incongruence or fractures on checking X-rays. Subsequently, three episodes of dislocation of the bones of the forearm were detected (in 2011, 2018, 2023) and chronic PLRI of the left elbow joint developed. Clinical tests (without conduction anesthesia): O'Driscoll dynamic valgus stress test "+", O'Driscoll lateral pivot-shift test "–", Regan/Lapner "+", Pollock gravitational stress test "–". Morphometry: flexion/extension — 55/160°, pronation/supination — 80/45°. Strength was assessed with a mechanical dynamometer: Dex. 90; Sin. 65 (2daN). Given the contradiction in the targeted clinical tests, an instrumental examination was performed in the volume of 1.5 T MRI of the elbow joint that detected damage to the area of the "anatomical imprint" of the MULC/LCLC (Fig. 1). Additionally, a defect in the articular surface of the trochlea humeri and fossa olecrani, intraligamentary ossification of the MULC with provocation of the cortical layer of the medial epicondyle of the left humerus and LCLC, and exostosis of the olecranon of the ulna were visualized.

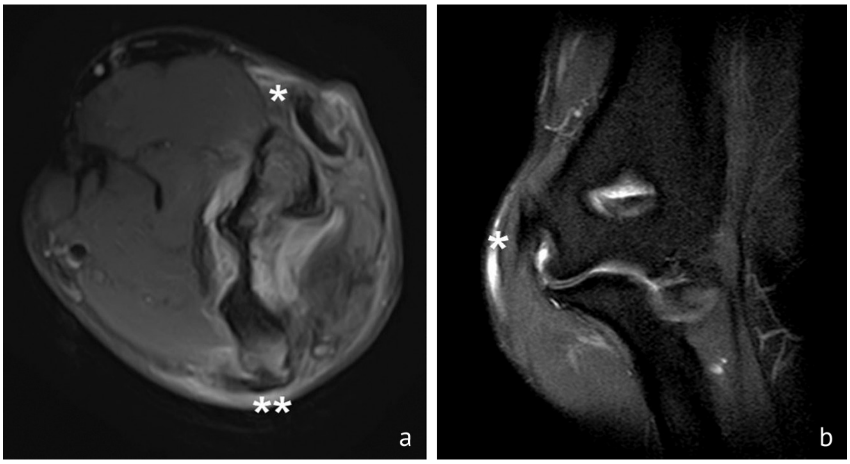

Fig. 1 Scans of the area of interest: post-traumatic instability of the elbow joint of the left upper limb in coronal (*a*) and sagittal (*b*) sections of T1-weighted MRI with measurement of the MUCL (*) and LCLC (**) the structures

Findings of orthopaedic questionnaires: VAS (Visual Analogue Scale) < 3, DASH (Disabilities of the Arm, Shoulder, and Hand) — 30.8; MEPS (Mayo Elbow Performance Score) — 45 points respectively; SF-36 (36-item Short Form Health Survey): physical condition — 25 %; physical health limitations — 0 %; limitations due to emotional state — 0%; energy/fatigue — 60 %; emotional well-being — 32 %; socialization — 50 %; pain — 45 %; general health — 25 %; change in health — 25 %.

SICSeG classification: type B, recurrent, bone + soft tissue; O'Driscoll classification: recurrent, radioulnar/humeral, PLRI, subluxation, coronoid process.

Anamnesis morbi: injury during domestic activities, chronic post-traumatic instability of the elbow joint for more than 17 years, left arm, non-dominant side.

On the day of hospitalization (03.11.2023), the following treatment was performed: arthroscopy of the left elbow joint, resection of pathological humeroradial folds; removal of chondral bodies; reinsertion of the radial collateral (RCL) and lateral ulnar collateral ligaments (LUCL); MUCL reconstruction with an autogenous graft of the split m. peroneus lon-gus; reinsertion with soft-tissue anchor fixators; debridement.

The patient was placed on the orthopaedic table in the prone position, with the arm abducted at 90° at the shoulder joint and bent at 90° at the elbow joint, in a hanging position. Before draping the surgical field, a pneumatic tourniquet was applied at the level of the upper third of the humerus, and the pressure was elevated to 250 mm Hg. Before using the incision film, anatomical landmarks were marked (medial, lateral epicondyles of the left humerus, olecranon of the ulna) marking the n. ulnaris and the main ports (proximal superomedial port, superlateral port, anteromedial port, anterolateral port, direct lateral port, posterocentral port) [19] (Fig. 2).

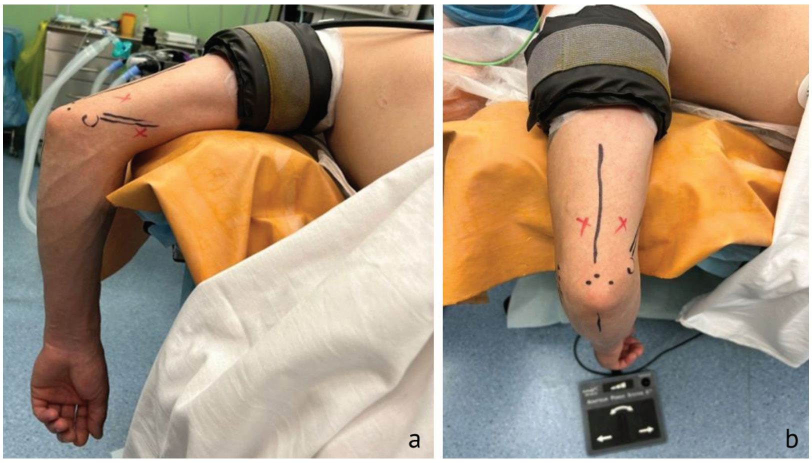

Fig. 2 Photo of the patient's position on the operating table with the application of a pneumatic tourniquet (*a*) and marks of the main ports (*b*)

The surgical intervention was performed under combined anesthesia: regional interscalene anesthesia (brachial plexus block from the supraclavicular approach with 0.5% Ropivacaine 20 ml under ultrasound navigation, stimuplex current 0.36 mA) in combination with intubation anesthesia.

Centesis of the elbow joint was performed via the standard anteromedial approach; revision revealed posttraumatic cubarthrosis grade 1–2, secondary chondromatosis of the trochlea humeri and fossa olecrani, and heterotopic ossification. O'Driscoll, Regan/Lapner, and Pollock "+" tests after the development of anesthesia confirmed PLRI. Lateral approach was performed under arthroscopic control, and articular surfaces were assessed with a manipulator. The hyaline cartilage was peeled off in some places. More than two chondral bodies were removed, sized approximately 3 × 2 mm. Cold plasma coblation of the enlarged synovial folds was performed (plical syndrome was resolved). An arthroscope was inserted via a separate posterior approach under the triceps into the cubital fossa area. The fossa was sealed and consisted of scar tissue and osteophytes. Debridement was performed using a shaver system and an ablator. Degeneration of the triceps tendon at the attachment site (foot print) was determined. The range of motion increased by more than 10–15° on average after elbow arthrolysis had been removed. A rupture of the MUCL with provocation of the cortical layer of the medial epicondyle of the left humerus and the RCL, degeneration of the radial head (chondromalacia stage 2) were visualized. Synovial folds were dissected.

Through a 1-cm skin approach in the area of the lateral malleolus of the left lower leg, the tendon of m. peroneus longus sin was isolated and extracted with an instrument; 2/3 was divided into two bundles and a 5 × 260 mm portion of the tendon was collected with an open pig tail extractor for subsequent preparation and formation of an autotenograft. In the medial compartment, the medial epicondyle of the humerus was visualized (Fig. 3 a; Fig. 4 a); n. ulnaris was retracted proximally in the cubital canal in order to prevent conflict and neuropathy and the cortical layer was processed with a drilling bur until "blood dew". Through a 5-mm approach, one anatomical soft-tissue anchor fixator, sized 2.7 mm, was implanted with immersion of the previously prepared autotenograft under arthroscopic control. The second anchor fixator, sized 2.7 mm, was installed distal to the incisura trochlearis.

The elbow joint was extended, and the radial collateral ligament formed from the graft was sutured and fixed in the position of maximum tension. In the lateral compartment, the lateral epicondyle of the humerus was visualized, the cortical layer was processed to the "blood dew" (Fig. 3 b; Fig. 4 b) and a 2.7-mm non-body soft-tissue anchor fixator was implanted in a similar manner; and a penetrator was used to perform transtendinous suturing of the radial collateral ligament using the "parachute" method and sliding knots were tightened in the neutral position of the elbow joint.

The repeated O'Driscoll 1/2, Regan / Lapner, Pollock "–" tests revealed the elimination of chronic PLRI of the elbow joint under image intensifier control. Sutures were applied to the skin. The left upper limb is immobilized with a sling bandage.

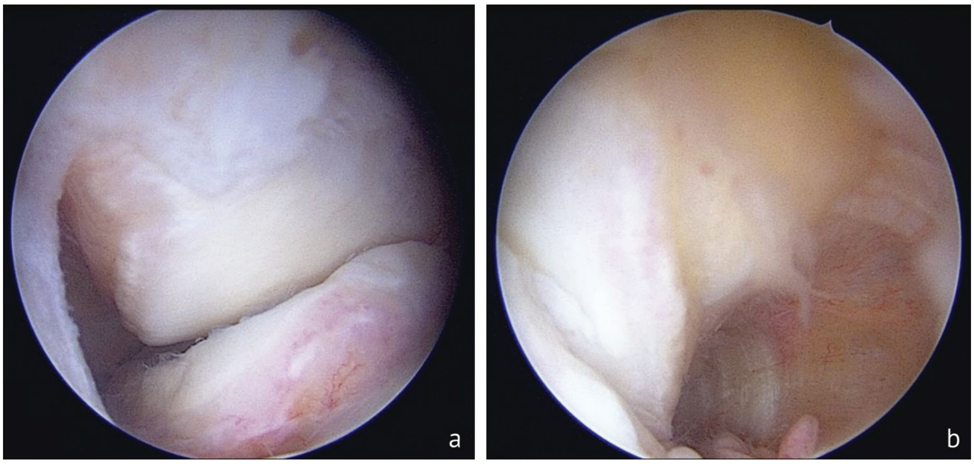

Fig. 3 Arthroscopic image through the posterocentral port with visualization of the provocation of the cortical layer of the medial epicondyle of the “anatomical impression” of the MUCL (*a*) and the disruption of the structures of the LCLC (*b*) during targeted clinical tests

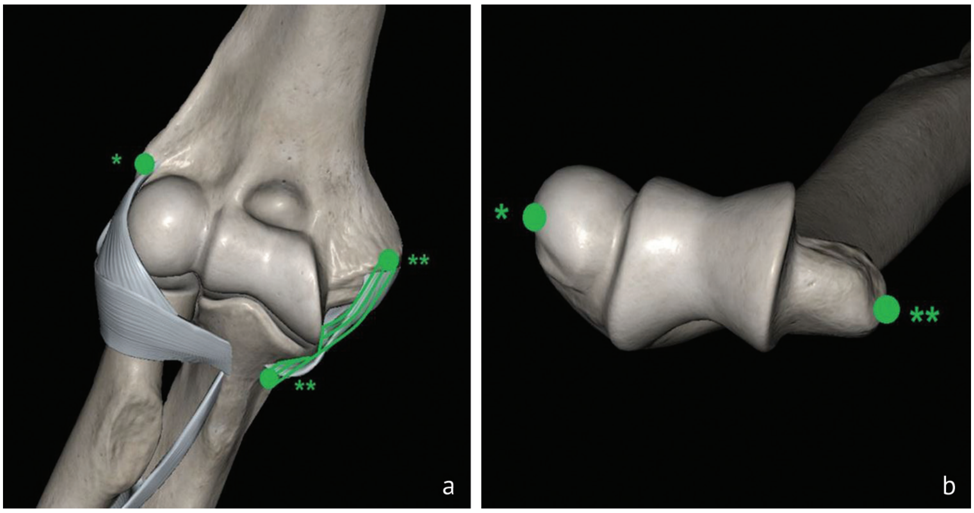

Fig. 4 3D model of the elbow joint (*a, b* visualization in different planes) with the location of the main reconstructive elements in the surgical treatment of chronic PLRI: anchor fixators for reinsertion (*) and autotenograft (**)

The patient was discharged on 05.11.2023 without signs of septic complications and was supervised by a physician of the outpatient department. The rehabilitation protocol included immobilization with a sling bandage for four weeks, cryotherapy (Kryotur), intake of non-steroidal anti-inflammatory drugs and muscle relaxants per os, and exercise therapy. In the first period, mechanotherapy of the elbow joint with some devices was recommended: manual kinesiotherapy, early passive movements from the second week (Kinetec Centura) and active movements from the fourth week. In the second period, exercise therapy under supervision of an instructor to restore complex motor stereotypes from the fifth week, limiting the axial and traction load (horizontal bar, parallel bars) on the upper limb for 12 weeks [3].

RESULTS

The results of treatment for chronic LRTI of the elbow joint by the method of arthroscopic reconstruction of the ligamentous apparatus were analyzed using a universal method of personalized assessment by questionnaire systems on an outpatient basis at the NNIITO after six and 24 weeks.

The absence of persistent pain, significant difference in the indicators of comparative dynamometry, O'Driscoll 1/2, Regan/Lapner, Pollock "-" tests were regarded as a positive result (Fig. 5).

Fig. 5 Photographic recording of the range of motion and targeted clinical tests of the left elbow joint after arthroscopic reconstruction of MUCL and reinsertion of LCLC in chronic PLRI of the elbow joint

First clinical examination (6 weeks): flexion/extension — 50/175°, pronation/supination — 90/90°, VAS 2, DASH 24.2, MEPS — 80 points respectively, SF-36: 60 %; 50 %; 66.7 %; 55 %; 64 %; 62.5 %; 77.5 %; 65 %; 50 %, dynamometry: Dex. 85; Sin. 90 (2daN),

Second follow-up examination (24 weeks): VAS 1, DASH 9.2, MEPS 95 and SF-36: 85 %; 75 %; 66.7 %; 70 %; 84 %; 75 %; 67.5 %; 80 %; 75 %, comparative ranges of motion corresponded to a healthy joint.

Postoperative complications were assessed after surgery at two control time-points. The first time-point was 45 days (12/18/2023): heterotopic ossification "–", neuropathy "–", contracture "+", muscle hypotrophy "+". The second time-point was 180 days (03/03/2024): heterotopic ossification "–", neuropathy "–", contracture "–", muscle hypotrophy "–".

Instrumental evaluation of the effectiveness: 1.5 T MRI of the affected joint with visualization of the course of the MUCL autotenograft to the "anatomical impression" (Fig. 6 a) and ligamentization of the RCL, absence of inflammatory changes, signs of ossification, heterotopic ossification (Fig. 6 b). The patient returned to everyday activities after 6 weeks and after 12 weeks to professional ones after completing the course of rehabilitation described above.

Fig. 6 MRI of post-traumatic instability of the elbow joint of the left upper limb in sagittal (*a*) and coronal (b) sections of the T1-weighted MRI mode, with visualization of the viability of the MULC autotenograft (**) and LCLC ligamentization (*) 6 weeks after surgical treatment

DISCUSSION

Outcomes of treatment in patients with uncomplicated dislocation of the forearm bones are usually favorable. However, studies show that 60% of these patients lose more than one bone or ligament stabilizer and may have residual symptoms: recurrent variant of post-traumatic instability of the elbow joint, joint contracture, pain associated with the development of degenerative processes, and transient ulnar neuropathy [4, 10, 20]. Available data on the incidence of complications leading to revision surgery average 12–15%, but they have limitations due to small cohorts of patients in most studies [14, 16].

Due to the fact that most injured patients are of working age, the problems of treating post-traumatic instability of the elbow joint and dislocation of the forearm bones, as well as subsequent rehabilitation measures, is of significant socio-economic nature. The clinical case presented is a case of successful arthroscopic treatment of ligamentous stabilizers of the elbow joint using an effective combination of implants in a posterolateral model of elbow instability. The technique is focused on the principles of minimally invasive reconstructive plastic surgery in order to restore the biomechanics of a large joint of the upper limb girdle and meets the objectives of careful treatment of soft tissues, allowing visualization of the damage and avoidance of contact with neuro-vascular structures. We have not found any publications about such experience in the domestic literature. Diagnostic and therapeutic arthroscopy is a generally accepted method of treating a wide range of elbow joint diseases. The rarity of the method is not dictated by its complexity or the presence of a large number of complications. The required experience of the surgeon, the level of qualification, knowledge of anatomy and biomechanics are determined by the complexity of clinical cases. The described technique, performed according to indications, seems to be effective in the treatment of patients with chronic posterolateral rotational instability of the elbow joint. However, a larger sample of patients with long-term follow-ups will certainly fully show its advantages and identify possible shortcomings.

CONCLUSION

The combination of arthroscopic and minimally invasive surgery in this clinical case avoids conflict with neurovascular structures, provides visual control of implantation of anchor fixators. The clinical case demonstrates a successful combination of arthroscopic and minimally invasive surgery methods for reconstruction of the ligamentous apparatus in elbow joint instability.

Conflict of interest *The authors report no obvious or potential conflicts of interest related to the publication of materials.*

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Informed consent *The patient voluntarily signed an informed consent for the publication of personal medical information in an anonymous form.*

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Hand injuries sustained while contacting operating electric meat grinders (literature review illustrated with authors' clinical cases)

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Abstract

Introduction Upper limb injuries sustained by children and adults with electric meat grinders in motion are mutilating. These injuries may lead to physical disability and severe psychological consequences not only for the injured subjects, but also for their family members.

Aim Based on current medical literature, to analyze the issues of incidence, etiopathogenesis, clinical symptoms, surgical treatment, rehabilitation, prevention of injuries to the upper limbs sustained with electric meat grinders and to illustrate the material with authors' own clinical cases.

