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Anatomical variations of the medial calcaneal nerve: a cadaveric study

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Abstract

Introduction One of the underestimated causes of pain in the heel area is neuropathy of the medial calcaneal nerve, which can both imitate and accompany plantar fasciitis. Some researchers note that neuropathy of the medial calcaneal branch of the tibial nerve is the cause of pain syndrome localized in the heel area. Knowledge of the main landmarks and anatomical variability of the medial calcaneal nerve passage in the foot can facilitate anesthesia, surgical interventions, including hydrodissection.

Purpose To determine the anatomical variability of the medial calcaneal nerve, including the level of its origin, transverse diameter and topographic location relative to the main anatomical landmarks of the medial calcaneal area in order to use the obtained data in foot surgery, regional anesthesia and differential diagnosis of pain syndrome localized in the calcaneal area.

Materials and methods Dissection of the medial heel region was performed in 16 cadavers (32 feet). For each specimen, we measured the thickness of the tibial and medial calcaneal nerves, as well as the distance (centimeters) from the tip of the medial malleolus to the point where the medial calcaneal nerve branched off from the tibial nerve, and to the bifurcation point of the tibial nerve into the medial and lateral plantar nerves.

Results The study found that the medial calcaneal nerve branched from the tibial nerve at a distance of 2.7 ± 0.7 cm distal to the tip of the medial malleolus. The cross-sectional diameter of the nerve varied and averaged 1.9 ± 1.2 cm. In 15.6 % of cases, the medial calcaneal nerve had an additional branch. In the vast majority of cases (72 %), it terminated within the subcutaneous fat of the medial aspect of the calcaneous.

Discussion The findings confirmed considerable anatomical variability of the medial calcaneal nerve. In 15.6 % of cases, it originated from the lateral plantar branch, which is consistent with the findings of other researchers. The morphological features of branching in the tibial nerve and its distal segments are of particular importance in foot surgery. Unintentional nerve injury is possible during interventions in the region of the tarsal tunnel (including radiofrequency denervation or endoscopic release).

Conclusion This cadaveric study confirmed marked anatomical variability of the medial calcaneal nerve. These findings expand our understanding of the variable anatomy of the heel area and may aid in interpreting clinical cases of pain caused by compression or trauma to the medial calcaneal nerve, as well as in performing regional anesthesia.

Keywords: medial calcaneal nerve, plantar fasciitis, anatomy of the medial calcaneous

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INTRODUCTION

Understanding the anatomy of the medial heel area of the foot is fundamental for the diagnosis and treatment of various diseases associated with pain in the foot. Plantar fasciitis is one of the most common diseases characterized by pain in the heel area. Pain in the heel area in patients with plantar fasciitis is often considered a manifestation of enthesopathy, but the cause of pain may also be associated with neuropathic factors [1]. Pathological changes in this disease occur primarily at the site of attachment of the plantar fascia to the calcaneus [2]. Pain persists throughout the period of professional activity, which has a significant negative impact on the quality of patients' life. The issue of chronic damage to the plantar fascia continues to be the subject of scientific discussions in contemporary traumatology and orthopaedics [3]. Researchers associate the development of plantar fasciitis with a number of predisposing factors, including biomechanical disorders, excessive mechanical loads, pronounced pronation of the foot, restriction of dorsiflexion in the ankle joint, as well as traumatic effects [4, 5].

One of the underestimated causes of pain in the heel area is neuropathy of the medial calcaneal nerve, which can both imitate and accompany plantar fasciitis. Some researchers note that neuropathy of the medial calcaneal branch of the tibial nerve is the cause of pain syndrome localized in the heel area [6, 7], which is also confirmed by electrophysiological studies [8]. Currently, this neuropathy is characterized as an independent nosological condition or as a concomitant condition in plantar fasciitis [9], since the transmission of afferent pain impulses occurs along the medial calcaneal nerve of the foot [10].

Purpose To determine the anatomical variability of the medial calcaneal nerve, including its origin level, transverse diameter and topographic location relative to the main anatomical landmarks of the medial calcaneal region in order to use the obtained data in foot surgery, regional anesthesia and differential diagnosis of pain syndrome localized in the calcaneal area.

MATERIAL AND METHODS

Dissection of the medial calcaneal region was performed in 32 feet of 16 cadavers (9 women and 7 men). The average age of women was (47 ± 11) years, their height averaged (164 ± 6) cm; the average age of men was (53 ± 12) years and their height was (175 ± 7) cm. Exclusion criteria for the use of cadaveric samples were visible signs of previous trauma or surgery in the ankle or foot area, pathological deformities, various injuries or external defects.

The study was conducted on the cadaveric material supplied for educational and scientific activities, in compliance with the current legislation of the Russian Federation regulating the handling of biological objects. All procedures complied with generally accepted ethical principles and did not contradict the Helsinki Declaration of the World Medical Association (2013 edition). The study was conducted at the facilities of the St. Petersburg State Healthcare Institution City Pathological Anatomy Bureau of the Kalininsky District (St. Petersburg).

Statistical processing was performed using Microsoft Excel and SPSS Statistics v.22. For quantitative variables, mean values, standard deviations (M±SD), and median (Me) were calculated. The normality of distribution was assessed using the Shapiro–Wilk test. For comparing two groups, Student's t-test or Mann–Whitney U-test were used depending on the type of distribution. Differences were considered statistically significant at $p < 0.05$.