Material and methods The search for scientific publications was carried out in the electronic databases and libraries PubMed, eLibrary.ru, CyberLeninka. The search depth was 47 years. In total, 49 scientific articles were analyzed and studied: 9 domestic sources (18.36 %) and 40 foreign ones (81.64 %).

Results and discussion Epidemiological data show that the incidence of injuries sustained by individuals while contacting with electric meat grinders in motion is 1.4 % to 11.1 % of open injuries to the upper limbs,. The main cause of this type of injury in children is the lack of control by adults, and in adults it is failure to comply with safety measures. The main mechanisms of trauma are traction and rotation. The right hand is most often injured, namely its fingers II, III and IV. Injuries are characterized by traumatic amputations, ruptures and crushing of hand segments. The most important goals of surgical treatment is excision of non-viable tissue, arrest of bleeding, shaping stumps of finger phalanges and metacarpal bones and / or osteosynthesis of broken bones, suturing of vessels and nerves, the maximum possible closure of the soft tissue wound with preserved skin flaps. As preventive measures, it is proposed to inform the population on safety measures by operating electric meat grinders. There should be careful supervision by adults over young children if they are in places where food is prepared. Services of professional butchers are highly recommended.

Conclusion Based on data from 49 scientific articles, information was obtained on the frequency of occurrence, causes, mechanisms, clinical features, surgical treatment, rehabilitation and prevention of severe hand injuries sustained by individuals contacting with operation electric meat grinders.

Keywords: mutilating injuries, upper limb, electric meat grinder, literature review, own case series

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INTRODUCTION

Injuries to the upper limbs caused by contact with operating electric meat grinders are mutilating [1, 2]. These injuries may lead to disability due to the loss of fingers or the entire hand [3, 4]. The relevance of the problem is also due to the fact that mutilating hand injuries have extremely severe psychological consequences not only for the injured individual but also for his/her family members [5].

Purpose Based on current medical literature, to analyze the issues of incidence, etiopathogenesis, clinical symptoms, surgical treatment, rehabilitation, prevention of injuries to the upper limbs sustained while contacting with electric meat grinders and to illustrate the material with authors' own clinical cases.

MATERIALS AND METHODS

The search for publications on the problem of upper limb injuries caused by operating electric meat grinders was carried out in the electronic databases and libraries PubMed, eLibrary.ru, CyberLeninka. The search depth was 47 years.

The search for literature sources was conducted using the following keywords: crippling injuries of upper limbs, working electric meat grinders.

The study used the following criteria for inclusion of scientific publications in the literature review: systematic reviews devoted to open hand injuries, monocentric cohort studies and clinical cases describing the treatment tactics and treatment outcomes of patients who sustained upper limb injuries with working electric meat grinders. A total of 49 scientific articles were analyzed, reflecting the most pressing issues and aspects of the topic under study: 9 domestic literary sources (18.36 %) and 40 foreign ones (81.64 %).

RESULTS AND DISCUSSION

There are few scientific articles in current medical literature devoted to injuries to the upper limbs caused with electric meat grinders. Suffice it to say that a group of Uzbek authors in their scientific work published in 2017 reported that they were unable to find publications devoted to this topic in current scientific information search systems [6]. At the same time, there are a large number of reports in electronic media in various countries about cases of hand injuries sustained with electric meat grinders in children and adults. Thus, in 2013 alone, the Occupational Safety and Health Administration in the United States officially recorded more than 4,000 cases of this type of injury [7].

The relevance of the topic under discussion is evidenced by the fact that to date the incidence of upper limb injuries caused by electric meat grinders in the structure of open hand injuries is not reliably known. It can be judged from indirect data provided in publications. Thus, Russian authors inform readers that among 70 children with open fractures and wounds of the hand, 1.4 % of the injured were contacting with working electric meat grinders [8]. According to Greek authors, 7 % of children under four years of age sustained severe hand injuries while contacting with various machines and tools [9]. A group of Chinese surgeons reports that in 11.1 % of cases, purulent tenosynovitis of the hand and forearm in the patients they examined was caused by injuries sustained during careless handling of electric meat grinders [10].

Table 1 presents information about scientific publications in which the authors describe their experience in providing medical care to patients with upper limb injuries resulting from contact with working electric meat grinders.

Table 1

Scientific publications on injuries of the upper limbs in children and adults sustained while contacting with electric meat grinders

No	Authors and reference list number	Quantitative characteristics by patients' age			
		children		adults	
		Number of case	Mean age, months	Number of case	Mean age, years
1.	Al-Arabi et al. [11]	22	21		
2.	Ibrahim et al. [12]	1	24		
3.	Ezhov et al. [13]	1	33		
4.	Novruzov et al. [6]	13	29		
5.	Cardoso et al. [14]	20	–	5	–
6.	Kassa [2]	2	36	1	24
7.	Yaldiran et al. [15]	13	–	49	–
8.	Duman [16]	22	132	42	42
9.	Al-Hassani et al. [17]			1	23
10.	Brandner et al. [18]			3	37
11.	Gearing et al. [19]			2	35
12.	Green et al. [20]			1	45
13.	Kinoschito et al. [21]			1	39
14.	Lubis [22]			3	24
15.	Patial et al. [23]			2	25
16.	Maajiid et al. [24]			1	29
Total		94		111	

As follows from the information in the table, four articles are devoted to the description of injuries only among children [6, 12, 13, 21], four publications describe injuries in children and adults [2, 14, 15, 16] and eight scientific papers characterize limb wounds, treatment tactics and treatment outcomes in patients over 18 years of age [17–24]. In total, the authors of scientific articles describe clinical cases of 94 children of average age (39 ± 6) months and 111 adults of average age (32 ± 1.8) years.

The main cause of injuries to small children is their curiosity and interest when, without adult supervision, they put their fingers into the mouth of a working electric meat grinder [12, 18]. Teenagers, as a rule, injure their hands when they use their fingers instead of a special device (pusher) to push pieces of meat onto a rotating auger [15]. Injuries to adult patients are mainly associated with violations of safety precautions in the food industry and at home [7, 25, 26]. Thus, Iranian authors report 49 typical errors they have uncovered, caused by personal, managerial and organizational factors that can lead to severe injuries to the hands of the personnel working with electric meat grinders [27].

The right hand is mostly injured [17, 22, 28], since the right hand is dominant in most people and, therefore, involved in most functions [2, 29]. However, there are frequent cases when the left upper limb is also injured [30, 31].

All injured patients are delivered to medical institutions with their hands trapped in electric meat grinders [6]. The authors of almost all the scientific articles named in Table 1 provide illustrations of the patients before removing their injured hands from the electric meat grinders.

The first and most important stage of providing medical care to such patients is adequate pain relief, which allows not only to alleviate the suffering but also to begin the fastest possible removal of the hand from electrical devices [21]. Most authors use the experience of special services for these purposes, often calling them directly to the operating rooms. Thus, Al-Hassani et al. involved the regional civil defense service of Qatar removal [17]; Gearing et al. called the fire brigade of the Australian city in which they worked [19]; Turkish doctors invited a rescue team with a special circular saw [12]; Indian surgeons used a welding machine to cut a meat grinder and to free a trapped hand [23]. Domestic surgeons involved specialists from the Ministry of Emergency Situations, who own special power equipment to free the hand of a girl, aged 2 years 9 months, trapped in an electric meat grinder [13]. While providing emergency medical care to 13 children with their hands trapped in electric meat grinders, a group of traumatologists from Uzbekistan used household electric saws of the "Bulgarian" type in 8 (61.5 %) cases, and a manual reverse (reverse unscrewing) technique with an adjustable wrench in 5 (38.5 %) cases [6]. Egyptian microsurgeons report a higher number of using the reverse unscrewing technique. Thus, Abdelmegeed et al. state that this technique was effective in 80 % ($n = 4$) of cases, and only one teenager required the use of a circular saw [32].

The same manual reverse technique was effective in freeing the trapped hands of two children and one adult reparted by Kassa BG [2]. It was used in a single case and then described in a scientific article by Green et al. [20]. Indonesian surgeons successfully used manual reverse method with an adjustable wrench on three female meat-processing workers aged 23, 24, and 25 [22]. An unusual method of freeing a hand trapped in an electric meat grinder was used by Indian doctors who delivered a 29-year-old man from the hospital to a nearby auto repair shop, where auto mechanics were able to remove the injured hand from the electric meat grinder. The decision was made after a medical consultation and preliminary agreement with the auto repair shop workers. Patient’s transportation and the process of cutting the electric meat grinder was carried out under adequate anesthetic support and medical supervision [6, 24].

After the injured limbs are removed from the electric meat grinders, the severity of the injuries should be assessed [33]. Based on the design and operating principle of the electric meat grinders, it becomes clear that the main mechanisms that injure the hand are traction/rotation and grinding/crushing [1, 25, 34]. Sharma et al. call such a combined impact of traumatic forces on the upper limb "unique mechanism” [36]. Multidirectional and at the same time coordinated actions of damaging forces lead to severe multiple contusions, crushing, smashing and ruptures of the skin, muscles, ligaments, tendons, vessels and nerves of the limb trapped in the meat grinder, open multi-level fractures of the phalanges of the fingers, metacarpal bones, wrist bones, and in some cases, the distal metaphysis of the forearm bones [23, 34].

Matveev et al. in a scientific article devoted to open wounds of the hand cite more than 30 existing and used in clinical practice classifications of these types of injuries [37]. In domestic traumatology, the most used classification is that of Gromov et al., according to which the injuries resulting from the action of working electric meat grinders should be classified as group V, traumatic amputations (complete and incomplete), avulsions and crushing of fingers and other segments of the hand [38].

The stages of surgical treatment of the injured include arrest of bleeding, excision of non-viable tissue, wound sanitation, formation of stumps of the phalanges of the fingers and metacarpal bones and/or osteosynthesis of broken bones, suturing of vessels and nerves, maximum possible “closure” of the soft tissue wound with intact or minimally injured simple or combined skin flaps [33, 35]. Surgical treatment of the wound should be carried out sparingly in order to preserve the maximum possible volume of the anatomical structures of the hand [13, 39]. Impaired blood circulation and innervation, development of inflammation are the main causes of necrosis of those anatomical structures of the hand that surgeons try to preserve during primary surgical treatment of wounds [14]. Immediately after the formation of stumps, all injured patients are prescribed a course of antibacterial therapy. As medications, cephalosporins of the 1^{st}–3^{rd} generations (ceftriaxone, cefazolin, cefuroxime, etc.) are used in age-related dosages [8]. In cases of particularly severe injuries to the upper limb, patients are prescribed antimicrobial and antiprotozoal drugs. Thus, Navruzov et al. gave preference to metronidazole, administered intravenously by drip for 6–7 days [6].

Being in contact with rotating electrical equipment, including meat grinders, the phalanges of the fingers and metacarpal bones are the most frequently affected anatomical structures of the hand [19, 40, 41, 42]. Analysis of literature sources shows that amputations at the level of the phalanges of the fingers or disarticulations at the level of the interphalangeal, metacarpophalangeal joints and proximally are performed frequently involving the 2nd, 3rd and 4th digits [12, 17] (Fig. 1). The 5th digit in combination with the listed fingers is less affected [2, 13].

a b c

Fig. 1 A crippling injury to the left upper limb in a 1.5-year-old child: *a* the child's left hand is in an electric meat grinder; *b* an X-ray of the left hand, direct view; *c* the child's left hand one year after the injury (authors' case, August 2022)

Duman, based on the experience of treating 22 children and 42 adults with open hand injuries resulting from patients' contact with electric meat grinders, reports that in the children's the incidence of disarticulations at the level of the metacarpophalangeal and wrist joints is statistically significantly higher compared to the group of adult patients [16] (Fig. 2). However, there are also cases of "high" amputation among adult patients. Thus, Patial et al. describe a clinical case of a 22-year-old man who underwent emergency disarticulation at the level of the wrist joint. He sustained a hand injury while grinding meat in an electric meat grinder. The authors of the article particularly emphasized the fact that after the hand wound had healed, the patient refused a hand prosthesis [23].

Fig. 2 Stump of the right forearm formed in a four-year-old child after a crippling injury resulting from trapping the hand in a working electric meat grinder (authors' case, September 2023)

F. del Pinal formulated a goal, which, in his opinion, should be sought when providing assistance to patients injured by an electric meat grinder. He named it "acceptable hand". The author describes "a hand with three fingers, one of which is the first, the fingers are of almost normal length and retain almost normal sensitivity." But the author does not report anything about the patients' requirements for the functional state of the hand with amputated fingers [43]. However, most authors dealing with the problem of hand injuries attach primary importance to the residual functional state of the injured limb [44, 45]. According to Chinese surgeons, Tsai et al., to achieve a satisfactory functional state of the injured limb in pediatric patients, it is necessary to use aggressive treatment methods, including early reconstruction and rehabilitation [46]. Sozbilen et al. are convinced that the final treatment results in children with hand injuries are better than in adults with similar severe injuries [47].

In some countries, mainly in the Muslim world, upper limb injuries resulting from contact with working electric meat grinders have been and are currently considered a national health problem [16, 48]. According to Yildiran et al., this is due to centuries-old traditions of sacrificing domestic animals during holidays, and it is on these days that the incidence of various limb injuries, including those caused by working electric meat grinders, increases [15].

As a preventive measure, it is necessary to inform better the population about the importance of safety measures when working with electric meat grinders and to illustrate the consequences of injuries, no matter how shocking they may be for the population [2, 19, 23]. Stronger supervision of young children by adults in places where food is prepared [9, 49] and the invitation of professional butchers at public holidays are also effective ways to prevent hand injuries caused by electric meat grinders [15].

CONCLUSION

In pursuit of the goal set in this study, we analyzed 49 current scientific publications covering the issues of incidence, etiopathogenesis, clinical symptoms, surgical treatment, rehabilitation and prevention of hand injuries sustained by contact with operating electric meat grinders. In the structure of open injuries of the upper limbs, these injuries accounts for 1.4 to 11.1 % of cases. The 2nd, 3rd and 4th digits of the right hand are mainly injured. The most important stages of surgical treatment are arrest of bleeding, excision of non-viable tissues, formation of stumps of the phalanges of the fingers and metacarpal bones and/or osteosynthesis of broken bones, suturing of vessels and nerves, the maximum possible closure of the soft tissue wound with the available skin flaps. As preventive measures, it is proposed to inform the population about safety precautions when operating electric meat grinders, good supervision of young children by adults in places where food is prepared, and invitation of professional butchers.

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Scaphoid nonunion and SNAC treatment

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Abstract

Introduction Scaphoid nonunion can result in progressive scaphoid nonunion advanced collapse (SNAC) and have an impact on the quality of life in younger patients. The social significance of the pathological condition induces original research and literature analysis.

The **objective** was to identify methods for preventing scaphoid nonunion and improving treatment outcomes for SNAC patients based on the literature on etiology, diagnosis and treatment of the disease.

Material and methods The original literature search was conducted on key resources including Scientific Electronic Library (www.elibrary.ru) and the National Library of Medicine (www.pubmed.org) and using the keywords: scaphoid nonunion, scaphoid, bone grafting, scaphoid nonunion, vascularized bone graft. The search yielded 355 results. Literature searches included both Russian and English studies published between 1984 and 2024. Inclusion criteria included original articles, systematic reviews, meta-analyses relevant to the search topic. Non-inclusion criteria included a case report, case/control, and articles available only on a fee-paying basis. There were 67 articles identified.

Results and discussion The topography of the scaphoid is associated with a high incidence of avascular necrosis, delayed healing and fracture nonunion. Clinical testing and imaging are essential for diagnosis of scaphoid fractures in the acute period of injury, and fracture instability would be important for surgical indications. There is a classification of scaphoid nonunions that is practical for the choice of a surgical treatment (osteosynthesis with compression screws, debridement and bone grafts or "salvage" operations). Scaphoid nonunions treated with the Ilizarov method employing no open approaches or grafts was reported in a few publications. Treatment of SNAC patients is traditionally based on the stage of the disease: 1 — scaphoid reconstruction, resection of the styloid process of the radius; 2–3 — 4-corner arthrodesis or the proximal row carpectomy. Meta-analyses highlight the need for the research into the effectiveness of various treatments. Arthroscopic techniques are common in wrist surgery improving diagnostic capabilities and minimally invasive interventions.

Conclusion Timely healing of a scaphoid fracture is essential for preventing carpal instability and SNAC. The choice of SNAC treatment is associated with the stage of the disease and functional needs of the patient.

Keywords: scaphoid nonunion, scaphoid, percutaneous fixation, bone graft, vascularized bone graft, SNAC

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INTRODUCTION

Wrist injury often results in metaepiphyseal distal radius fractures in elderly patients. Fractures of the carpals (scaphoid, triquetrum and hamate) or the styloid process of the ulna are common for younger individuals. The fractures can be associated with injury to the ligaments, disturbed anatomy and biomechanics of the wrist complicating the diagnosis [1], and the choice of treatment strategy [2]. The scaphoid is the largest bone in the wrist and is critical for the stabilization. Scaphoid fractures are common in athletes and military personnel [3]. Nonunion of scaphoid fractures is a common complication that can lead to the scaphoid nonunion advanced collapse, arthrosis of the wrist joint. Recent reviews indicate problems of choosing treatment methods for patients with scaphoid nonunion and arthrosis of the wrist joint [4, 5]. The social significance of the pathological condition induces original research and literature analysis. The objective was to identify methods for preventing scaphoid nonunion and improving treatment outcomes for SNAC patients based on the literature on etiology, diagnosis and treatment of the disease.