Each lower limb was moved to the anatomical position and the foot was perpendicular to the tibial axis to minimize measurement errors. Skin and subcutaneous fat were dissected by forming a Y-shaped incision and the flaps were retracted for better visualization. The medial foot

tendon-muscle complex and plantar aponeurosis were partially removed to expose the nerve fibers. The tibial nerve and its branches were dissected from the distal third of the lower leg to the plantar surface. In this study, the thickness of the tibial nerve and medial calcaneal nerve, the distance (cm) from the apex of the medial malleolus to the point of origin of the medial calcaneal nerve from the tibial nerve, and the point of division of the tibial nerve into the medial and lateral plantar nerves were measured in each specimen. Additionally, the number of trunks of the medial calcaneal nerve (the number of separate branches extending from the tibial nerve to the calcaneal region) and the anatomical zone of the medial calcaneal nerve ending (in the subcutaneous fat of the calcaneal region or at the medial tuberosity of the calcaneus) were determined.

RESULTS

During dissection, the medial calcaneal nerve was found in all 32 feet. The diameter (thickness) of the tibial nerve in the tarsal canal region was (5.6 ± 0.5) mm (4.3–5.9 mm). The thickness (external diameter) of the medial calcaneal nerve varied from 0.5 to 5.4 mm, averaging (1.9 ± 1.2) mm (Fig. 1).

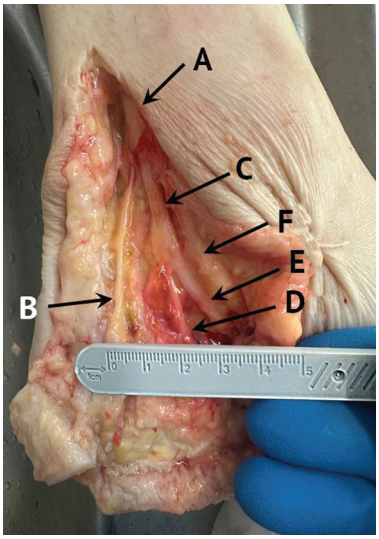

Fig. 1 Topographical picture of the medial calcaneal region: A — tibial nerve; B — medial calcaneal nerve; C — lateral plantar nerve; D — the first branch of the lateral plantar nerve; E — continuation of the lateral plantar nerve; F — medial plantar nerve

In most specimen (68.8 %, 22 cases), the thickness of the medial calcaneal nerve was 0.5–2.0 mm, in five cases (15.6 %) it was 2.1–3.0 mm, in two cases (6.3 %) it was 3.1–4.9 mm, and in three cases (9.4 %) it was greater than or equal to 5.0 mm (the maximum value was 5.4 mm) (Fig. 2).

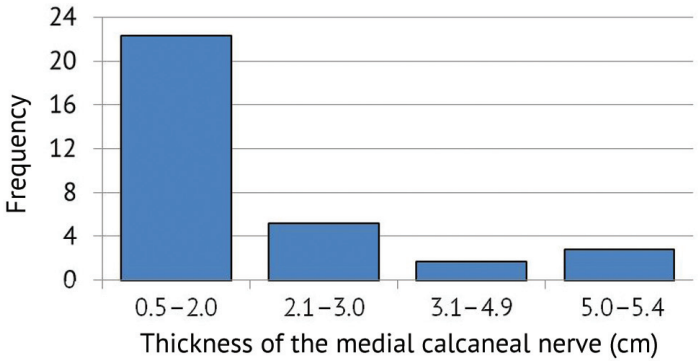

Fig. 2 Diagram of the distribution of the thickness of the medial calcaneal nerve

The medial calcaneal nerve originated from the tibial nerve at different levels relative to the apex of the medial malleolus: the minimum distance was 1.0 cm (proximal to the apex), the maximum was 4.5 cm (distal, towards the foot). The average level of origin of the medial calcaneal nerve was (2.7 ± 0.7) cm distal to the apex of the medial malleolus (Fig. 3).

In the absolute majority of specimen (84.4 %), the medial calcaneal nerve branched off from the tibial nerve as a single trunk. In five cases (15.6 %), two separate trunks of the medial calcaneal nerve were identified, branching off from the tibial nerve and directed to the medial tuberosity of the calcaneus and into the subcutaneous fat layer (Fig. 4).

Comparison of right and left feet revealed no significant differences in the morphometric parameters of the medial calcaneal nerve. There were also no differences in the thickness or origin of the medial calcaneal nerve depending on gender ($p = 0.541$) (Table 1).

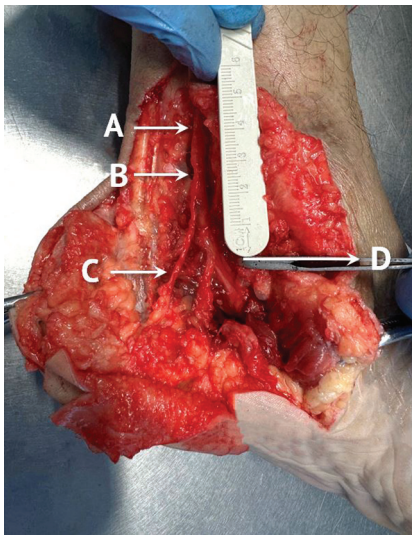

Fig. 3 Topographical picture of the medial calcaneal region: A — tibial nerve; B — level of the medial calcaneal nerve origination from the tibial nerve; C — medial calcaneal nerve; D — level of the apex of the medial malleolus

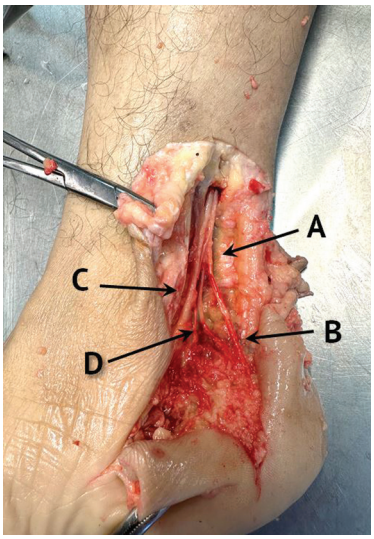

Fig. 4 Topographical picture of the medial calcaneal region: A — origin of the additional nerve trunk of the medial calcaneal nerve; B — medial calcaneal nerve; C — lateral plantar nerve; D — additional nerve trunk of the medial calcaneal nerve

Table 1

Medial calcaneal nerve thickness in the study group

Gender	*n*	Average thickness of the medial calcaneal nerve, mm	Standard deviation	Minimal value	Maximum value
Males	18	1.9	1.4	0.5	5.4
Females	14	2.1	1.2	0.7	5

In typical cases (more than 80 %), the medial calcaneal nerve branched off from the tibial nerve proximal to the bifurcation point for the medial and lateral plantar nerves. However, in five cases (15.6 %), an atypical picture was found: the medial calcaneal nerve branched off distal to the bifurcation. Thus, it branched off not directly from the trunk of the tibial nerve but from the lateral plantar nerve. Therefore, the medial calcaneal nerve was a branch of the lateral plantar nerve, indicating a developmental variant that is significant for understanding the variability of innervation of the calcaneal region. The termination point of the medial calcaneal nerve turned out to be relatively constant: 23 nerves (72 %) terminated in the subcutaneous fat of the calcaneal region, forming there a branched network of thin branches that provide sensitive innervation of the skin of the calcaneal region of the foot. In the remaining nine cases (28 %), the branch of the medial calcaneal nerve reached the region of the medial tuberosity of the calcaneus, where its terminal branches ran deep into the periosteum and ligamentous structures.

DISCUSSION

The medial calcaneal nerve is a small but clinically significant sensory branch that innervates the medial and posteromedial surfaces of the heel of the foot, including the area above the calcaneal tuberosity, the flexor retinaculum, and the subcutaneous fat of the calcaneal region [11]. The clinical picture of medial calcaneal nerve neuropathy includes burning pain, paresthesia, numbness, and hyperesthesia in the heel area. The pain increases with weight-bearing and in some cases occurs at night. Patients often describe the sensation as “electric shocks” or “burning” [12]. The relationship between plantar fasciitis and medial calcaneal nerve neuropathy has been confirmed by a number of clinical studies. According to a number of authors, up to 18 % of patients with chronic plantar fasciitis have signs of neuropathy. Verification of the diagnosis is especially important, since treatment methods for these conditions may differ [13].

Imaging techniques such as high-resolution ultrasonography and MRI can detect various morphological changes in tissues, including fibrosis, fascial thickening, and nerve compression [14]. Combining imaging data with electrophysiological studies helps differentiate neuropathic pain from enthesopathy and clarify the cause of chronic heel pain.

Chronic pain in the heel area can cause gait disturbance, compensatory overload of adjacent joints, and, as a consequence, secondary pathologies in other parts of the musculoskeletal system [15]. Early diagnosis and a multidisciplinary approach based on knowledge of anatomical features are key components of effective treatment of patients with pain in the heel area. Understanding the anatomy, topography, and branching patterns of the medial calcaneal nerve of the foot is essential in diagnosing heel pain, planning surgical interventions, and administering anesthesia.

According to anatomical studies, the sciatic nerve in the distal direction divides into its main trunks at the level of the popliteal fossa: the peroneal and tibial nerves. The tibial nerve passes behind the medial malleolus and enters the proximal part of the tarsal canal where it divides into the lateral plantar nerve, medial plantar nerve and medial calcaneal nerve. The branching of the main nerve trunks has anatomical variability, including the medial calcaneal nerve [16].

There is evidence in the literature that the medial calcaneal nerve arises from the tibial nerve within or proximal to the tarsal canal in most cases [17, 18]. The location of the medial calcaneal nerve is of great importance for the diagnosis and treatment of pain in the heel area, tarsal canal syndrome, soft tissue and joint injuries, and pain caused by perineurium fibrosis [19]. According to the literature, when the medial calcaneal nerve branches off from the main trunk, the tibial nerve, it is most often located superficially to the muscle that abducts the big toe and passes through or above the flexor retinaculum. The medial calcaneal nerve and its branches do not penetrate the plantar arch or deep structures of the foot [20]. The results obtained in the course of the study describe the origination of the medial calcaneal nerve from the tibial nerve (in more than 80 % of cases), which is consistent with the literature data.