MATERIAL AND METHODS

The original literature search was conducted on key resources including Scientific Electronic Library (www.elibrary.ru) and the National Library of Medicine (www.pubmed.org) and using the keywords: scaphoid nonunion, scaphoid, bone grafting, scaphoid nonunion, vascularized bone graft. The search yielded 355 results. Literature searches included both Russian and English studies published between 1984 and 2024. Inclusion criteria included original articles, systematic reviews, meta-analyses relevant to the search topic. Non-inclusion criteria included a case report, case/control, and articles available only on a fee-paying basis.

RESULTS

Epidemiology of scaphoid fractures

The incidence of scaphoid fractures is 2–7 % of all fractures and almost 90 % of carpal fractures [6]. Scaphoid fractures are more common for young men aged 10 to 29 years [7, 8]., The fractures are rare in elderly individuals [9]. Epidemiology of scaphoid fractures and nonunions is heterogeneous [10].

Functional anatomy and blood supply to the scaphoid bone

The scaphoid is the largest bone of the wrist, which articulates with five neighboring bones through a predominantly cartilaginous surface and has a complex network of ligamentous attachments; these specific features predetermine a variety of disturbances in the wrist kinematics after fractures and play a significant role in the development of carpal instability syndrome [11]. The shape, size, location of the scaphoid bone and radiological density of its different parts are individually variable [12]. Narrowing of the scaphoid at the waist combined with reduced bone density, predetermines a high incidence of fractures (75 %) in this particular location [13]. The scaphoid bone participates in the kinematics of the proximal and distal rows of the bones of the wrist; palmar flexion of the scaphoid bone occurs with a longitudinal load; sharp extension and ulnar deviation of the wrist combined with a longitudinal load predispose to fractures, with ligament ruptures, in particular; fractures proximal to the waist contribute to displacement and ischemia of the proximal fragment [14]. The main mechanism of scaphoid fractures is a fall on an outstretched arm. Forced dorsiflexion or ulnar deviation of the wrist under axial load leads to dorsal subluxation of the midcarpal joints and increased stress on the scaphoid cortex on the palmar side [15]. Scaphoid fractures are associated with compromised blood supply [16]. They are characterized by a high rate of complications including avascular necrosis, delayed fusion and nonunion, osteoarthritis, which significantly reduce the quality of life of patients. The peculiarities of the blood supply to the scaphoid bone are that the palmar branch of the radial artery supplies blood to the distal pole, and the branch of the dorsal carpal branch of the radial artery also enters the scaphoid bone distally (Fig. 1), being the only source of blood supply to the proximal pole through retrograde intraosseous blood flow [17].

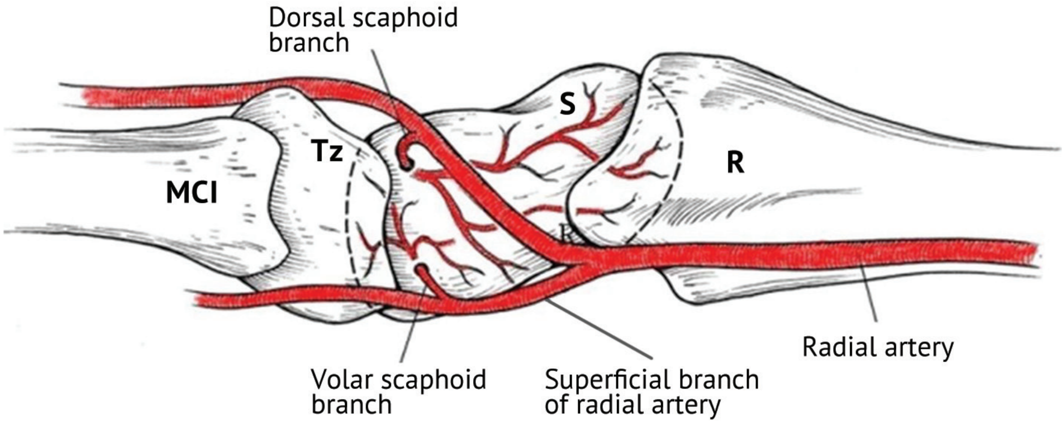

Fig. 1 Diagram showing blood supply of the scaphoid: MCI, first metacarpal bone; Tz, trapezium; S, scaphoid bone, R, radius. Reproduced from T. E. Trumble et al. [18] with changes

Problems in diagnosing scaphoid fractures

There are problems in diagnosing scaphoid fractures which are radiographically missed in 40 % of patients in the acute period of injury [19]. Clinical tests that have high sensitivity and low specificity are essential. Anatomic snuffbox tenderness or tenderness of the scaphoid tubercle and axial load on the first metacarpal have 100 % sensitivity for scaphoid fractures. However, their specificity is only 9 %, 30 % and 48 %, respectively. Thumb limitation has a sensitivity of 69 % and specificity of 66 %, and a combination of symptoms is important for clinical diagnosis [20]. Grover reported pain in the scaphoid and swelling of the wrist as the most important symptoms that can be more pronounced with fractures than with soft tissue injuries [21]. Attempts are being made to develop a prognostic formula that would include five parameters: male gender, anatomical snuffbox swelling, anatomical snuffbox tenderness, ulnar deviation tenderness, and thumb compression tenderness. This method of predicting fracture has a sensitivity of 97 % and a specificity of only 20 % [22]. According to the authors, the use of the prognostic formula reduces the likelihood of underdiagnosis of scaphoid fractures. Four radiological views of the wrist bones can be practical if a fracture of the scaphoid is suspected; an anteroposterior ulnar deviation radiograph is performed in addition to the three standard projections for the hand [23]. The authors report that 21.5 % of scaphoid fractures are missed with this type of radiography, but with 81.5 % sensitivity of computed tomography (CT) the sensitivity of four radiographic views appears to be similar to that with CT. The diagnostic algorithm developed by the authors (Fig. 2), along with radiography in four projections, includes CT and magnetic resonance imaging (MRI).

Four radiological views of both wrists were offered previously to improve the information content of the radiography in identifying unstable scaphoid fractures, with both AP views produced with deviated ulna and radius [24].

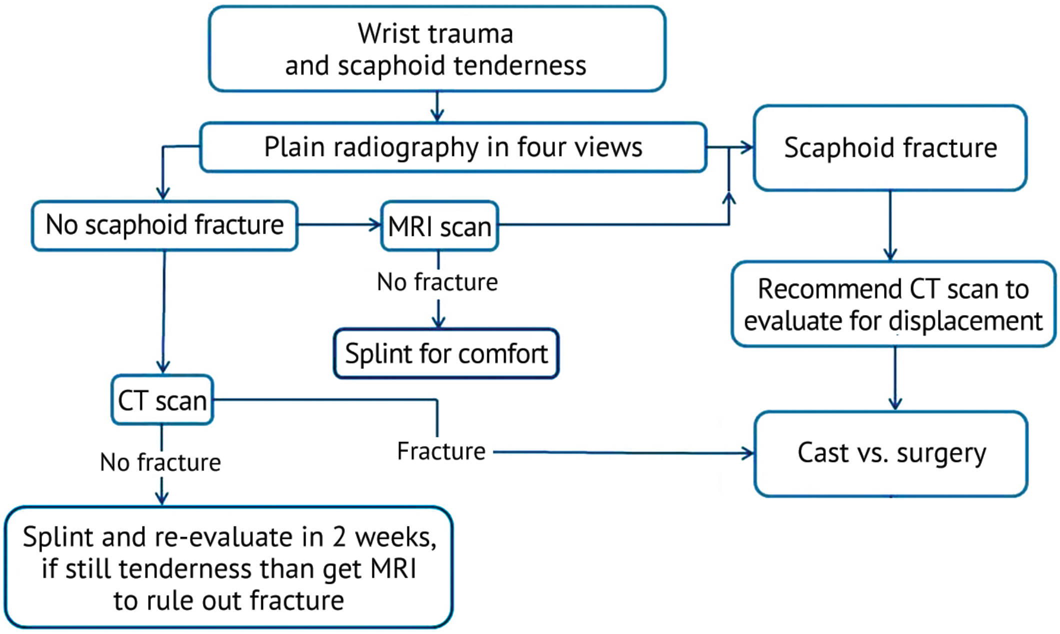

Fig. 2 Algorithm for diagnosing scaphoid fractures as reported by H.C. Bäcker, C.H. Wu, R.J. Strauch [23]

Classifications of scaphoid fractures

Thirteen different (sub)classification systems are found in literature based on (1) fracture location, (2) fracture plane orientation, and (3) fracture stability/displacement. Looking at citations numbers, the Herbert classification appeared to be most popular. According to this classification, most scaphoid fractures are unstable; only type A fractures are stable (Fig. 3).

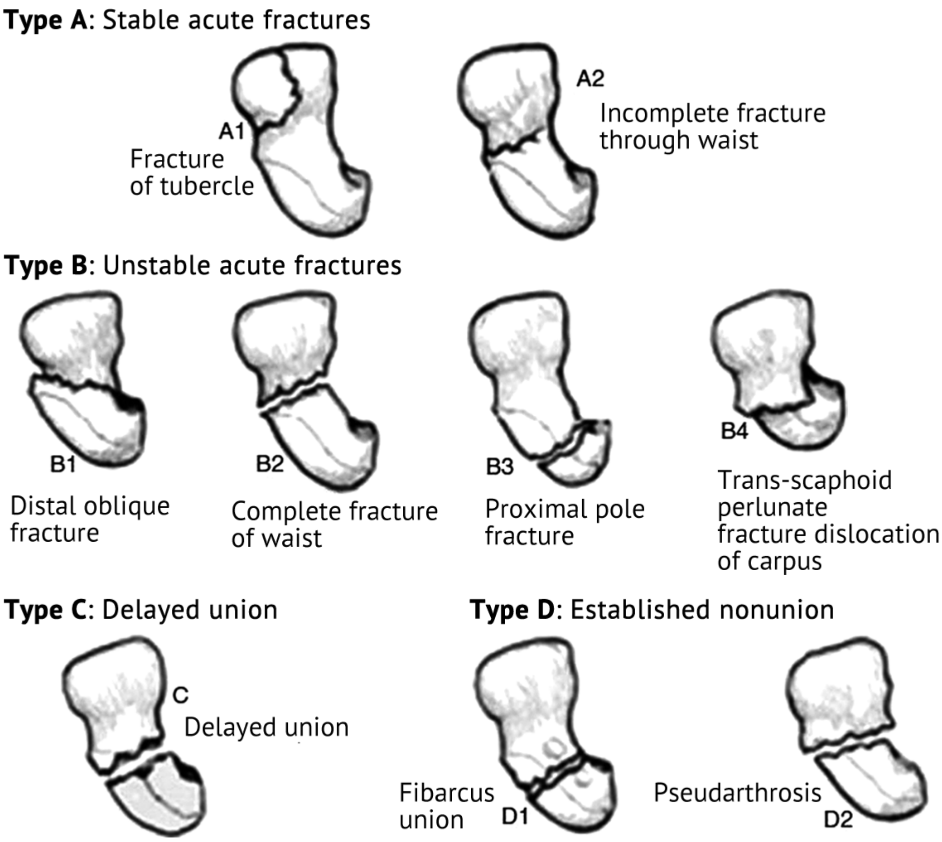

Fig. 3 Herbert's classification scheme for wrist fractures. Reproduced with modifications of T.G. Sommerkamp [8]

A more simplified classification approach of grading scaphoid fractures into proximal, distal and waist fractures is employed in clinical practice indicating the presence and magnitude of displacement and the duration of the injury [17]. Three algorithms for the treatment have been developed in accordance with the simplified classification of the fracture location [26]. Displacements greater than 1 mm are associated with 55 % of nonunion and 50 % of avascular necrosis; displaced fractures that heal spontaneously require long-term immobilization; malunions or nonunions are often accompanied by pain and lead to osteoarthritis of the wrist [27]. Displaced scaphoid fractures are conventionally classified into minimally displaced (⩽ 0.5 mm), moderately displaced (0.5–1.5 mm) and severely displaced (⩾ 1.5 mm) [28]. A displaced fracture is usually a sign of instability, but non-displaced fractures can also be unstable. The main criteria for instability are: displacement of greater than 1 mm, dorsal intercalated segment instability (DISI), a scapholunate angle of greater than 60° and a lateral intrascaphoid angle of greater than 35°, comminuted fractures and scaphoid fractures as part of a perilunate injury [26]. Arthroscopically verified ruptures of the scapholunate ligament are combined with non-displaced scaphoid fractures in about 25 % and are classified as unstable [29].

Causes of scaphoid nonunion and methods of their treatment

If a scaphoid fracture does not heal within 3 months, it is regarded delayed healing, and if it does not consolidate after 6 months, it is considered as non-union. Scaphoid nonunion can be caused by untimely diagnosis and vascularization disorders [30], inadequate immobilization of the fracture in terms of quality and timing [31]. The causes of scaphoid nonunion include patient related factors (non-compliance), iatrogenic and biological factors [32]. Review of the epidemiology of fracture nonunions in 18 locations of about 300 thousand patients indicate an average nonunion rate of 4.9 % with the rate of scaphoid nonunions being the highest and amounted to 15.5 %; the risk of nonunion was increased with open and multiple fractures, high weight-height ratio, smoking and alcoholism [33]. Treatment of scaphoid fractures with open reduction and internal fixation initiated after 31 days of injury and the volume of the scaphoid bone being less than 38 % of the volume of the bone can result in nonunion [34]. The clinical picture of scaphoid nonunion is characterized by variability; severe pain, manifestations of capsulitis, contractures of the wrist joint, and decreased height of the wrist joint are the most frequently reported symptoms. Pathomorphological changes in the wrist joint include destruction, reparation and inflammation [35]. A strategical classification has been offered for scaphoid nonunion [36] (Table 1).

Table 1

Strategical classification of nonunions reported by J.F. Slade et al., 2005 [36]

Group	Description
I	Fractures treated 4–12 weeks of injury
II	Fibrous fusion: minimal fracture line, no cysts or sclerosis
III	Minimal sclerosis: bone resorption occupies ⩽ 1 mm of the nonunion interface
IV	Cysts and sclerosis: bone resorption > 1 ⩽ 5 mm nonunion interface
V	Deformity and pseudarthrosis: bone resorption > 5 mm interface
VI	Arthrosis of the wrist: nonunion with signs of radiocarpal and midcarpal arthrosis

Osteosynthesis with compression screws is indicated for patients of groups I–III, debridement and bone grafts can be used for patients of groups IV–V and salvage operations are recommended for patients of group VI. There is a paucity of publications reporting the use of compression cortical screws made from human allobone to repair scaphoid fractures and nonunions. Allobone screws provide high fusion rates, low complication rates and do not require removal [37]. Bone grafts used for scaphoid nonunions include traditional non-vascularized grafts, and non-free or free vascular grafts (on a vascular pedicle). Non-free vascularized grafts are associated with high rate of unions reported in 96.3 % of patients with nonunions and bone defects [38]. However, these data are contradictory: M.A. Chang et al. reported fusion in 68 % of patients [39], C. Hirche reported consolidation in 75 % [40]. Some authors report a lower fusion rate of 27 % due to avascular necrosis of the proximal pole of the scaphoid [41].

A systematic review of 48 publications [42] showed that the incidence of fusion with use of vascularized and non-vascularized grafts did not differ significantly for the condition. Similar fusion rate was achieved with grafts sourced from the distal radius or the iliac crest, but the latter resulted in a greater complication rate. Fixation with screws and Kirschner wires also resulted in similar fusion rates, but patients with screw fixation could ambulate earlier. The results of a meta-analysis of randomised controlled trials and comparative studies from 1500 patients [43] indicated that the postoperative union rate in non-vascularised bone grafts is similar to that in vascularised bone grafts; so, the less invasive procedure could be the first choice of treatment for scaphoid nonunion. Analysis of the treatment results and surgical histological examination of 35 patients with nonunions treated with non-vascularized grafting showed a rare case of “infarction” of the proximal pole, and therefore vascularized grafts were not common [44].

Successful outcomes of arthroscopic bone grafting and K-wire fixation in treatment of scaphoid nonunion were reported in a retrospective study [45], but the procedure can be used as a surgical treatment for scaphoid non-union of the proximal and middle third without intracarpal deformity or osteoarthritis. Two screws without graft can be used as a first-line treatment for scaphoid nonunion with or without humpback deformity and cyst formation. [30]. Electrical or ultrasound bone stimulation combined with plaster immobilization can be offered for patients who do not agree to surgery for a variety of reasons [46]. Bone grafting procedures, such as arthroscopic fixation with bone grafting and the Fisk-Fernandez approach (iliac crest graft and internal fixation) have excellent outcomes as identified by a search in Embase and Pubmed between 2000 and 2023. Ultrasonic treatment is also needed, but evidence is limited [47]. The use of the Ilizarov method and external fixation device in the treatment of scaphoid nonunions is reported in a few publications. Outcomes were rated as good or excellent (n=14) in a group of 18 patients; the length of immobilization with the device on did not exceed 9 weeks [31]. Similar results were reported by another group of authors who used compression pins with olives; the immobilization period in the series did not exceed 6 weeks [48]. The advantage of this approach is that it does not require open surgical approaches and bone grafts. The patients did not develop humpback deformity, carpal instability, progressive collapse or avascular necrosis. Regardless of the method used to repair scaphoid nonunion a successful outcome suggests preservation of blood supply, stable fixation, bone grafting to replace the defect and stimulate union, which must be achieved before the onset of degenerative changes [49].