The division of the medial calcaneal nerve into two main branches has been described: the anterior branch which goes to the muscle that abducts the big toe, and the posterior branch which runs to the skin, the medial surface of the Achilles tendon, the calcaneus, and the plantar fat pad [21]. Another study noted that the medial calcaneal nerve may branch off from the tibial nerve and/or the lateral plantar nerve [22]. Our data confirm this statement: the medial calcaneal nerve may branch off not directly from the tibial nerve but from the lateral plantar nerve. Similar variants have been mentioned previously, but according to our data, their frequency is about 15 %. This is somewhat lower than reported in some foreign studies (about 27 %), which may be due to the sample size [23].

Researchers have found that the medial calcaneal nerve can also arise from the medial plantar nerve, cross blood vessels in the calcaneal canal, and innervate the calcaneal region [24]. The number of medial calcaneal nerves may vary from one to four, but five also were described [25, 26]. In the present study, two separate trunks of the medial calcaneal nerve were found in five cases (15.6 %), arising from the tibial nerve and running to the medial tuberosity of the calcaneus and into the subcutaneous fat layer. More than two trunks were not found, which may be due to the sample size or individual characteristics of the biological samples studied.

The present study complements the existing anatomical data on the medial calcaneal nerve and highlights the need for an individualized approach to interventions in the heel area. The results may serve as a morphological basis for improving the diagnosis and prevention of neuropathic heel pain.

The results demonstrate significant anatomical variability of the medial calcaneal nerve. In particular, the level of origination of the medial calcaneal nerve from the tibial nerve varies in the range from 1 cm distal to 4.5 cm proximal relative to the landmark (apex of the medial malleolus). This confirms the data of several studies on the variability of the routes of the calcaneal branches of the tibial nerve. The study presents data on the thickness (diameter) of the medial calcaneal nerve on cadaveric material, quantitatively describing this parameter with the calculation of average and extreme values.

CONCLUSION

The anatomy of the tarsal canal and calcaneal nerves is important for orthopedists, traumatologists, and neurosurgeons who perform foot surgery. Moreover, the variability in the thickness of the medial calcaneal nerve means that the severity of clinical manifestations in its neuropathy may vary as larger trunks are potentially more vulnerable to compression. For neurologists, knowledge of the variants of the medial calcaneal nerve termination is important in diagnosing lesions. Thus, in subcutaneous position of the medial calcaneal nerve end, a superficial location of pain points is possible, while if it terminates at the calcaneus, symptoms can imitate plantar fasciitis. Knowledge of the main landmarks and anatomical variability of the passage of additional trunks of the medial calcaneal nerve can facilitate anesthesia, surgical interventions, including hydrodissection.

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Serdobintsev M.S. — reviewing and editing.

Karpovich N.I. — data collection, analysis or interpretation.

Khanmuradov R.A. — validation, data processing.

Naumov D.G. — approval of the final manuscript for publication

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A comparative study between functional outcomes of proximal humerus fracture treated using closed reduction and JESS external stabilization system and open reduction and internal fixation with PHILOS plate at a tertiary health care center

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Abstract

Introduction Proximal humerus fractures account for 5 % of all fractures. Their incidence increases with age, especially in women over 60. Most of them (85 %) are minimally displaced and managed non-operatively, while 15 % require surgery. Neer's classification guides treatment, which includes conservative methods and operative methods. The operative techniques are PHILOS plating, pinning, nailing, or arthroplasty. The JESS fixator, developed by Dr. B.B. Joshi, offers a minimally invasive alternative.

Purpose To compare the functional results of proximal humerus fractures treated with PHILOS plating and JESS fixation.

Material and method The prospective observational study was conducted over 24 months on 36 patients with proximal humerus fractures. Patients were divided into two groups, 18 in each group, based on the surgical technique used: JESS fixation and PHILLOS plating. JESS group had more females, while PHILOS had more males. The Constant-Murley Scores were used to compare the functional outcome in both groups at regular intervals. Complications of both techniques were assessed.

Results Falls were the main cause in JESS (72.22 %), while road accidents were more common in PHILOS (55.55 %) group. Both groups showed significant improvement in Constant-Murley Scores ($p < 0.005$). JESS group had one case each of avascular necrosis, malunion, and pin tract infection. PHILOS group had one implant failure and one avascular necrosis case, both managed effectively.

Conclusion In the management of proximal humerus fractures, JESS fixation and PHILOS plating are equally effective. This study also led us to the conclusion that JESS fixation for proximal humerus fractures is a semi-rigid, inexpensive technique that permits early mobilization, needs few implants, requires a short hospital stay and surgical period, resulting in good to excellent functional results with a minimal risk of complications.

Keywords: JESS, PHILOS, proximal humerus, Constant-Murley Scores, osteoporosis

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INTRODUCTION

Roughly 5 % of all fractures are proximal humerus fractures, making them common injuries [1]. Their frequency rises with age, especially in individuals over 60 with a female-to-male ratio of 3:1 in this age group [2]. While 15 % of these fractures necessitate surgical intervention because of the substantial displacement of fracture fragments, the majority (85 %) are minimally displaced and manageable non-operatively [3]. Falling on an outstretched arm is the most common cause of proximal humerus fractures, especially in older individuals with osteoporosis [4]. A thorough clinical history is essential, including the patient's age, hand dominance, mechanism of injury, and injury severity [5]. Additionally, any pre-existing medical conditions, previous shoulder surgeries, and symptoms such as paresthesia, elbow or wrist pain, or functional impairment of the affected limb should be evaluated [6].

Neer CS classified these fractures to determine which cases would benefit from open reduction and which were at higher risk of avascular necrosis, necessitating prosthetic replacement [7]. Successful therapy depends on the correct diagnosis and classification of the fracture [8]. The formation and displacement of fracture fragments depend on the force exerted by muscles attached to the greater and lesser tuberosities and the humeral shaft [9].

The treatment of proximal humerus fractures varies based on fracture severity and patient factors. Conservative management includes the use of a U-slab (hanging cast), a universal shoulder immobilizer (USI), or functional bracing [10]. Surgical alternatives include closed reduction with percutaneous pinning, open reduction with internal fixation utilizing a locked PHILOS plate, trans-osseous suture fixation, intramedullary nailing, hemiarthroplasty, total shoulder arthroplasty, and reverse shoulder arthroplasty [11]. The surgical procedure used is determined by criteria such as fracture type, patient's age, bone quality, comorbidities, and the surgeon's expertise and preferences [12].

Dr. B.B. Joshi of Bombay devised a highly modular small external fixator device that offers a simple and effective solution for handling difficult upper limb fractures [13]. This method is minimally invasive, has a high safety rating, and enables early physiotherapy [14]. It is simple to use, even in remote locations, and requires little instrumentation, making it a viable alternative to the present treatment options [15].

The **purpose** of this study is to compare the functional results of proximal humerus fractures treated with PHILOS plating and JESS fixation.

MATERIALS AND METHODS

This prospective observational study was conducted over 24 months and included 36 patients with proximal humerus fractures. Institutional ethics committee approval was obtained, and informed consent was collected from all participants. Patient details were documented using a standardized clinical history proforma at a tertiary care center.

Inclusion Criteria:

- Patients with displaced two- or three-part humerus fractures;
- Age over 18 years;
- Injury that occurred within two weeks before surgery.

Exclusion Criteria:

- Pediatric patients with active growth plates;
- Open fractures;

- Proximal humerus fractures with pre-existing shoulder conditions such as arthritis, rotator cuff tears, or frozen shoulder;
- Associated ipsilateral upper limb injuries or fractures;
- Cases with neurovascular compromise.

Preoperative evaluation included an assessment of the patient's general health and a thorough examination of the neurovascular status of the upper extremity. Radiographic evaluation consisted of anteroposterior and axillary views of the shoulder and a CT scan for detailed fracture visualization.

Surgical Procedure

Joshi External Stabilizing System (JESS)

The surgical technique was carried out under general or local anesthesia, with the patient lying supine and a sandbag used to elevate the shoulder. We used 2.5-mm pins. The greater tuberosity pins posed a risk to the axillary nerve and the posterior humeral circumflex artery. In contrast, the proximal lateral pins posed a risk to the anterior branch of the axillary nerve. Additionally, the cephalic vein, biceps tendon, and musculocutaneous nerve were at risk during anterior pin implantation. The greater tuberosity pins were inserted with the shoulder externally rotated to reduce danger, moving the axillary nerve and posterior circumflex artery away from the humeral neck. Three pins were placed into the humeral head at 30° intervals in the same horizontal plane: one just lateral to the bicipital groove, another in the appropriate lateral plane, and a third posterior to the central one. Two more wires were inserted into the shaft near the greater tuberosity. These fixator wires functioned as joysticks to aid with reduction before attaching the frame. The purpose of reduction was to re-establish proper alignment, with an angulation of less than 45° and displacement of less than 1 cm.

After reduction, beta clamps were used to secure each pin to the external fixator bars, resulting in a stable construction. On the first day following surgery, patients were advised to start actively mobilizing the afflicted extremity while wearing a triangle sling for comfort. After evaluating radiological union and functional improvement, the external fixator was removed.

PHILOS (Proximal Humeral Internal Locking System) Plate Fixation

In this technique, a “beach chair” position was given to the patient after general or regional anaesthesia. A single preoperative dose of 1.5 grams of Cefuroxime was administered intravenously at the initiation of anaesthesia. Surgical landmarks for the deltopectoral approach were marked. A 10-cm incision from the coracoid process to the shaft of the humerus was taken. The conjoint tendon retracted medially to allow access to the fracture site.

With the help of an image intensifier, the fracture fragments were directly reduced, and K-wires were used for the temporary fixation of these fragments. Ethibond No 5 was also used for manipulation of the proximal fracture to aid in reduction. After confirmation of fracture reduction, the PHILOS plate was positioned. Care was taken to position this plate at least 8 mm distal to the upper end of the greater tuberosity using an insertion guide. The biceps tendon was also used to guide for plate positioning. To avoid tendon impingement, the plate was positioned laterally to the long head of the biceps tendon. The locking screws were used to secure the humeral head fragment and metaphyseal shaft. The appropriate-length locking screws were inserted using a specially designed star drive screwdriver. The anteroposterior and axillary views were taken using an image intensifier for the final confirmation of fracture reduction and plate positioning. Before the procedure was completed, the stability, range of motion, and absence of impingement were evaluated intraoperatively. Following surgery, all patients were placed in either a sling or an abduction brace for support.

Postoperative Protocol

Following surgery, physical therapy was started right away on the next day. It started with pendulum exercises, passive forward flexion, and external rotation exercises, and advanced to unrestricted range of motion by 6–7 weeks. Exercises including active range of motion and active assistance were recommended. Patients were monitored for clinical and radiological union at 4, 8, and 12 weeks.