Progressive collapse due to scaphoid non-union (SNAC)

Untreated scaphoid nonunions would lead to degenerative changes in the wrist joints. A 30-year observation of patients with scaphoid fractures demonstrated marked radiocarpal osteoarthrosis in only one (2 per cent) of the forty-seven patients who had a healed fracture and it was more common in the group that had a pseudarthrosis, in which the prevalence was five of nine patients [50]. Osteoarthritis of the wrist and midcarpal joints indicates progressive wrist collapse or SNAC wrists affecting the wrist joint at the styloid process, causing a narrowing of the joint space (stage 1). Bone cysts of the scaphoid develop later involving the whole scaphoid fossa (stage 2), midcarpal osteoarthritis and narrowing of the lunate-capitate joint gap (stage 3), and diffuse involvement of the capitate bone (stage 4) [51]. A low reliability of the classification was reported [52], and no other classifications were available for assessment. The incidence of SNAC depends on the level of the original scaphoid fracture. Obvious degenerative changes occurred in 85.7 %, 40.0 % and 33.3 %, for the six proximal-, eight middle- and two distal-third nonunions, respectively [53].

The choice of surgical treatment method would be determined by the stage of the disease. For SNAC I, scaphoid reconstruction combined with resection of the scaphoid styloid process is a promising method. Denervation procedures, resection of the proximal row of wrist bones and partial arthrodesis are performed to reduce pain and preserve wrist function in more advanced stages. Total arthrodesis and total arthroplasty are used for panarthritis and failures of "salvage operations" [54]. For SNAC I, arthroscopically assisted bone grafting without resection of the styloid process was reported to be highly effective [55]. Successful use of bone grafts in SNAC II and SNAC III can prevent progression of arthrosis, so the method is superior to four-corner arthrodesis [56]. Four-corner arthrodesis with screw fixation and proximal row carpectomy were reported as cost-effective options based on forty studies yielding 1730 scapholunate advanced collapse/scaphoid nonunion advanced collapse wrists [57]. Four-corner arthrodesis with plate fixation and four-corner arthrodesis with Kirschner wire fixation were inferior strategies and therefore not cost-effective. Ten patients with symptomatic grade IV non union of the scaphoid were treated using the four-corner arthrodesis with Kirschner wire fixation. Good results were achieved in 7 patients according to the modified Mayo Wrist Scoring Chart. There were no intraoperative complications [58]. The technique of the four-corner fusion with two retrograde crossed headless screws used in six cases of carpal collapse is reported as a gold standard [59].

A comparative meta-analysis of long-term functional results of proximal row carpectomy and four-corner arthrodesis performed on the basis of 7 articles reporting 1059 wrists showed that proximal row carpectomy produced significantly better range of motion and lower complication rate. There was no significant difference in the grip strength and conversion to total wrist arthrodesis [60]. Advanced carpal collapse with osteoarthritis of the midcarpal joint cannot be solely treated with proximal row carpectomy. The procedure should be added by pyrocarbon prosthesis implant to replace the head of the capitate [61]. Partial arthrodesis is used as an alternative to four-corner arthrodesis to stabilize the SNAC wrist with osteoarthritis and pain with intact joints retaining mobility [62]. The authors suggests that this approach reduces complication rates and improves functional outcomes as compared to four-corner arthrodesis. Single-column fusion [63], bicolumn limited intercarpal fusion/lunatocapitate and triquetrohamate arthrodesis [64] were described as less invasive techniques as compared to four-corner arthrodesis. A union rate of 95 % and an acceptable complication rate were achieved in 78 patients with single- or bicolumn limited intercarpal fusion that showed significant improvement in pain and function. Three patients were converted to total wrist fusion and one to total wrist arthroplasty [65]. The patients treated with proximal row carpectomy were reported to have osteoarthritis at follow-up, whereas it was seen in 19 % of patients treated with limited carpal fusion at 31/2 years. The range of motion and the grip strength were comparable in men and were found to be better in women after limited carpal fusion [66]. The authors concluded that further comparative studies on the effectiveness of different treatments are needed.

DISCUSSION

The scaphoid location determines high prevalence of fractures among wrist injuries. The geometry of the scaphoid as it relates to its retrograde blood supply renders it particularly prone to avascular necrosis, delayed healing and nonunion of the fracture. Suspected scaphoid fractures are a diagnostic and therapeutic challenge and up to 40 % of scaphoid fractures can be missed at initial presentation and radiological investigation. Anatomic snuffbox tenderness or tenderness of the scaphoid tubercle and axial load on the first metacarpal tests are practical to improve the prognosis of the outcome. Prognostic formulas based on several parameters including sex, swelling and tenderness could significantly reduce the incidence of underdiagnosis despite the low specificity of the tests. A multilevel approach with combined clinical data, imaging methods and diagnostic algorithms can help improve the accuracy of diagnosis of scaphoid fractures. At present, established strategical classification has been used to guide the surgical treatment of scaphoid nonunion including osteosynthesis with compression screws, debridement and bone grafts or salvage procedures. Treatment strategy for SNAC patients are traditionally determined depending on the stage of the disease. Radial styloidectomy along with scaphoid nonunion reconstructive surgery is considered an acceptable surgical treatment for stage 1 scaphoid nonunion. Both proximal row carpectomy (PRC) and four-corner arthrodesis (FCA) are motion-sparing surgical procedures commonly used to treat certain painful, degenerative wrist conditions of SNAC 2 and SNAC 3. Arthroscopic wrist surgery has become one of the most common forms of arthroscopy.

CONCLUSION

Multidisciplinary approach and comprehensive care are essential to diagnosing scaphoid fractures improving patient outcomes and reducing the risk of underdiagnosis. SNAC is a condition that have an impact on the quality of life with associated reduced range of motion, grip strength and persistent pain. Imaging techniques are important for evaluation of scaphoid fracture, posttraumatic condition and the SNAC wrist can be finally diagnosed intraoperatively. Appropriate healing time of the scaphoid fracture helps to prevent carpal instability. For this purpose, a variety of surgical treatments have been developed and the strategical classification of nonunions would be practical for the choice of a treatment modality. A nonoperative approach may be the first choice for patients with wrist arthrosis prior to surgical treatment. A surgical treatment of the SNAC wrist would rely on the stage of the disease and functional needs of the patient. Meta-analyses highlight the need for the research into the effectiveness of various treatments. Arthroscopic techniques are common in wrist surgery improving diagnostic capabilities and minimally invasive interventions.

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Reconstruction of finger function in case of joint defects

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Abstract

Introduction Repair of bone defects in the hand is still a challenge despite advancements in hand surgery and improved surgical techniques. However, the main difficulty still lies in restoring the function of the injured segment when the defect affects functionally significant joints including the proximal interphalangeal and metacarpophalangeal joints of the fingers. Loss of mobility in the joints significantly impairs the physical capabilities of patients and the quality of life. A reconstructive intervention is primarily aimed at restoration of the useful range of motion of the involved finger with minimal risks of postoperative complications.

The **objective** was to evaluate the possibilities with finger function restoration and the effectiveness of the techniques used to repair defects in the fingers joints based on literature analysis.

Material and methods The original literature search was conducted on key resources including Scientific Electronic Library (www.elibrary.ru) and the National Library of Medicine (www.pubmed.org), Elseiver, Google Scholar (2008 to 2024) and using keywords: finger joint defects, bone loss, intra-articular injuries of the fingers, arthroplasty, small joint replacement, reconstruction of finger joints, joint restoration, metacarpophalangeal joint, proximal interphalangeal joint, bone graft, joint transplantation, joint transfer, microsurgery, vascular bone joint transfer. Sixty articles by foreign authors and 11 publications of Russian researchers were selected for analysis.

Results and discussion With the variety of surgical techniques, there is no universal method for replacing defects in the finger joints. Along with the high rate of postoperative complications, the lack of an optimal method requires careful preoperative planning. Reconstructive interventions should be considered as a method of choice and an alternative to arthrodesis in young, physically active patients. Limited postoperative range of motion in the reconstructed joint is a challenge in the treatment of patients with this pathology. The choice of surgical strategy relies on the patient’s compliance for a complex and lengthy rehabilitation in achievement of a functionally satisfying result.

Conclusion Reconstructive interventions for repair of a bone defect in the joint are practical for increasing the useful range of motion of the involved finger and improving the physical capabilities of the hand.

Keywords: finger joint defects, bone defect, intra-articular injuries of the fingers, arthroplasty, small joint replacement, finger joint reconstruction, joint restoration, metacarpophalangeal joint, proximal interphalangeal joint, bone graft, joint transplant

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INTRODUCTION

Bone defects in the hand are a common problem that significantly reduces the functionality of patients and impairs the quality of life. Trauma, infections or tumor are three main causes of bone defects [1]. The cause of the defect, the choice of surgical technique is largely determined by its location and size, and concomitant injury to neurovascular structures, tendons and/or soft tissue defects [1, 2].

The metacarpophalangeal and proximal interphalangeal joints play a decisive role in the hand functioning, providing the basic range of motion of the fingers and the ability to accurately position them for fine motor skills [3]. Bone defects are often observed in young active patients with high functional demands. Restoration and preservation of the optimal range of motion in the joints is one of the goals of a reconstruction in case of a complex injury [4, 5]. The surgical treatment is aimed at anatomical repair of the defect and increase of the functional range of motion of the finger to facilitate everyday use [1].

With the variety of methods used to repair bone defects as an emergency or a selective procedure and variations in the implementation they are associated with a high risk of postoperative complications and have a number of contraindications [2, 6]. The choice of a reconstruction method for the finger joints remains a challenge with no evident clear solution identified [3]. The lack of a “gold standard” in the treatment of patients with the condition and high frequency of its occurrence mainly in the working population, determines the significance of the problem of treating patients with defects of the metacarpophalangeal and proximal interphalangeal joints of the fingers.

The **objective** was to evaluate the possibilities with finger function restoration and the effectiveness of the techniques used to repair defects in the finger joints based on literature analysis.

MATERIAL AND METHODS

The original literature search was conducted on key resources including Scientific Electronic Library (www.elibrary.ru) and the National Library of Medicine (www.pubmed.org), Elseiver, Google Scholar (2008 to 2024) and using keywords: finger joint defects, bone loss, intra-articular injuries of the fingers, arthroplasty, small joint replacement, reconstruction of finger joints, joint restoration, metacarpophalangeal joint, proximal interphalangeal joint, bone graft, joint transplantation, joint transfer, microsurgery, vascular bone joint transfer. Sixty articles by foreign authors and 11 publications of Russian researchers were selected for analysis.

RESULTS AND DISCUSSION

Useful range of motion of the fingers

Loss of normal movement in the fingers and decreased functionality of the hand can be extremely distressing for the patient. According to various authors, the active range of motion (amplitude of full flexion) is 0–100° (mean 84°) in the metacarpophalangeal joints (MCP), 0–105° (mean 105°) in the proximal interphalangeal (IPJ) joints, 0–85° (mean 69°) in the distal interphalangeal joints (DIPJ) [7, 8]. The full amplitude of finger flexion is not required for everyday physical activities with the functional range being sufficient measuring 19–71° (mean 61°) for the MCP joint, 23–87°

(mean 60 °) within for the PIP joint and 10–64° (mean 39°) for DIPJ [8, 9]. Therefore, different surgical treatments is mainly aimed at achieving a functional range of motion in the injured finger to improve the patient's quality of life.

Types of surgical treatments

The choice of surgical strategy relies on the location and size of the defect. The patient's age and level of daily activity, compliance with the intended treatment plan are the key factors influencing decision-making [10, 11, 12, 13]. The operation can be aimed at eliminating movement in the injured joint (arthrodesis) or restoring the function through reconstructive surgery. If reconstructive surgery cannot be performed or there are contraindications to reconstruction, arthrodesis is the method of choice with a primary downside being the loss of joint mobility [2, 11, 14]. With significant soft tissue damage, tendon and nerve defects, shortening and joint fusion in a functional position may be a better choice is distinguished from the need for repeated surgical interventions, which may be the best solution for the patient who wants to reduce the recovery time and resume other activities [15]. Like any surgical intervention, joint fusion can be associated with a risk of postoperative complications including peri-implant infection and postoperative pain; the non-union (failed arthrodesis) rate is reported in 3.9–8.6 % of cases [16]. Although the end result of pain-free stability provided by arthrodesis may be acceptable to the patient, maintaining mobility in a functionally significant joint remains the primary goal of surgical treatment [13].

Interpositional arthroplasty [17, 18], arthroplasty using a free osteochondral autograft [14, 19, 20, 21, 22, 23] or allograft [2], arthroplasty with blood-supplied bone transplant [12, 24] can be used to replace a bone defect, reconstruct the articular surfaces forming the MCP joint or PIP joint, and restore mobility in the joints. Vascularized or non-vascularized joints from the foot [4, 6, 10, 25, 26], toe [27] or joint replacement can be employed for reconstruction of the MCP or PIP joint [28, 29].

Interpositional arthroplasty suggests resection of the involved portion of the joint and grafting between the articular surfaces to regain some mobility and relative stability of the joint. Fascia, tendon, allograft or synthetic material can be used as a graft. Early mobilization of the joint can be initiated with sufficient graft fixation to achieve a satisfactory range of motion. However, this technique does not help to repair the bone defect of the articular surface, and graft survival is rather short. Over time, it transforms into scar tissue and loses its sliding characteristics leading to persistent contractures in the involved joint [17, 18, 30, 31].

Osteochondral autografts are commonly used for reconstructions. The bases of the metacarpals [24], the distal femur [12], the proximal tibia [32], the foot joints [4] or potentially the toe [27], and rib fragments [19, 20] can be used as donors for the restoration of the articular surface.

The plastic surgery with a blood-supplied non-free osteochondral graft is associated with the lower risk of resorption and infection. However, the limited size of the graft and the length of the vascular pedicle reduces indications for reconstruction of larger bone defects using the method [13, 24]. Hemi-hamate arthroplasty can be used to replace bone defects in the articular surface of the base of the middle phalanx in treatment of fracture-dislocations in the PIPJ (sometimes in combination with volar plate plastic surgery to provide greater stability in the joint) [33, 34]. The technique is impractical in cases of absent articular surface; it is associated with the risk of dislocation in the reconstructed joint due to the difficulty of simultaneous restoration of the capsular-ligamentous apparatus, graft resorption and progression of deforming arthrosis reported in 16 % [34]. Osteochondral grafts from the femoral condyle are used for post-traumatic defects of the cartilage [35, 36] but there are examples of its use for larger bone defects [12]. The technique has limitations due to the size of the graft and difficulties in shaping the graft to fit the articular surface defect. Pain at the donor site that would require therapy and correction of physical activity is a common postoperative complication [35].

The advantages of a rib graft include the possibility of reconstructing a damaged joint without affecting other (healthy) joints and giving the graft any shape comparable to the size of the defect, with minimal risk for the donor site. This reconstruction option has age restrictions (not recommended for patients aged 60 years and older due to ossification of the cartilage), the graft is at risk of a fracture, cartilage degeneration and narrowing of the joint space. The technique can be associated with additional interventions for reconstruction of the capsular-ligamentous apparatus, tenolysis, corrective osteotomy at the graft site or removal of metal constructs reported in 40 % [19].

The choice of a donor site is essential for repair of the joint or a large intra-articular defect. Hand grafts are technically accessible and anatomically suitable. The transplants can be used for reconstruction of several injured fingers with high level of trauma to the donor area and with one to be used as a donor graft [26, 27, 37, 38].

Extensive metacarpophalangeal defects can be repaired with combined use of bone grafts to address metacarpal defect and restore joint mobility with a silicone implant [39, 40]. The authors reported the free vascularized fibula graft as an ideal option for metacarpal bone defects with the harvesting being less complicated compared to other free vascularized grafts [39].

Allografts have good osteoconductive properties and can be used for reconstruction in cases where other techniques are difficult to perform or are contraindicated [2]. Although their use is not associated with trauma to healthy tissue, they are less resistant to infection and are more often subject to rejection or progressive resorption with the risk of fractures/nonunion, which may subsequently require joint replacement [41]. Repair of the defect with an allograft would require preserved ligaments to achieve stability in the joint, which is not always feasible in the case of a complex injury to the finger [6].

Joint replacement is often the method of choice for the treatment of post-traumatic or other types of arthrosis of the DIPJ and MCP in older patients. This method can be used for acute intra-articular injuries in the cases, when a traumatic defect of the phalanx or the metacarpal is equivalent to joint resection and is an indication for implantation [29, 42, 43, 44]. Nonunited intra-articular fractures of the phalanges of the fingers can be treated with joint replacement [45]. With the variety of small joint implant, none of them has an unconditional advantage in case of bone deficiency, defects of the capsular-ligamentous apparatus [46] or in the presence of post-burn contractures [47, 48]. Despite improvements in modern prostheses and surgical techniques, components may be difficult to stabilize. There is a high risk of infection, a significantly reduced range of motion in the operated finger and the development of peri-implant fractures in 22–35 % with 5–7-year survival prior to revision [28, 49, 50, 51, 52, 53]. The range of motion in the joint fails to reach the functional level after joint replacement [54] and repeated interventions including tenolysis, arthrolysis, tenodesis, plastic surgery of the capsular ligament apparatus may be required in about 58 % of cases to improve mobility and endoprosthetic components would be replaced in cases with progressive instability [50, 55, 56, 57]. Arthrodesis can be performed during revision operations in case of severe deformity, bone defect and ligamentous failure that cannot be corrected with an implant [55, 58, 59]. Although the role of limited functional loads and extreme positions in the operated joint [60] is essential to predict the risks of postoperative complications including peri-implant fractures and destruction of endoprosthetic components, these data require additional research.

Transplantation of a vascularized or non-vascularized toe joint can be produced in cases where joint replacement is contraindicated or cannot be performed, and the use of another technique would not satisfy the final goal of the surgical intervention [10].

The main indications include joint destruction in younger adults with high functional demands on finger movements [14, 61], in children [62], and in the presence of extensive complex soft tissue injuries [63].

The advantages of the intervention include the comparability of the bone anatomy of the donor and recipient joints, good blood supply to facilitate better fusion, and the possibility of transplanting a joint together with tendons, nerves and skin to compensate for the deficiency in the recipient site. Repair of the donor defect with a resected damaged toe joint minimizes the impact of surgical intervention on the appearance and functionality of the donor foot [5]. Advantages with a foot joint include long graft survival, resistance to resorption and infection, and stability due to transfer with an intact ligamentous complex.

In addition to age restrictions (patients aged 18–25 years reported in various studies) and a formidable list of contraindications (peripheral vascular diseases, previous trauma to the donor site, taking immunosuppressants, smoking, autoimmune diseases, etc.), the technique has some disadvantages including technical difficulties, traumatic impact on the donor site and difficulties in the rehabilitation [6, 64]. The low functional range of motion expected after surgery is the main disadvantage of the method, which is associated with anatomical differences in the structure of the extensor apparatus and an initially smaller range of motion in the toes. Various methods are used to correct anatomical differences, including rotation of the donor joint during placement or performing an oblique osteotomy of the metatarsal head [65, 66]. With all the attempts to improve the technique of grafting a blood-supplied joint, a significant deficit in extension in the reconstructed joint still remains the main problem. According to a 2021 systematic review, the mean range of motion in the PIPJ averaged to (40.3 ± 12.9)° after toe joint grafting with an extension deficit of approximately 30° [61]. The comparison of functional results after transplantation of the blood-supplied joint of the foot and replacement of the involved joint showed it was noted that the range of motion measured (37 ± 9)° and (44 ± 11)° after PIPJ reconstruction and (34 ± 10)° and (47 ± 16)° after MCP reconstruction, respectively. The authors reported the best range of motion in the MCP joint and PIP joint achieved after joint replacement with silicone implants with the rate of complications requiring revision intervention being 18 % compared to 33 % of revisions after joint replacement using a pyrocarbon implant and 29 % after joint transplantation from the foot. The authors concluded that additional research was needed to compare and evaluate the effectiveness of joint replacement using silicone implants and toe joint transplantation in order to determine the optimal type of intervention [67]. According to various authors complications (thrombosis of anastomoses, degenerative changes in the joint, nonunion/union with deformity, fractures, contractures, pain at the donor site) requiring repeated surgical interventions range from 22 to 50 % of cases after transplantation of toe joints from the foot [26, 61]. Along with the high percentage of postoperative complications, poor clinical results are cause by continued improvement of surgical techniques to improve the functionality and appearance of the reconstructed finger, and reduce trauma to the donor site [25, 68, 69, 70, 71].

CONCLUSION

The literature analysis showed that replacement of intra-articular defects and restoration of the functional amplitude of finger movements remains a challenge in modern hand surgery. There are many surgical techniques aimed at restoring mobility in a lost joint, from low-traumatic ones (interpositional arthroplasty) to extensive microsurgical interventions (joint transplanted from the foot). Reconstructive interventions can be associated with postoperative complications and specific rehabilitation program, so the choice of technique must be deliberate and individual in each clinical case. If a patients want to regain mobility in the impaired joint a reconstructive procedure a reasonable option is a reasonable option in young, physically active patients. Compliance is essential for the patients who undergo difficult and long-term restorative treatment. There are attempts to improve surgical interventions addressing postoperative range of motion and reducing traumatic impact on donor sites. A great number of contraindications to extensive reconstructive operations are limitations to the applications, and a defect in the capsular-ligamentous apparatus and tendons would prevent total joint replacement. Complications requiring revisions due to significant defects in the bone and stabilizing structures would result in arthrodesis, which can be disappointing for the patient and the physician.

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Current concepts in the management of infected non-union of the femur: internal versus external fixation

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Abstract

Introduction The management of infected non-unions continues to be a herculean task for the orthopaedic surgeon due to the emergence of microbial resistance, failure of fixation, frequent re-fractures and resurgence of previously treated infection.

The **aim** of the paper was to structure the approach to the management of patients with infected femoral non-union based on the literature review and surgeons' experience.

Material and methods A detailed literature review, including current updates on the management of fracture-resistant infections (FRI) and non-union of the femur was conducted. Search words and phrases used for navigation in the international medical literature platforms were: osteomyelitis, non-union, diagnostic solutions, local antibiotics, biomechanical stability.

Results and Discussion The principles of surgical management of infected non-union of the femur remain the same: (a) adequate soft tissue sampling; (b) thorough debridement; (c) fracture stabilization; (d) dead space and defect management; (e) delivery of local antibiotics and (f) soft tissue coverage. The goal of surgery is to get rid of infection. There is no place for empirical treatment of suspected infection. Therapy should be initiated based upon microbial cultures of deep tissue specimens. While selecting the type of hardware for non-union of the femur, one often encounters a dilemma concerning the most appropriate surgical tool for stabilization. Internal fixation with bone grafting would depend on the size of the gap; commonly defects < 6 cm are treated with this modality. External fixation becomes indispensable in certain scenarios such as poor local skin and soft tissue conditions, associated limb length discrepancy > 2 cm, large defect gaps ⩾ 6 cm, concomitant deformity, small fragments or osteopenic bone.

Conclusion Based on this review of current concepts, the authors conclude that there is no ideal or universal approach for management of infected non-union of the femur, and the approach may vary depending on the technical expertise available and the institutional practices. Irrespective of the modality used, the golden rules of fixation remain the same, alignment, preservation of biology, contact of fragments, stability and early restoration of function.

Keywords: osteomyelitis, non-union, femur, diagnostic solutions, local antibiotics, biomechanical stability

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INTRODUCTION

The term ‘infected non-union’ of long bones has now been largely replaced by the term ‘fracture related infection’ (FRI) based upon the research conducted by the FRI consensus group in 2018 [1]. The term ‘FRI’ encompasses: (a) all infections which occur in the presence of a fracture; (b) early infection around a fracture; (c) infected non-unions; (d) haematogenous infections following fracture healing and (e) infections in fractures with no internal fixation. The diagnostic criteria for FRI include serum inflammatory markers, medical imaging, microbiology, molecular biology, and histopathology [2]. Standard diagnostic aids are mandatory in all cases, such as total leukocyte count (TLC), C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), of which, CRP is the most useful serum inflammatory marker [2] with a sensitivity ranging between 60–100 % and specificity between 34.3 % and 85.7 %.Newer modalities which are useful in prosthetic joint infections, such as biomarkers in synovial fluid, namely interleukin 6 (IL-6), leukocyte esterase strips, alpha defensin and synovial fluid CRP, are yet to establish a role in FRI [3]. Conventional radiography may not give much information, but sinograms are extremely useful to indicate where the discharge leads to, superficial or deeper tissues. Computerized tomography (CT) can detect bone resorption, sequestration, periosteal or endosteal new bone formation, cortical irregularities, and atrophic non-union. Magnetic resonance imaging (MRI) can differentiate between bone and soft tissue infection. Bone scans have a high sensitivity but low specificity for infections [4]. The most recent diagnostic adjunct is 18-Fluorodeoxyglucose Positron Emission Tomography (FDG–PET), which can detect the extent of infection in remote locations, especially intramedullary, and in the presence of an implant. Many studies have reported a high sensitivity and positive predictive value in patients for whom clinical findings are inconclusive for a local infection [5].

METHODS

A detailed analysis of literature, including current updates on the management of fracture related infections (FRI) and non-unions was conducted, with the objective of simplifying and putting together a structured approach in the management of infected non-unions of the femur. Search words and phrases used for navigation in the international medical literature platforms were: osteomyelitis, non-union, femur, diagnostic solutions, local antibiotics, biomechanical stability. Key points are enlisted below.

RESULTS AND DISCUSSION

A. Approach to surgical management

The principles of surgical management of infected non-unions remain the same, irrespective of the anatomical location, and these are: (a) adequate soft tissue sampling; (b) thorough debridement; (c) fracture stabilization; (d) dead space and defect management; (e) delivery of local antibiotics and (f) soft tissue coverage [6]. These are discussed as under.

a–b) *Debridement and sampling* One must have clarity on 'what' and 'how much' to take out, since all sclerotic bone is not necessarily dead bone. An MRI/PET scan can provide valuable information and aids in decision making [7]. The role of methylene blue is debatable, but can be a useful adjunct in determining the extent of inviable bone [8]. It is essential to administer antibiotics immediately *after* sampling [9]. If the patient was previously on antibiotics, an antibiotic free holiday of at least 1–2 weeks is mandatory [10]. Five or more deep tissue samples should be collected in separate containers, using un-used surgical instruments for each sample [2]. Samples should preferably be inoculated directly into the culture broth. Superficial, skin, or sinus tract, swabs should *not* to be used.

c) *Fracture stabilization* The peculiarities of the femur include large deforming muscular forces which tend to pull the proximal femur into flexion and abduction, thereby creating a varus and procurvatum deformity of the proximal femur. This is especially true when a subtrochanteric corticotomy is used for lengthening along with an external fixator [11]. The deforming forces can be overcome by using a sturdy construct consisting of 4–5 Shanz pins in the proximal segment in a 'delta' configuration, or by using commercially available clamp modifications (ALFA fixator, SH Pitkar, Pune, India), which can accommodate up to 5 pins in the same plane or in two planes at a variable angle, as highlighted in Figure 1.

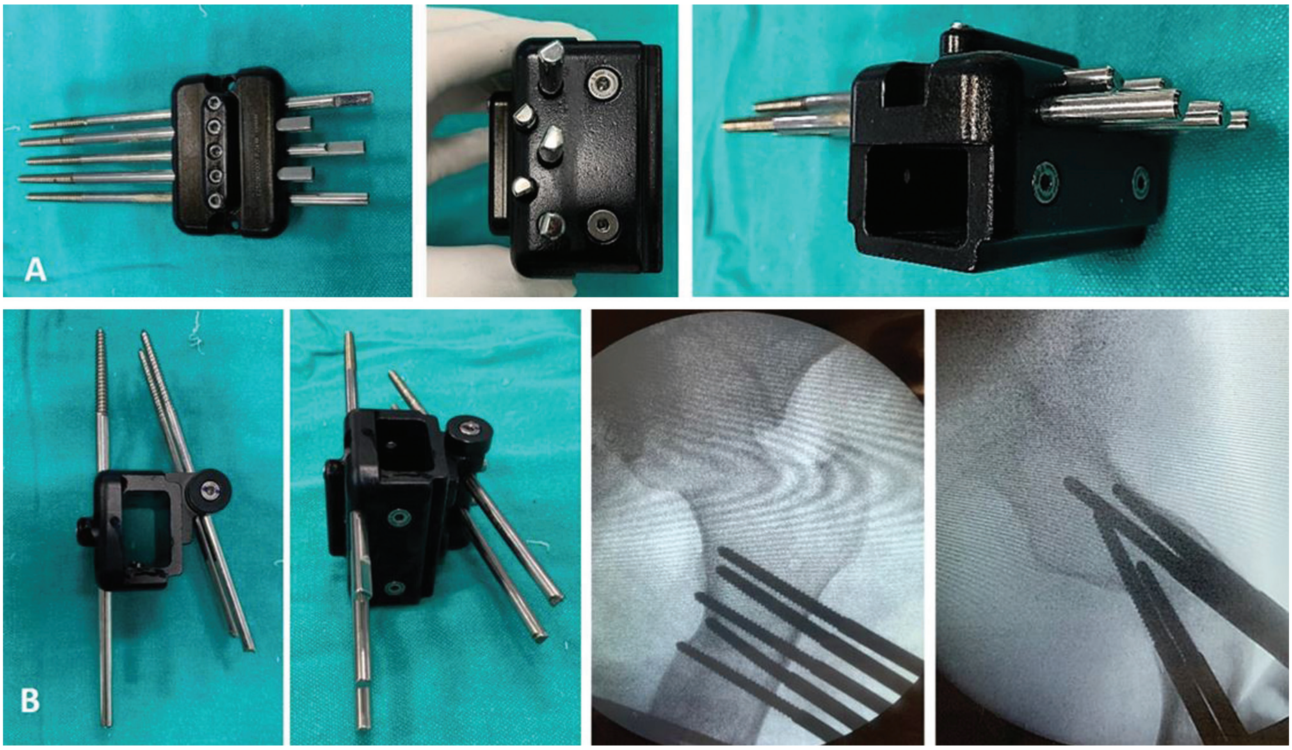

Fig. 1 (A) Clamp with 5 pins in same direction; (B) Clamp with 5 pins with variable angle adjustment and its clinical application in the proximal femur

Large ring fixators in the femur are poorly tolerated by patients due to difficulty in maintaining personal hygiene, the need for a modified bed to accommodate the frame and the laboriousness in ambulation [12]. Possible remedies include the use of a monolateral rail fixator, with pins driven up into the neck for a stronger purchase, where the bone stock is better as compared to the trochanteric region. The swivel clamp of the rail fixator is very useful in this regard (Fig. 2). The rail fixator weighs less and is less cumbersome to the patient [12].

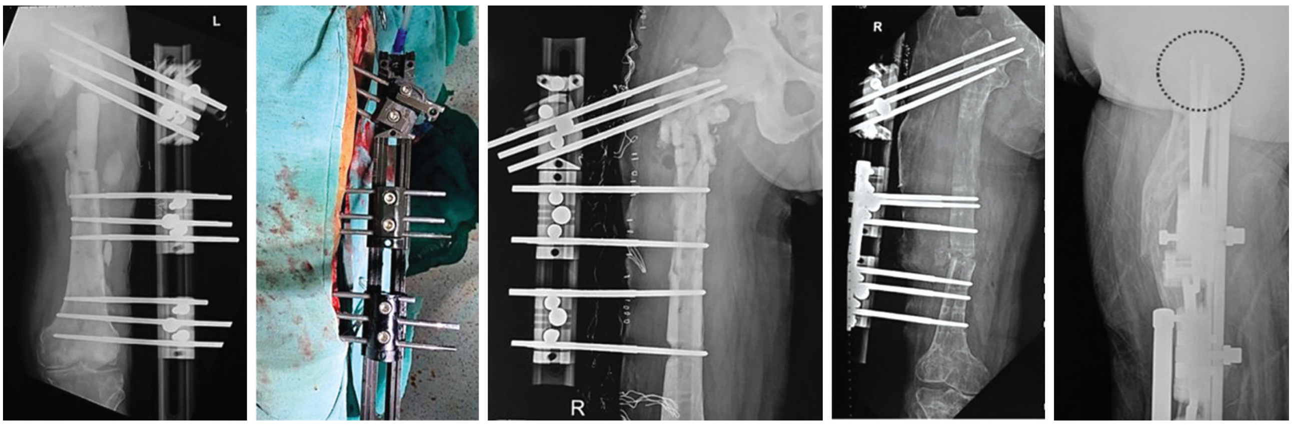

Fig. 2 Swivel clamp of the rail fixator system with pins that can be angled upwards into the femoral neck; care is taken to ensure their central location in the lateral view

For small fragments, such as the distal femur condylar block, or osteopenic bone or those with pre-existing knee stifness, a knee-spanning construct is desirable to counterbalance undesirable movements at the non-union site, consequent to a long lever arm [13]. Spanning frames may be hinged (commercially available) or non-hinged and can be taken off after satisfactory union has been achieved to resume range of motion (ROM) exercises (Fig. 3). A quadriceps-plasty may be added at the end in cases of residual knee stiffness [14]. The use of olive wires can be extremely useful in tackling small coronal plane fragments [15], wherein the wires are placed perpendicular to the fracture plane and tensioned using a traction assembly to achieve interfragmentary compression and union (Fig. 4).

Fig. 3 (A) Commercially available modular knee spanning frame with articulating knee hinge; (B) indigenous modification of the same using Ilizarov components

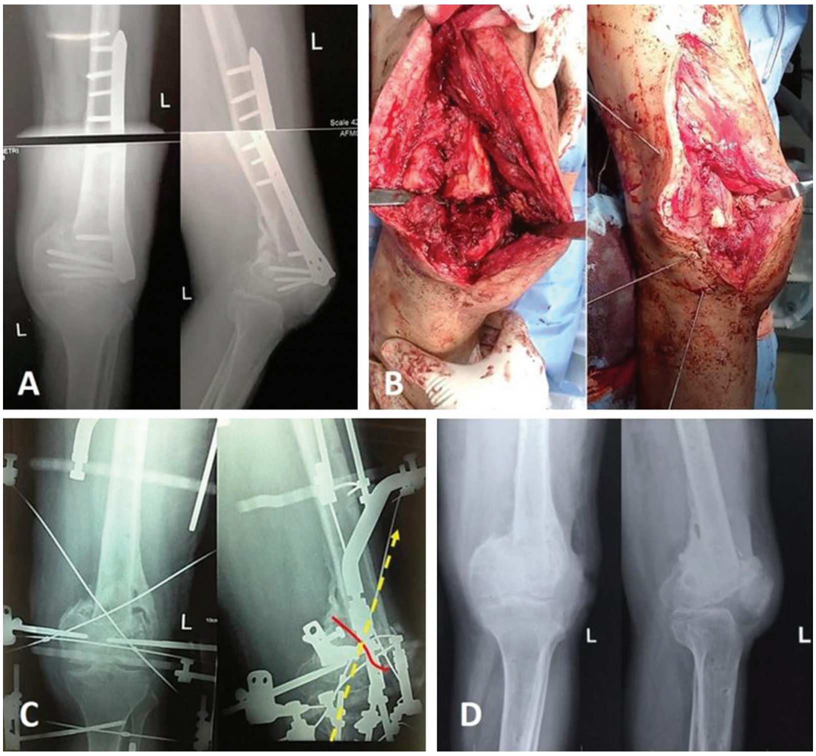

Fig. 4 (A, B) Infected non-union Hoffa fracture with a small, osteopenic, condylar segment; (C) counter-opposed olive wires are driven from down upwards, perpendicular to fracture plane (in red), and tensioned using a traction assembly at the top to achieve interfragmentary compression, resulting in union (D)

d) *Defect management* Detailed description of defect management is beyond the scope of this study, hence, a generalised approach [1] to defect management is summarized as a flow chart in Figure 5.