Outcome Assessment

Functional outcomes were assessed using the Constant-Murley Score (CMS), a 100-point scale evaluating pain levels and the patient's ability to perform daily activities [15]. The CMS is interpreted as follows:

• 0–55 points = Poor;

• 56–70 points = Fair;

• 71–85 points = Good;

• 86–100 points = Excellent.

Complications, including pin-tract infections, malunion, avascular necrosis, and implant failure, were documented throughout the follow-up period.

Statistical Analysis

Statistical analysis was performed using SPSS software, version 22. Qualitative data were presented as frequency and percentage, while quantitative data were analyzed using a paired t-test. A *p*-value of < 0.05 was considered statistically significant.

RESULTS

This study included 36 patients. Both groups had a total of 18 patients each. In the JESS group, there were eight males (44.44 %) and 10 females (55.55 %), while in the PHILOS group there were 15 males (83.33 %) and three females (16.67 %). The mode of injury in the JESS group was fall in 13 cases (72.22 %) and road traffic accidents in five cases (27.78 %), whereas in the PHILOS group, eight cases (44.44 %) were due to falls and 10 cases (55.55 %) resulted from road traffic accidents. Neer's classification showed seven two-part (38.90 %) and 11 three-part (61.10 %) fractures in the JESS group, while the PHILOS group had nine two-part (50 %) and nine three-part (50 %) fractures. Both groups had a total of 18 patients each (Table 1).

Table 1

Demographic details

		JESS (*n* = 18)		PHILOS (*n* = 18)	
		n	%	*n*	%
Male		8	44.44	15	83.33
Female		10	55.55	3	16.67
Mode of injury	Fall	13	72.22	8	44.44
	Road traffic accident	5	27.78	10	55.55
Neer's type	2 parts	7	38.90	9	50
	3 parts	11	61.10	9	50

In the JESS group, the mean Constant-Murley Score increased from 29.02 before surgery to 60.27 at four weeks postoperatively, 70 at eight weeks postoperatively, and 82.33 at 12 weeks postoperatively. Similarly, in the PHILOS group, the mean Constant-Murley Score increased from 32.12 preoperatively to 55.82 at four weeks postoperatively, 66.76 at eight weeks postoperatively, and 77.06 at 12 weeks ostoperatively. When comparing preoperative assessments with postoperative scores at 4, 8, and 12 weeks, the *p*-value for both groups was less than 0.005, suggesting a highly significant improvement (Table 2).

Table 2

Constant Murley Score at a regular interval

Technique	Constant Murley Score								*P*-value
	Pre-op		Post-op 4 weeks		Post-op 8 weeks		Post-op 12 weeks		
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
JESS	29.22	5.58	60.27	8.04	70	8.6	82.33	11	< 0.001
PHILOS	32.12	5.02	55.82	5.04	66.76	7.88	77.06	11.42	< 0.001

In the JESS fixation group, there were three cases of complications: one case of avascular necrosis of the humeral head (successfully treated with hemiarthroplasty), one case of malunion (without significant impact on the functional outcome), and one case of pin-tract infection (successfully managed with daily dressing and oral antibiotics). On the other hand, with PHILOS fixation, there were two complications: one case of avascular necrosis (treated with hemiarthroplasty) and one case of implant failure (screw backout) (Table 3).

Table 3

Complications

Technique	Implant failure		Malunion		Avascular necrosis		Infection		None	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%
JESS (*n* = 18)	0		1	5.55	1	5.55	1	5.55	15	83.33
PHILOS (*n* = 18)	1	5.55	0		1	5.55	0		16	88.88