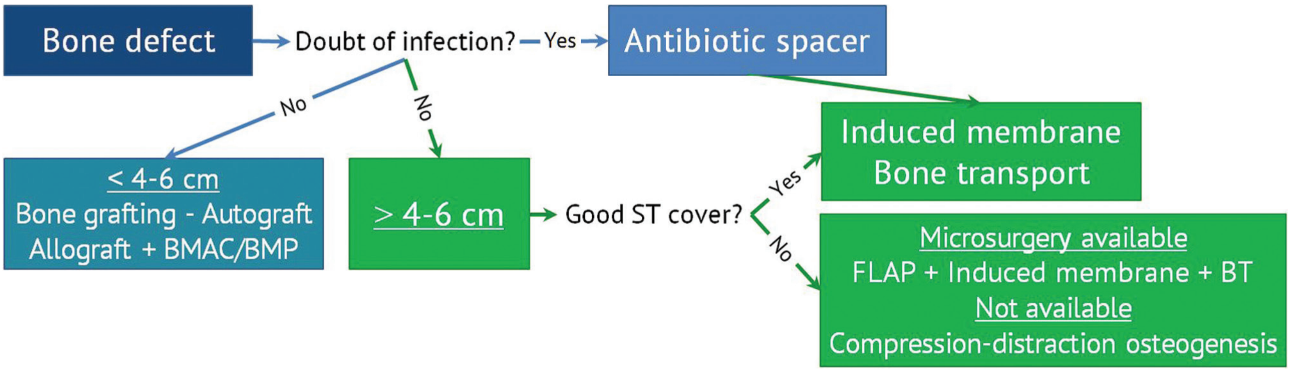

Fig. 5 Approach for dead space and defect management

e) *Local antibiotic delivery* This is the crux of treatment. Commonly used vehicles for local antibiotic delivery include polymethyl methacrylate (PMMA) cement spacers or beads on a string, the 'bead pouch' technique [17], cement coated nails, antibiotic coated implants, and absorbable calcium sulphate-based carriers, and are selected depending upon the availability of resources and anatomical location of the infection [6]. The choice and duration of antibiotics is a topic of contention. General guidelines are as follows [6]; the antibiotic should be (a) heat stable, (b) be available in powder form, (c) should not be cytotoxic to host tissues, (d) have minimal systemic side effects and (e) released at concentrations exceeding several times the minimum inhibitory concentration (MIC). Note that cement can hold up to 8 g of antibiotics per 40 g of PMMA [18]. The combined duration of parenteral and oral antibiotics is generally 6–12 weeks, in consultation with the infectious diseases' specialist [19].

f) *Soft tissue coverage* Early flap cover for exposed bone or musculo-tendinous units should be performed as soon as possible, once the general condition of the patient stabilizes. For this, a close association between the orthopaedic and plastic surgeons is warranted, often referred as the 'ortho-plastic' approach [20]. For uncomplicated, discharging wounds, negative pressure wound therapy (NPWT) is an extremely rewarding modality, with several advantages [21] such as (a) enhancement of wound healing, (b) cyclic cleansing and dilution of wound debris, (c) disruption of biofilm, (d) accelerated granulation tissue formation and (e) earlier reduction in wound size.

Rehabilitation phase Bracing is highly recommended to protect the regenerated bone and the healed non-union site from re-fracture (Fig. 6) and should be continued for a period of 2–3 months following frame removal [22]. Early weight bearing with an appropriate walking aid and active ROM exercises are quintessential.

B. Implant selection: internal versus external fixation

While selecting the type of hardware for non-unions of the femur, one often encounters a dilemma concerning the *most* appropriate surgical tool for stabilization. The following guidelines have been drafted to help simplify the arduous task of decision making.

<u>Choice of internal fixation</u>

1. Bulky frames result in poor compliance. Long periods in a frame can cause tremendous psychiatric problems and considerable patient discomfort and dissatisfaction [11].

Fig. 6 Customised thigh brace for post-operative rehabilitation in non-union of the distal femur

2. Due to closely spaced components, frames leave little space for future reconstructive surgery, such as flap cover and bone grafting.

Pre-requisites to be fulfilled Internal fixation with bone grafting would depend on the size of the gap; commonly defects < 6 cm are treated with this modality [23]. The distal fragment should be of sufficient size to hold screws. The plate should be a robust, locking plate and long enough for adequate stability [22]. It may be augmented with a medial plate or a plate can be augmented over a retained nail. Cortical auto- or allografts, such as a non-vascularised fibula, provide additional stability, in combination with locking plates [22]

The induced membrane technique, first described by AC Masquelet [24] in 1986, is based upon the principle that the cement spacer provokes a biological reaction resulting in a pseudo-synovial membrane formation, which is rich in BMPs and TGF Beta, VEG-F, angiotensin 2, vWF and prevents graft resorption at the second stage. The second step is performed 6–8 weeks later, in which bone grafting is done, and may be augmented with bone substitutes (in the ratio < 1:2), only *after* infection has been cleared. One must try to close the membrane over the graft, without packing it too tightly. Several studies have also reported satisfactory outcomes with a single stage protocol, consisting of debridement and internal fixation with bone grafting [25]. The choice ultimately depends upon the surgeon's preference and institutional practices. Disadvantages of internal fixation include a prolonged period of non-weight bearing ambulation and its limited application in large sized bone defects (> 6 cm) or small fragments [23].

Choice of external fixation:

External fixation becomes indispensable in certain scenarios such as:

1. Poor local skin and soft tissue conditions.
2. Associated limb length discrepancy > 2 cm [26].
3. Large gaps ⩾ 6 cm.
4. Concomitant deformity.
5. Small fragments or osteopenic bone.

Salvaging traumatised limbs with bone loss has always been a vexing challenge for orthopaedic surgeons across the globe. Initial attempts were often plagued by downright failure or unacceptable functionality. The introduction of the Ilizarov method instilled hope for many patients and physicians alike and produced remarkable results [27]. It has been adopted as the last resort in the management of segmental bone defects and non-unions of the lower extremities. Two Ilizarov techniques can be adopted for bone defects: (a) compression with approximation of fragments (resulting in shortening), and concomitant distraction through an osteotomy (for lengthening) *or* (b) bone transport and regeneration of the missing bone segment through distraction osteogenesis, with subsequent compression at the docking site to achieve union [28]. Either of these methods can be used to address the problems associated with bone defects, namely bone loss, soft tissue loss and infection, without the need for major reconstructive surgery [28]. The intrinsic biomechanical stability of the ring or rail fixators provides the requisite milieu to stimulate neo-histogenesis and promote bone union. Co-existing deformities can be corrected simultaneously and early weight-bearing is possible. Disadvantages of this method include tethering of soft tissues, potential risk of neurovascular injuries, regenerate-associated problems, pin-site infections, and joint stiffness [12, 29].

<u>Choice of implant in proximal femur non-unions</u>:

These are extremely vexing and challenging to treat because of a small sized fragment and difficulty in obtaining adequate purchase in this segment [30]. Ring fixators become cumbersome, especially when rings are used in upper thigh [12]. Monolateral fixators may improve patients' compliance and quality of life, but are delimited by the size and bone quality of the proximal fragment. Antibiotic-cement nails (Fig. 7, Fig. 8) are extremely useful in treating this variant, since they have adequate hold in the small proximal segment, and can address the intramedullary infection [32]. Antibiotic coated plates [33] have also been described, wherein the plate is retained following removal of the cement coating during the second stage, and the gap is bone grafted. Large volumes of bone graft can be obtained by the Reamer Irrigator Aspirator (RIA, De Puy Synthes) in cases of sizeable defects [32].

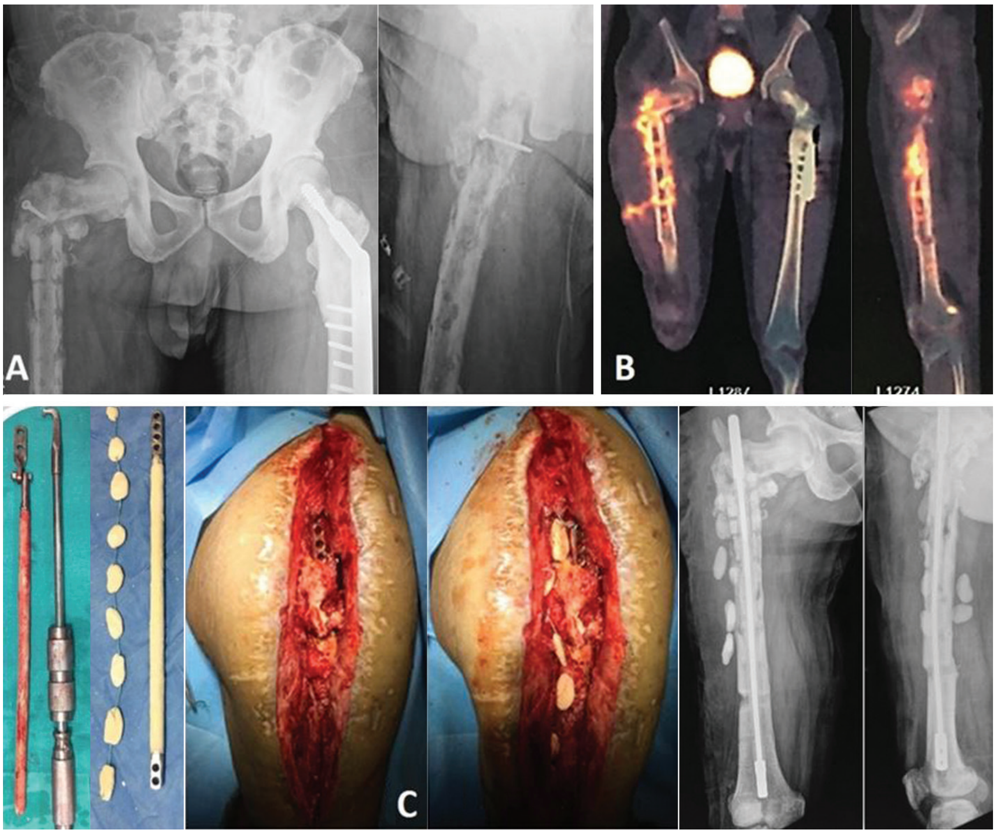

Fig. 7 (A) Infected non-united subtrochanteric fracture in a 49-year male with multiple previous failed surgeries; (B) FDG-PET scan showing hot spots in the entire medullary canal and proximal femur; (C) custom made Ilizarov antibiotic nail, comprising of a threaded rod with posts at either end, coated uniformly with antibiotic impregnated cement (3 such nails were used), to control the medullary infection, until the discharge ceased

Fig. 8 Rail fixator application followed with compression across the non-union (A) to achieve union in about 5 months (B)

CONCLUSION

The authors concluded that there is no ideal or universal approach for management of infected non-unions of the femur, and the approach may vary depending on the technical expertise available and the institutional practices. In general, the following guidelines have been drafted to have a consensus on the modus operandi when dealing with bone infections, and to assist in implant selection for fracture stabilization. The goal of surgery, at the very least, is to get rid of the infection. There is *no place* for empirical treatment of suspected infection. Therapy should be initiated based upon microbial cultures of deep tissue specimens. Nuclear imaging with localizing scans is the newest refinement in diagnosis and planning. There are multiple ways of treating gaps; in general, small gaps with sizeable fragments are amenable to internal fixation, whereas larger gaps or small sized fragments are better managed with external fixation. The golden rules of fixation remain the same, irrespective of the modality used, and these can be abbreviated as 'ABCF' — restoring **A**lignment, preservation of **B**iology, achieving good **C**ontact (stability) and early restoration of **F**unction.

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Review article
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Elution of antibiotics from bone cement: problems and ways to solution

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Abstract

Introduction The widespread use of bone cement in the treatment of patients with orthopedic infections can be associated with limited elution of antibiotics with use of local spacers.

The **objective** was to determine problems of elution of antibiotics from bone cement and ways to solve them based on literature data.

Material and methods The original literature search was conducted on key resources including Scientific Electronic Library (www.elibrary.ru) and the National Library of Medicine (www.pubmed.org) (1994 to 2024) and using keywords: bone cement, PMMA, polymethylmethacrylate, antibiotic elution, bone cement, antibiotic elution, additive manufacturing, porous constructions, lattice structures. The sources were included based on the hypothesis that preformed implants based on a lattice structure could be used in combinations with bone cement.

Results and discussion The elution of antibiotics from bone cement can be improved through examination of the cement type, the porosity, the implant/spacer shape, the type of antibiotics, quantities and combinations administered that pose a difficult scientific problem in the absence of an acceptable solution along with the variety of publications. However, research in this area has not led to any complete solution.

Conclusion A paradigm has been developed for improving the elution of antibiotics from polymethyl methacrylate (PMMA) to include working with the cement: its composition, geometry and pyrogenicity. Solutions offered for improving the elution of antibiotics from PMMA are often impracticable and can deteriorate the performance properties of cement. Another approach can involve a research aimed at studying the effectiveness of spacers with a preformed base and bone cement coating, without or with minimal interference with the properties specified by the manufacturer.

Keywords: bone cement, polymethyl methacrylate, antibiotic elution, additive manufacturing, lattice structures

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INTRODUCTION

Discovered in the 30s of the last century, bone cement (BC) based on polymethyl methacrylate (PMMA) has become an integral part of joint replacement due to its mechanical properties, commercial availability, the ability to release antibiotics, and greater knowledge compared to other transport systems. Since its introduction in 1970, antibiotic-impregnated cement has been used for the prevention and treatment of orthopedic infections [1, 2]. Despite the current use of other depot systems that are potentially superior to BC in the elution properties of antibiotics, as shown by *in vitro* and *in vivo* studies, BC will be in demand in clinical practice for many years to come [3, 4]. However, the study of the characteristics of antibiotic-impregnated cement has revealed a number of problems including the control of the antibiotic elution.

Despite the large number of publications on to the topic, there seems to be no confidence that the problem has been solved [5–11]. The elution of antibiotics from bone cement can be improved through examination of the cement type, the porosity, the implant/spacer shape, the type of antibiotics, quantities and combinations administered that pose a difficult scientific problem.

The **objective** was to determine problems of elution of antibiotics from bone cement and ways to solve them based on literature data.

MATERIAL AND METHODS

The original literature search was conducted on key resources including Scientific Electronic Library (www.elibrary.ru) and the National Library of Medicine (www.pubmed.org) (1994 to 2024) and using keywords: bone cement, PMMA, polymethylmethacrylate, antibiotic elution, bone cement, antibiotic elution. The review included articles that contained information about elution of antibiotics from bone cement and/or ways to improve it. The sources included in the Discussion were selected based on the hypothesis that preformed lattice-based implants can be used with bone cement. Search words in the "Discussion" section included additive manufacturing, porous constructions, lattice structures, additive manufacturing, lattice structures.

RESULTS

Elution depending on the type of cement

BCs vary depending on the manufacturer, viscosity, duration of polymerization, intended use, the presence of additional inclusions and, accordingly, have different antibiotic release abilities. For example, comparison of antibiotic elution from medium- and high-viscosity cement illustrates the specific release for each species. Although both cements contain the same amount of antibiotic, it is Palacos® R+G that releases more gentamicin [9].

Ensig et al. [12] reported the release of gentamicin and clindamycin from Copal bone cement (Biomet Merck, Darmstadt, Germany) over 28 days with long-lasting inhibition of *S. aureus* GS and coagulase-negative *S. aureus* GR. However, Palacos R-G bone cement (Schering-Plough, Maarssen, the Netherlands) failed to provide a continuous significant release of gentamicin after the first 24 hours [13].

Antibiotic elution depending on the shape of the bone cement implant

Although the shape of the implanted bone cement component depends on anatomical features, there is a proven correlation between shape and antibiotic elution. Duey et al. [14] were unable to detect a difference between the volumes of implanted BCs, and reported a direct relationship between the implant area and antibiotic release.

The larger the area, the higher the release of the antibiotic, as reported by Masri et al. [15]. Their study revealed an increase in antibiotic elution with increased antibiotic area and constant cement volume. This circumstance is explained by the fact that the release of the antibiotic occurs from the most superficial layers of cement. The overwhelming amount of antibiotic was eluted from the 100-μm-thick superficial layer, whereas only 19 % was eluted from the deeper 700-μm-thick layer [9].

Antibiotic elution depending on bone cement porosity

The porous structure of bone cement increases the surface area of the release (due to contact with the environment), hence the release of the antibiotic. Miller et al. [16] created highly porous bone cement by adding vancomycin pieces. A significantly higher elution of the antibiotic was observed with the antibiotic being thoroughly ground before adding it to the BC [16]. The nonhomogeneous distribution of the antibiotic in the BC can lead to uneven release of the antibiotic. McLaren et al. [17] compared different methods for manual homogenization of cement and antibiotic and did not find that manual mixing resulted in uneven release of the antibiotic. Lewis et al. [18] analyzed manually loaded and premixed Cemex (Tecres, Sommacampagna, Italy). Although similar cement structures were reported in the series after polymerization, the elution rate of the artisanal antibiotic was on average 36 % lower [18]. Because of these rather contradictory results, some authors would not recommend the use of artisanal addition of antibiotics to BC, arguing that industrially produced BC with antibiotic ensure a uniform release of the latter [18].

Regardless of the method used to add antibiotic to bone cement, porosity can be altered using a vacuum mixing system that is designed to reduce air entrapment into the cement. However, the effect of vacuum method on antibiotic elution would depend on factors such as the solubility of the antibiotic in water, the diffusion gradient and the type of cement [19, 20].

Meyer et al. compared the effect of a vacuum mixing system on various commercially available BCs containing gentamicin. Antibiotic elution was increased using a vacuum mixer for Palacos® R+G and Cobalt® G-HV (Biomet, Warsaw, IN, USA), and was decreased for Cemex® Genta (Exactech, Gainesville, FL, USA), SmartSet® GMV (DePuy, Warsaw, IN, USA) and VersaBond® AB (Smith & Nephew, London, UK) [21].

Porosity can be further modified *in vitro* using special additives [22]. Shi et al. found that gelatin promoted the formation of pores in bone cement [23]. Chen et al. explored the correlation of PMMA porosity, the particle size and gelatin mass fraction [24]. Other components that can increase bone cement porosity include calcium phosphate (CaP) compounds, thereby increasing drug elution [25]. Calcium carbonate is another porogenic compound, which is a component of the commercially available Copal® spacem bone cement, specifically designed for use as a spacer base. Bitsch et al. [26] reported the microporous structure of the cement, in contrast to the dense structure of Palacos® R+G, several antibiotics showed better washing out with Copal® spacem. However, another study was unable to confirm the claimed antibiotic elution characteristics of Copal® spacem and Palacos® R+G cements with a combination of vancomycin and gentamicin loaded into the two cements [27]. Biodegradable polymers based on polylactic-glycolic acid (PLGA) can be used to increase the porosity of the BC controlling the elution of antibiotics [28–30]. Large crystals of table salt can be optionally used in the outer layers of the BC implant. The dissolved salt leaves voluminous lacunae in the superficial layers of the implant increasing the antibiotic volume releasing into the environment [31]. Perforation of the implant at the stage of manufacturing from BC is a simple way to increase the effectiveness of the antibiotic [32].

Elution of antibiotics and combinations depending on the type, quantity and technology of inclusion into the BC

Antibiotics added to BC reduces the mechanical characteristics due to changes in the cement polymerization with antibiotic molecules. Hsieh et al. reported a 37 % reduction in compressive strength with a gentamicin solution added to Simplex CC (Stryker, Kalamazoo, MI, USA) [33]. The current consensus is that only crystalline antibiotics that have been found to be suitable for inclusion in BC *in vitro* should be added to BC [34, 35]. The mechanical properties of BC can be affected by the shape and the type. Some antibiotics can impair BC polymerization to a greater extent. For example, rifampicin, which has a crystalline structure, can completely suppress the BC polymerization processes [36].

The temperature stability of antibiotic is to be evaluated prior to the use since BC can heat up above 50–60° Celsius during polymerization. A short-term heating to 80° during polymerization did not lead to the destruction of anti-tuberculosis drugs [37]. The quantity of antibiotic to be added has not yet been definitively established. The BC Palacos® R+G and Copal® spacem added as a 2.5 % antibiotic fraction reduced the compressive strength of bone cement to a value close to the required 70 MPa [27].

Lilikakis et al. reported the effect of vancomycin added to BC Palamed® (Haereus, Hanau, Germany) and Copal® G+C (Haereus, Hanau, Germany) and found that the addition of 5 % vancomycin maintained the compressive strength of BC well above the required 70 MPa for both cements. Addition of 10 % vancomycin decreased the compressive strength by 18.15 and 17.48 %, respectively, and the compressive strength of both cements remained above the threshold value of 70 MPa [38]. A 5–10 % antibiotic concentration in BC is considered sufficient for a temporary spacer [34, 35, 38, 39]. Since the mechanical load on the temporary spacer can be controlled by limiting the weight, some authors allow an increase in the proportion of antibiotic to 20 % during its manufacture [40], but the dose of antibiotic increased above 5 % can lead to a slowdown polymerization of bone cement [37].

The technique of adding antibiotics to BC raises questions. Kuhn et al. reported the need for careful homogenization of the antibiotic crystals and the dry BC when adding the antibiotic in fractions [34]. Parvizi et al. offered the immediate addition of an antibiotic to the cement powder leading to “rough” homogenization. The technique facilitates maximum washing out of the antibiotic after the solidification of the BC due to the formation of conglomerates of the added drug [41]. Laine et al. compared the effects of different methods of adding antibiotics and confirmed the effect of the difference in the degree of homogenization of BC and antibiotic. Failed homogenization can result in the formation of pores in the BC. Subsequent mechanical tests revealed no significant difference in its strength [42].

Thus, the choice of an antibiotic for inclusion in the BC is determined by its availability, sterility, thermal stability, the presence or absence of a crystalline powder form, and sufficient elution kinetics.

The release of antibiotics occurs either continuously or in an “explosive” manner. Gentamicin is a typical representative of elution with continuous kinetics [9]. Vancomycin is usually released explosively with a high initial release rate followed by a sharp decline. Galvez-Lopez et al. compared the elution kinetics of 11 different antibiotics and concluded that each antibiotic exhibited its own release pattern. For example, moxifloxacin showed a longer release than vancomycin, meropenem showed continuously decreasing elution kinetics over a long period of time [36].

The combination of antibiotics affects differently on elution. The synergistic and antagonistic effects of antibiotics included in BC have been described. Hsieh et al. studied the elution of gentamicin and vancomycin from Simplex® BC. This combination increased the release of vancomycin by 145 % and gentamicin by 45 %, respectively [33]. Paz et al. explored combinations of more than two antibiotics: the addition of cefazolin significantly increased the elution of vancomycin from BC, which also contained gentamicin [43]. However, the kinetics of elution can be changed by the combination of antibiotics and by their relative mass in the BC. The significant increase in the kinetics of gentamicin elution with an increase in the proportion of vancomycin in cement is an example [20]. Kaplan et al. studied the combination of daptomycin and tobramycin and found an increase in the release kinetics of daptomycin with an initial increase in the amount of tobramycin [44].

An increased proportion of antibiotic in the cement is a simple way to increase the kinetics of antibiotic elution for a local effect on the microflora with use of the BC spacer in a number of combinations. An increased amount of vancomycin led to an increase in the elution of the antibiotic from cement [27].

A combination of silver preparations with various antibiotics can be used to increase the activity of antibiotics against pathogenic microflora [45–47]. A summary of factors affecting antibiotic elution and ways to improve it is given in Table 1.

Table 1

Factors affecting the elution of antibiotics

Author, year	Type of BC used	Antibiotics used (AB)	Factor influencing AB elution	Result
Ensing et al., 2014 [12]	Copal, Palacos R-G	Gentamicin, Clindamycin	Depending on the type of BC	BC Copal outperforms Palacos R-G
Duey et al., 2012 [14]	Simplex P	Tobramycin, Vancomycin	Increased BC area	An increased area leads to an increase in AB elution
Masri et al., 1995 [15]	Simplex P	Gentamicin	Increased BC area	An increased area leads to an increase in AB elution
Miller et al., 2012 [16]	Simplex P	Vancomycin	Increasing the porosity of BC during mixing due to the inclusion of greater volume of AB	An increase in BC porosity led to an increase in AB elution
McLaren et al., 2009 [17]	Cemex G, Cobalt G-HV, Palacos G, Simplex P, Smart Set G HV	Gentamicin	Method of BC mixing	There was no difference between “handicraft” and factory mixing of BC and AB
Lewis et al., 2005 [18]	Cemex G	Gentamicin	Method of BC mixing	Artisanal mixing of CC with AB reduces the elution rate
Meyer et al., 2011 [21]	Palacos R+G, Cobalt G-HV, Cemex Genta	Gentamicin	Using Vacuum Mixing	AB elution is increased in Palacos R+G and Cobalt G-HV, and decreased in Cemex Genta
Wu et al., 2016 [22]	Osteobond copolymer bone cement, Zimmer	Gentamicin	Increasing the porosity of BC by adding gelatin and ceramic granules	The addition of porogens increased AB elution. AB elution was higher with the addition of gelatin
Shi et al., 2011 [23]	SmartSet	Colistin	Increasing the porosity of BC by adding gelatin	Addition of gelatin increases the porosity of BC
Chen et al., 2019 [24]	Mendec Spine Resin and Kit	Gentamicin	Increasing the porosity of BC by adding gelatin	An increase in the mass fraction of gelatin correlates with an increase in AB elution

Table 1 (continued)

Factors affecting the elution of antibiotics

Author, year	Type of BC used	Antibiotics used (AB)	Factor influencing AB elution	Result
Bitsch et al., 2015 [26]	Copal, Palacos R+G	Gentamicin	Increasing the porosity of BC by adding $CaCO_3$ to Copal BC	Addition of $CaCO_3$ increases AB elution
Boelch et al., 2018 [27]	Copal, Palacos R+G	Gentamicin	Increasing the porosity of BC by adding $CaCO_3$ to Copal BC	No difference in elution detected
Spicer et al., 2013 [30]		Colistin	Increasing the porosity of BC by adding polylactic-co-glycolic acid (PGLA)	Addition of PGLA increases elution
Akhtyamov et al., 2015 [31]	Not specified	Not specified	Adding table salt crystals to the solidifying BC	When dissolved, table salt increases the area of AB release
Kuropatkin, Akhtyamov, 2014 [32]	Not specified	Not specified	Increasing the area of the BC due to the perforation	Increased BC area increases AB elution
Zahar, Hannah, 2016 [40]	Not specified	Not specified	Increasing the mass fraction of AB up to 20 %	An increase in the AB mass fraction leads to an increase in AB elution
Laine et al., 2011 [42]	DePuy SmartSet MV Bone Cement	Vancomycin	Elimination of homogenization process during mixing	Increase in pores in the BC with homogenization failure during mixing
Galvez-Lopez et al., 2014 [36]	Medium viscosity bone cement DePuy	Vancomycin Gentamicin Daptomycin Moxifloxacin, Rifampicin, Cefotaxime, Cefepime, Amoxicillin clavulanate, Ampicillin, Meropenem Ertapenem	Type of AB	Elution varies depending on the type of AB
Hsieh et al., 2009 [33]	Simplex	Vancomycin Gentamicin	Combined AB	Both ABs potentiated an increase in each other's elution
Paz et al., 2015 [43]	Palacos R + G	Cefazolin Vancomycin	Combined AB	The addition of cefazolin significantly increased the elution of vancomycin from bone cement also containing gentamicin
Kaplan et al., 2012 [44]	Not specified	Daptomycin Tobramycin	Combined AB	Increasing the initial concentration of tobramycin increases the elution of daptomycin
Peretsmanas et al., 2021 [37]	Cemex	Isoniazid Cycloserine, Rifampicin Amikacin, Kanamycin, Ethambutol	Type of AB	Different types of anti-tuberculosis drugs showed different elution dynamics
Gordina et al., 2024 [45]	Depuy CMW 1 Gentamicin	Ceftazidime Vancomycin Poviargol	Adding silver preparations	Increasing silver preparations increased the AB efficiency of the samples
Bozhkova et al., 2023 [46]	Depuy CMW 1 Gentamicin	Vancomycin Poviargol	Adding silver preparations	The addition of silver preparations increased the AB efficiency of the samples
Bozhkova et al., 2021 [47]	Depuy CMW 1 Gentamicin	Vancomycin Poviargol	Adding silver preparations	The combination of vancomycin with highly dispersed silver prolonged the antimicrobial activity of the samples

DISCUSSION

Publications indicated a paradigm that emerged to improve the elution of antibiotics from PMMA involving the quality of the cement: the composition, geometry and structure. However, the investigation did not lead to any complete solution, being often impracticable/cannot be implemented, and sometimes neglecting the costs and quality properties of BC.

Hypothetically, an increase in cement surface area, porosity, and therefore antibiotic release could be achieved through customized design. In this case, the structure of the implant should allow to place the cement inside the product and form a contact area of the implant with cement and the bone, allowing the antibiotic to elute from the deeper layers of the BC. An implant with a lattice structure can be one of the solutions to allow the antibiotic loaded cement be placed inside the product, increasing the contact area and porosity maintaining the quality and performance properties.

Bolshakov et al. [48] reported the results of the design and optimization of a lattice implant for a rabbit leg; a morphological study indicates maintained diffusion of substances and cell migration through the latticed implant. Cement can be placed inside the latticed implant using a special silicone matrix, similar to the one used for casting spacers. Eminences are essential for the silicone matrix to form a contact area and increase the free surface area of the cement.

Latticed implants are commonly manufactured using additive technologies [49–51]. The technology facilitate production of customized products for the patient and a complex irregular three-dimensional geometry [52, 53]. Products manufactured with additive technologies provide the strength, biocompatibility, biodegradability and sterilizability [54, 55]. With SLM metal printing, medical device manufacturers can produce patient-specific implants and prosthetics with exact dimensions and optimal surface finishes, ensuring perfect compatibility and function. SLM metal printing supports the incorporation of porous structures into implants, promoting osseointegration [56, 57]. With advances in personalized medicine, organs to be replaced can be scanned preoperatively. Computed tomography is one of the methods for obtaining a digital image of an organ [58–61]. This solution allows for numerical calculations to assess the stress-strain state of implants and bone organs [57].

The most common are Two methods are common to design products manufactured with additive technologies [62]. The first method suggests the use of elementary cells for design, they are also the basic elements that fill the volume of the product [63]. Kharin et al. [64] report the influence of the distribution of the unit cell on the strength of the construct. The second method suggests topological or structural optimization. Bolshakov et al. [65] explored optimization methods for hip implants and reported 11 % porosity of the implants achieved without compromising the strength characteristics.

Therefore, lattice implants in conjunction with BC and antibiotics could improve the elution of the antibiotic from BC without interfering or minimally interfering with the parameters specified by the manufacturer and could be one of the options for solving the problem. With the paucity of publications on this issue, the hypothesis requires confirmation.

CONCLUSION

The disadvantages of PMMA-based BC can be leveled up by its obvious advantages in the treatment and prevention of orthopedic infections, which will remain relevant for many years with the advances of antibiotic-resistant microflora.

Numerous publications on experimental and clinical use of BC demonstrate a striking contradiction in approaches to the use of PMMA-based BC. Local control of the infectious process, control of the elution of antibiotics with use of BC spacers are essential.

A paradigm has been developed for improving the elution of antibiotics from PMMA to include the cement parameters: its composition, geometry and structure. However, adherence to the paradigm demonstrated no complete solution, and was shown to be impracticable reducing the performance of the BC.

Another approach suggests a research aimed at exploring the efficacy of preformed bone cement spacers, without or with minimal interference with the characteristics specified by the manufacturer.

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Microbiological factors in osteoarthritis

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Abstract

Introduction Osteoarthritis (OA) is a common polyetiological disease of the musculoskeletal system, leading to disability. The condition can prevent a person from work, affect mental health, increasing mortality and affecting health care resources around the world as a current and future disease burden. OA had been considered an aseptic disease in the past and now the microbiological factor is viewed as one of the significant etiological aspects of the condition.

The **objective** was to summarize the literature data on the role of microorganisms in the etiology and pathogenesis of osteoarthritis, including concomitant HIV infection.

Material and methods The original literature search (2010 to 2023) was conducted on key resources including Scientific Electronic Library (www.elibrary.ru) and the National Library of Medicine (www.pubmed.org). Literature searches included both Russian and English studies reporting the effect of microbiological factors on the development of arthropathy.

Results and discussion New, more advanced microbiological diagnostic methods have been used. There has been evidence of a variety of microorganisms including pathogenic and opportunistic pathogens in the absence of clinical and radiological signs of arthritis. This changes ideas about the etiology and pathogenesis of degenerative processes in the articular cartilage and necessitates a revision of treatment protocols for some joint diseases. Multicenter comprehensive studies of the microbiome of joint formations, blood and intestines are needed.

Conclusions The presence of pathogenic microflora in the joint structures is evident in a significant number of observations. There is evidence of a local infectious process in the local cellular elements of osteochondral tissue in patients with previously diagnosed aseptic osteoarthritis. Intestinal microbiomes and the urogenital tract are most common sources of infection. A local influence of the immunodeficiency virus on the development of osteonecrotic processes in joint formations can be suggested in HIV patients.

Keywords: osteoarthritis, microbiome, osteonecrosis, HIV, aseptic necrosis

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INTRODUCTION

Osteoarthritis (OA) is a common musculoskeletal condition affecting millions of people. OA has considerable impact on quality of life and is a significant cause of disability imposing a significant burden on healthcare systems worldwide. According to the World Health Organization, about 10 % of the global population suffer from OA affecting approximately 830 million people [1]. OA is characterized by pathological changes in the joint structure causing pain [2], disability [3], can prevent a person from work [4], affect mental health [5] increasing mortality [6]. OA can affect any joint but is most common in the knees, hips and small joints in the hands [7]. According to reports from the Russian Ministry of Health, prevalent cases of OA increased Russia by 3.7 % over 5 years (from 2013 to 2017) affecting more than 4.3 million people [8]. However, these data cannot be considered accurate since they include identified and registered cases of the disease. The results of a large-scale Russian epidemiological study indicate to the knee and hip OA being detected in 13 % of the adult population. The true number of OA cases in the Russian Federation may reach 14–16 million people [9]. The unrecognized pandemic of OA is the leading cause of disability in the United States, with rates higher than the other four leading causes of disability combined [10]. OA accounts for approximately 23 % of the general population in the United States, representing approximately half of people aged 65 years and older [11]. It is the third fastest growing chronic disease associated with disability worldwide [12, 13]. Recent estimates place the cost of OA treatment in the United States at $128 billion, representing nearly 1 % of the gross domestic product [14], and the incidence of severe OA requiring joint replacement is increasing due to obesity and aging [15]. The incidence of OA has approximately doubled in the post-industrial era due to demographic factors and body mass index, a fact that remains to be fully explained [16]. Despite the significant economic component, there is no fully effective conservative treatment of OA [17].