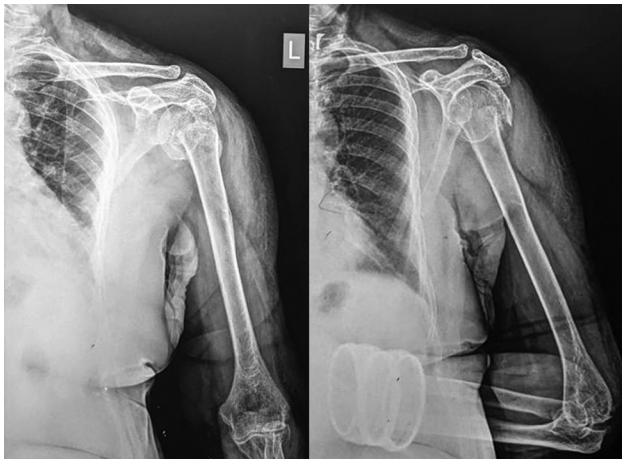

Fig. 1 Pre-op JESS

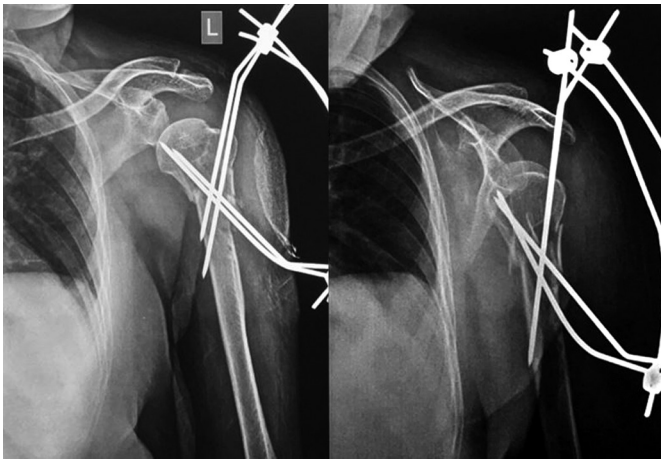

Fig. 2 Post-op JESS

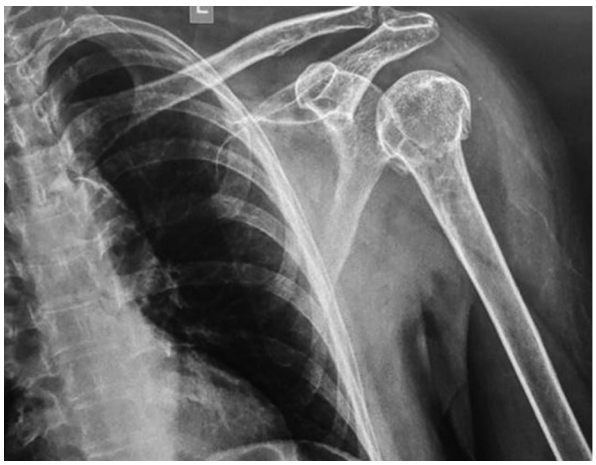

Fig. 3 12 weeks post-op JESS

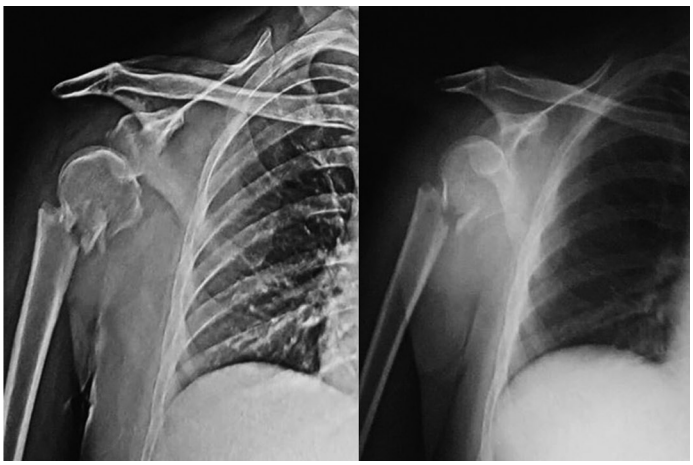

Fig. 4 Pre-op PHILOS

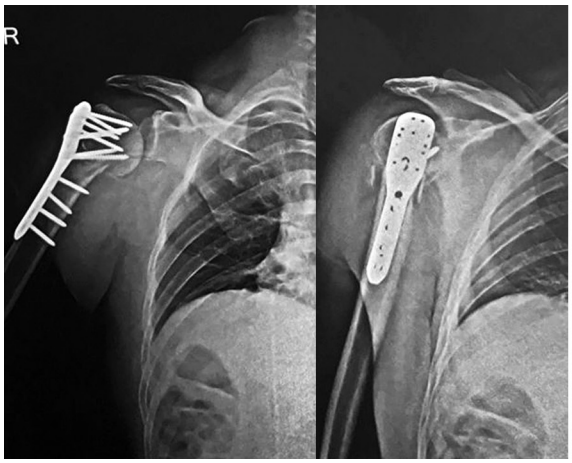

Fig. 5 Post-op PHILOS

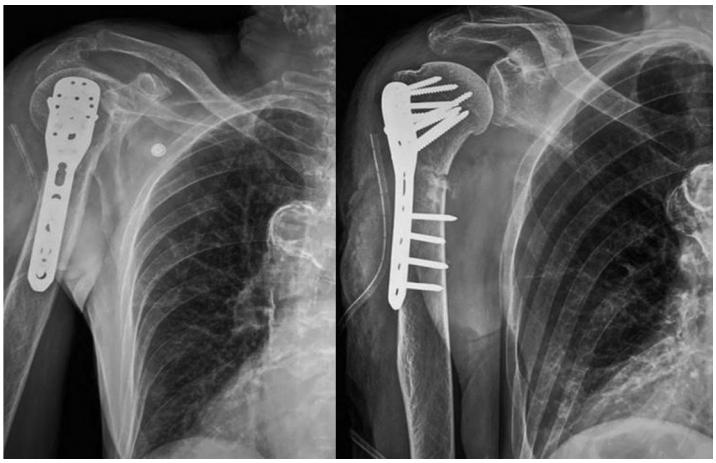

Fig. 6 12 weeks Post-op PHILOS

DISCUSSION

Proximal humerus fractures are rather common in the elderl y, and there are numerous treatment options for closed fractures. These options range from minimally invasive percutaneous pinning to hemiarthroplasty, and each has pros and downsides. One main disadvantage of non-operative treatment is delayed mobilization, which frequently results in joint stiffness. Additionally, conservative treatment increases the risk of malunion or nonunion of fractures.

Joshi External Stabilization

In our research, the application of an external fixator system facilitated satisfactory bone healing, accompanied by favourable to outstanding functional results. The procedure generally took less time, under 30 minutes, was economical, and utilized minimal resources. Despite the suboptimal anatomical reduction achieved through this percutaneous fixation method, the functional results remained favorable. These findings are supported by multiple studies. Some techniques incorporate a locking mechanism attached to the pins to prevent migration while operating on the same principle as percutaneous fixation. Additionally, the mutual connection of K-wires generates extra valgus force, counteracting the deforming forces exerted by the supraspinatus and deltoid muscles. However, further biomechanical studies are needed to validate this claim.