It is generally accepted that the pathogenesis of OA involves the interaction of three main factors: genetic predisposition, aging and environment [18]. Genetic heritability, for knee OA in particular, is relatively low, less than 50 % [19]. Significant research efforts are aimed at identifying non-genetic risk factors in the pathogenesis of the condition.

The prevalence of OA increases with age, in people aged >65 years, in particular. It is estimated that more than 30 % of people aged 65 to 74 suffer from OA, with the number rising to 65 % in people over 75 [1]. The incidence of osteonecrotic processes in the joints is 2.5–100 times higher in HIV patients than in the general population [20, 21].

OA remains a naturally progressive disease that requires radical treatment in the terminal stage in the form of total joint replacement. Arthroplasty can be associated with loosening of the implant and periprosthetic joint infection [22, 23].

Alternative treatments of OA are limited in the effectiveness and can be associated with adverse effects. Non-surgical treatments include non-pharmacological and medicinal methods. Non-drug methods include physiotherapy and exercise therapy, diet and weight control. There is a wide range of medications used for the treatment of this pathology. These are non-steroidal anti-inflammatory drugs, corticosteroids, structure-modifying drugs based on glucosamine and chondroitin, hyaluronic acid. Relatively new biological and immunological methods of treating OA include the use of stem cells to restore cartilage, introduction of genetically modified cells,the use of inhibitors of inflammatory cytokines and monoclonal antibodies [24]. These methods are not etiological and are aimed at suppressing the inflammatory process and its consequences in the form of degeneration of hyaline cartilage [25]. Primarily, the treatment methods were developed with an absolute interpretation of the disease as an aseptic process. However, the improvement of microbiological diagnostic methods has led to the emergence of data on the presence of microbiological and viral agents in previously considered aseptic joint. These data allow us to take a new look at the mechanism of joint destruction that is irreversible in OA.

The **objective** was to summarize the literature data on the role of microorganisms in the etiology and pathogenesis of osteoarthritis, including concomitant HIV infection.

MATERIAL AND METHODS

The original literature search (2010 to 2023) was conducted on key resources including Scientific Electronic Library (www.elibrary.ru) and the National Library of Medicine (www.pubmed.org). Literature searches included both Russian and English studies reporting the effect of microbiological factors on the development of arthropathy. 53 full-text articles were selected based on keywords and abstracts. The choice was determined by the relevance of data on the results of studies on the role of microorganisms in the etiology and pathogenesis of osteoarthritis, including concomitant HIV infection. Based on keywords and abstracts 53 full-text articles were selected. The choice was determined by the relevance of data on the results of studies on the role of microorganisms in the etiology and pathogenesis of osteoarthritis, including concomitant HIV infection.

RESULTS AND DISCUSSION

Treatment of chronic joint diseases with degeneration of the articular cartilage can be associated with failures. With the use of new techniques and drugs for conservative treatment and sparing surgical technologies we still observe the inevitable progression of the pathological process. Radical functional restoration can be achieved with total joint replacement that can be associated with risks and disadvantages. In our opinion, failures of organ-preserving treatments of OA are associated with erroneous ideas about the etiology and pathogenesis of the disease, including underestimation of the microbiological factor. OA is defined as a degenerative-dystrophic disease in the Russian-language literature with primary damage to cartilage, there is an inflammatory component with the activation of pro-inflammatory cytokines in all tissues of the synovial joint and characteristic tissue reactions [26, 27]. More advanced microbiological methods indicate the presence of a variety of microorganisms, including pathogenic and opportunistic pathogens, in joint formations in the absence of clinical and radiological signs of OA. This changes ideas about the etiology and pathogenesis of degenerative processes in articular cartilage and necessitates a revision of treatment protocols for joint diseases.

A role of microorganisms can be suggested in the development of OA. Mycoplasmas were among the first microorganisms isolated from animal and human joints. The role of mycoplasmas in the development of synovitis in rheumatological and orthopedic patients was reported at the end of the last century. Mycoplasmas were isolated from arthritic joints of many animals [28]. Some patients with serologically confirmed *M. pneumoniae* developed arthritis [29, 30, 31], and four-year peaks in the incidence of *M. pneumoniae* in Canada showed a significant epidemiological association with new cases of juvenile chronic arthritis [32]. *M. pneumoniae* and *M. salivarium* were isolated from the joints of patients with hypogammaglobulinemia [33, 34, 35]. Although this microorganism is not usually considered pathogenic, it was reported as causing inflammatory changes in the joint [36]. *M. pneumoniae* and *M. salivarium* were also found in the synovial fluid of 24 of 33 patients with temporomandibular pathology [37].

Rozin, a rheumatologist from the Rambam Medical Center, reported the infectious nature of arthropathy and the successful use of the antibacterial drug co-trimoxazole (sulfometaxazole/trimethoprim) in the treatment of OA. Based on his study and analysis of global experience, he concluded that degenerative diseases of the joints and spine may be associated with infection [38].

The expanded range of microorganisms isolated from joints were reported. Stirling et al. detected Propionibacterium acnes in degenerative intervertebral discs in sciatica patients [39].

In 2016, Belarusian scientists explored 90 patients using polymerase chain reaction (PCR) and enzyme-linked immunosorbent assay (ELISA) "to identify etiologically significant microorganisms and antibodies in the biological material of patients with AVN of the femoral head of non-traumatic origin."Articular synovial fluid, removed femoral head and joint capsule during arthroplasty were examined. PCR of 59 synovial samples demonstrated DNA of the Epstein-Barr virus detected in 15.3 %, DNA of herpes simplex virus (HSV) types 1 and 2 in 5.1 %, DNA of cytomegalovirus infection (CMV) in 3.4 %, *C. trachomatis* DNA in 5.1 % of samples. *Mycoplasma hominis* DNA was detected in 3.4 % of samples. CMV DNA was detected in the synovium of 1 of 51 (2.0 %) patients and the presence of a *C. trachomatis* plasmid DNA fragment in 1 (2.0 %) patient. Epstein-Barr virus DNA was detected in 9 (17.7 %) samples. *M. genitalium* DNA and *U. urealyticum/parvum* DNA were detected in 2.0 %. *C. trachomatis* DNA was detected in the cartilage of the hip joint in 2 out of 53 (3.8 %) cases. HSV type 1 and 2 DNA was detected in 1 case (1.9 %). Epstein-Barr virus DNA was detected in 4 cases (7.6 %). *Ureaplasma urealyticum/parvum* DNA was detected in 1 case (1.9 %). Several intracellular microorganisms were isolated in 26 of 90 (28.9 %) patients with AVN of the femoral head of non-traumatic origin with aseptic necrosis established microbiologically. Markers of the herpes and chlamydial infection were determined in 22.2 % and 14.4 %, respectively. The authors concluded about possible dissemination of pathogens from primary urogenital foci of infection and their role in the development and progression of AVN of the femoral head [40].

The human microbiome, including the microbiota of joints has been explored in recent years, with the advent of more advanced methods. In 2020, a group of researchers examined composition of the microbiota in the knee and hip joints in OA patients in comparison with healthy patients. *Micrococcaceae* family, *Exiguobacterium* were common microorganisms isolated from the knee joint. *Rhodocyclaceae* and *Proteobacteria* were predominant bacterial families in the hip joint. Microorganisms isolated from different joints were genetically distant from each other [41].

Composition and diversity of the gut microbiome were examined in OA patients. Bacterial diversity (alpha diversity) was reported in OA patients, and some authors reported an increase in microbial burden associated with OA. In 2019, Boer et al. reported the fecal microbiome examined in a large series of 1427 patients with knee OA and a control group of healthy patients [42]. Bacterial markers (class *Bacilli*, order *Lactobacillales*, family *Streptococcaceae*, genus *Streptococcus*) associated with pain and effusion in the knee joint were identified in OA patients with MRI [43]. Changes in the microbiome are closely associated with OA and individual OA risk factors. Interventions targeting the microbiome have been shown to potentially prevent or slow the progression of OA [44].

In 2018, Chen et al. reported a comparative analysis of the oropharyngeal microflora in 155 healthy patients, 110 patients with rheumatoid arthritis and 67 patients with knee OA, identified using 16S rRNA gene sequencing. OA patients showed increased bacterial diversity compared to controls, including *Firmicutes*, *Streptococcus*, *Actinomyces*, *Ruminococcus*, *Bifdobacterium* [45].

Using next-generation sequencing (NGS) Torchia et al isolated at least one microorganism from the affected knee in 12 of 40 patients (30 %) undergoing primary total arthroplasty. Forty-eight unique microorganisms were identified in the patients including four fungi (*Cladosporium herbarum*, *Alternaria alternata*, *Filobasidium magnum*, *Naganishia friedmannii*). *E. coli* was a common organism identified in seven patients from 10 separate samples) [46]. The authors suggest that the greatest danger is not, but the native microbiome poses more threat than pathogenic microbes. The role of the microbiome as an etiological factor in the development of OA was supported by other authors.

Researchers from the USA showed that a microbiome is present in the synovial membranes and illustrated its role in the progression of OA. Synovial RNA sequencing from an OA patient was compared to a library of microbial reference genomes to identify microbial reads indicative of microbial abundance. With contamination adjusted, the authors identified 43 microbes that differed in abundance between the OA group and healthy samples. The authors emphasized that the isolated microbes were part of the gut microbiome. Legitimate individual bacterial sequences were identified using high-throughput RNA sequencing, and the microbial mass was significantly higher in OA compared with normal, although all biopsies were obtained from the same medical institution [47]. The mechanism of infection of the joint cavity suggested impaired intestinal barrier function, leading to microbial translocation. A pathogenic bacteria migrated from the intestine into the synovium in OA patients may contribute to the pathogenesis of OA [48, 49, 50]. In contrast to the initial belief that joints are sterile, increasing evidence indicates the presence of a synovial fluid and synovial tissue microbiome [51, 52].

Goswami et al. performed a multicenter review with a high level of evidence and reported the presence of microflora in the form of pathogenic and opportunistic bacteria in the cavity of large joints in patients with arthrosis after intra-articular injections and administration of sodium hyaluronate and corticosteroids using the 16S-rRNA sequencing method [53]. The results of the study confirm that previous intra-articular injection and nosocomial flora can influence the microbial composition of the joint.

Patients with HIV infection constitute a special cohort of orthopedic patients. The influence of microorganisms on the etiology and pathogenesis of OA in the cohort of patients was reported by several authors. Back in 1987, Withrington et al. isolated HIV from the synovial fluid of a patient with HIV-associated oligoarthritis and suggested “a direct inflammatory effect of the immunodeficiency virus on the osteoarticular system” [54]. Lamers et al. reported the presence of HIV DNA in pathological tissues obtained at autopsy [55]. The p24 antigen detected in the synovial fluid of affected joints can be higher than in blood, HIV DNA and tuboreticular inclusions [55, 56], which may be indicative of a viral etiology of the inflammatory process. In 2018, French scientists experimentally proved the role of osteoclasts as a reservoir of the HIV virus, and *in vivo* demonstrated “the direct destructive effect of HIV-1 on the structure and function of osteoclasts” [57]. Russian researchers from the National Medical Research Center FPI discovered RNA of the immunodeficiency virus in bone biopsies from the femoral head with a previously established diagnosis of avascular necrosis [58].

CONCLUSION

There is evidence of pathogenic microflora in the joints in significant number of observations; there is evidence of a local infectious process in the local cellular elements of osteochondral tissue in patients with previously diagnosed aseptic OA. The intestinal microbiome and the urogenital tract are common sources of infection. Multicenter comprehensive studies of the microbiome of joint formations, blood and intestines are needed. A local effect of the immunodeficiency virus on osteonecrotic processes in the joint can be suggested in HIV patients.

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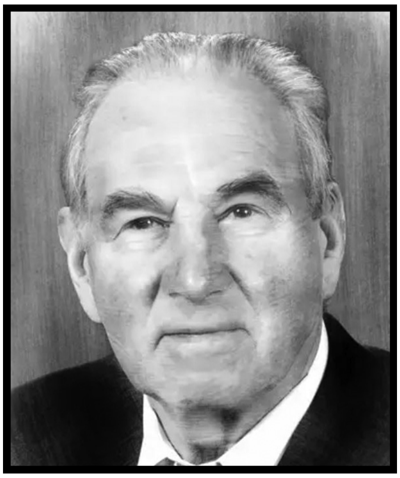
Professor Vvedensky Stanislav Petrovich (2.06.1930–11.11.2024)



An outstanding surgeon, doctor of medical sciences, professor Stanislav Petrovich Vvedensky passed away on December 11, 2024, at the age of 94. Stanislav Petrovich Vvedensky was born on July 2, 1930 in Nizhny Novgorod in a family of doctors. After completing his studies at high school, he entered the Gorky Medical Institute, from which he graduated with honors in 1954. He was referred to serve as a surgeon to a district hospital in the village of Vakhtan, Gorky Region. In 1958, he entered post-graduate studies at the Department of Surgery at the Gorky Medical Institute. Under the supervision of Professor B.V. Parin, he successfully defended his PhD thesis on the topic "Mechanical suture of the ureter using a vascular suturing device in an experiment" in 1961.

From 1960 to 1984, S.P. Vvedensky worked at the Gorky Research Institute of Traumatology and Orthopaedics as a junior and then senior researcher. For 18 years, he headed the department of flaccid and spastic paralysis of pediatric orthopaedics and traumatology, and later the department of compression-distraction osteosynthesis. In 1983, Stanislav Petrovich defended his doctoral dissertation "Clinical and biomechanical substantiation and differentiated use of methods for lower limb lengthening" at the Central Institute of Traumatology and Orthopaedics. In 1984, he was professor at the department of traumatology, orthopaedics and military field surgery at the Nizhny Novgorod State Medical Academy. The department was based on the premises of the Gorky Research Institute of Traumatology, where Stanislav Petrovich continued his active surgical work. In 1990, he was conferred the academic title of professor. From 1993 to 2002, S.P. Vvedensky headed the Department of Traumatology, Orthopaedics and Military Field Surgery, and later held the position of professor at the department. From 2005 to 2010, he worked as a professor of the Department of Hospital and Military Field Surgery reading the course in traumatology, orthopaedics and burn injuries at the FSB Institute. Combining the work at the Department of Traumatology and Orthopaedics of the Nizhny Novgorod State Medical Academy, Stanislav Petrovich continued his surgical activity at the Research Institute of Traumatology and Orthopaedics.

For many years, the main focus and passion in the surgical and scientific work of S.P. Vvedensky was limb lengthening and reconstruction using the compression-distraction method. He made a significant contribution to the development and dissemination of the Ilizarov method. Stanislav Petrovich knew Gavriil Abramovich Ilizarov personally well. Their first meeting took place at the Gorky Research Institute of Traumatology and Orthopaedics in 1968, where the author of the new method performed demonstration operations. Later, they repeatedly met in Kurgan and at various conferences and congresses. It should be noted that G.A. Ilizarov, then the director of KNIIEKOT, gave a positive review of the doctoral dissertation of S.P. Vvedensky. Stanislav Petrovich deeply mastered the principles of G.A. Ilizarov's method and actively worked to disseminate compression-distraction osteosynthesis not only at traumatology departments of the Gorky region, but also in twelve regions of the institute's supervision zone. He organized a specialized pediatric orthopaedic department at the Gorky Research Institute of Traumatology and Orthopaedics for treating children and adolescents with the Ilizarov method, and extensive scientific work was carried out on the study and further development of compression-distraction osteosynthesis. The department's employees defended five candidate and two doctoral dissertations on the treatment of patients using the external fixation method, and received 26 patents for new methods and technical solutions in the field of extrafocal osteosynthesis.

S.P. Vvedensky conducted extensive research in the field of biomechanics and physiology of compression-distraction osteosynthesis in limb lengthening. On his initiative and with his participation, dynamometers were developed, with the help of which distraction forces were studied in lengthening of the femur, tibia, humerus, and distraction epiphysiolysis. The causes of deformities in lengthening of limb segments were revealed. The effect of distraction forces on adjacent joints was studied. Based on clinical and electrophysiological studies, objective criteria for acceptable limb lengthening in shortenings of various origins were established for the first time, indications and contraindications for distraction epiphysiolysis in bloodless lengthening of the tibia were developed, original methods for eliminating contractures of the hip, knee and ankle joints were proposed.

S.P. Vvedensky offerred a lot of innovative design solutions based on his extensive experience in clinical work and results of his biomechanical studies. In 1971, he was among the first in the country to introduce hinge units into the Ilizarov apparatus and patented an apparatus for shoulder joint arthrodesis. In 1975, Stanislav Petrovich was the first to propose and use a wire-and-halfpin fixator, which principle found widespread use in the world. In 1979, he proposed and used clinically the world's first automated compression-distraction apparatus for limb lengthening.

Stanislav Petrovich is the author of more than 150 scientific papers, 13 patents for inventions, 50 rationalization proposals, was awarded the titles of "Excellent Healthcare Worker", "Veteran of Labor", "Inventor of the USSR", Honorary Professor of the National Ilizarov Medical Research Center of Traumatology and Orthopaedics, laureate of the Academician I.N. Blokhin Prize for work in the field of development of medical biotechnology.

Stanislav Petrovich will be remembered by his colleagues, friends and students as a talented scientist, experimenter, teacher and a wonderful person.

The staff of the Volga Region Research Medical University and the editorial board of the journal "Genij Ortopedii" express sincere condolences to his family and friends.

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