Another approach, known as the "hybrid technique", involves initial open reduction followed by stabilization with K-wires and an external fixator [16]. While this method yields comparable functional and radiographic results, it is associated with wound healing complications.

Our study included eight female and ten male patients, with a mean age of 61 years. All patients underwent surgery within three days of injury, and the procedure took less than 30 minutes, with minimal to no blood loss. Postoperatively, active-assisted shoulder flexion and extension exercises, along with wrist and elbow range-of-motion exercises, were initiated on the first day. Patients were advised to maintain upper limb exercises and perform external fixator care at home. Follow-up assessments were conducted at four, eight, and twelve weeks.

A steady improvement in functional outcomes, as assessed by the Constant – Murley Score, was observed: 60.27 at four weeks, 70.00 at eight weeks, and 82.33 at twelve weeks. Complications such as avascular necrosis, pin-tract infection, and malunion were rare, with only one case of each; all of which were successfully treated. Gupta et al. [17] found that in their research of JESS fixation, the average postoperative VAS score was 2.1 (± 0.73), while the Constant Score averaged 78.1 (± 9.61)

over a follow-up period of six months. The average time required for union was 6.5 (± 1.18) weeks. Reported complications included one instance of K-wire loosening and one occurrence of pin tract infection.

Goyal et al. [18] in their study found that the mean preoperative Constant-Murley Score was 29.09, which improved to 60.39 at four weeks postoperatively, 69.97 at eight weeks postoperatively, and 79.64 at twelve weeks postoperatively. Similarly, Kandel et al. [19] reported comparable results and concluded that surgically treating displaced proximal humerus fractures with JESS leads to good functional and radiological outcomes. It results in less pain, reduced stiffness, and greater range of motion (ROM). Consequently, the JESS fixator serves as an economical and effective alternative treatment for proximal humerus fractures, presenting minimal complications.

Internal Fixation with Locking Plates

Historically, internal fixation using non-locking plates was associated with high failure rates and unsatisfactory clinical outcomes. Pre-contoured anatomical locking compression plates offer greater adaptability and higher union rates, particularly in osteoporotic bone [20]. Regardless of the fixation method, fracture reduction remains critical for optimal surgical outcomes. Proper plate positioning is equally important, as even minor displacement can result in shoulder impingement. According to AO-OTA principles, the upper edge of the plate should be placed 5–8 mm distal to the greater tuberosity to avoid impingement.

Our study included fifteen male and three female patients, with a mean age of 48 years. Physiotherapy was initiated in the second postoperative week, beginning with passive-assisted range-of-motion exercises, followed by active exercises starting from the third week. Follow-up assessments at four, eight, and twelve weeks showed continuous improvement in functional outcomes, with Constant-Murley Scores of 55.82 at four weeks, 66.76 at eight weeks, and 77.06 at twelve weeks.

Despite the advantages of locking plates, they are associated with complications such as plate breakage, screw cutout, avascular necrosis, varus malreduction, and the need for revision surgery. Jhamnani et al. [21] studied 32 proximal humerus fractures treated with PHILOS plating, reporting excellent outcomes in 62.5 %, satisfactory in 21.87 %, poor in 9.38 %, and failure in 6.25 %. Two-part fractures had better results than three-part fractures. Complications were minimal, with 65.6 % showing stiffness, malunion (9.38 %), and avascular necrosis (6.25 %) were noted. In the study by Spolia et al. [22], the mean Constant – Murley Score at six months was 79.4 (range: 38–92). Among 30 patients, 40 % had excellent, 30 % good, 20 % moderate, and 10 % poor outcomes. One four-part fracture had the lowest score (38). Complications (16.7 %) included varus malunion, avascular necrosis, and stiffness. A similar study was done by Ethirajk et al. [23], on 40 patients and reported that the functional outcome was found to be excellent in 2 patients (5 %), good in 22 patients (55 %), fair in 7 patients (17.5 %), and poor in 9 patients (22.5 %). The mean Constant – Murley score achieved was 68.75±14.03.

In our study, the screw cutout (implant failure) rate was significantly lower at 5.55 %. In a study by Owsley et al. [24], involving 53 patients, the screw cutout rate was reported to be 23 %, identifying it as a leading cause of revision surgery. Doshi et al. [25] also reported 5.66 % screw cutout rate in their study. Another long-term complication observed in comminuted three- and four-part fractures is avascular necrosis, which typically develops years after fixation and can compromise functional outcomes. We encountered avascular necrosis in 5.55 % of cases. Geiger et al. [26] reported 7.28 % cases of avascular necrosis in their study on 28 patients. Kaushal et al. [27] showed 2.5 % cases of avascular necrosis following PHILOS plating.

Alternative Surgical Approaches

Hemiarthroplasty and reverse total shoulder arthroplasty are viable alternatives, particularly for complex fractures. However, these procedures require advanced surgical skills and tertiary healthcare facilities, which are often inaccessible in our country. A more biological approach has been proposed, though it poses risks to the articular cartilage and is commonly associated with persistent shoulder pain. Intramedullary nailing is another technique preferred by some orthopaedic surgeons.

The main limitation of this study was a relatively small sample size. A larger randomized controlled trial comparing various fixation techniques would provide more comprehensive insights into this treatment approach.

CONCLUSION

This study concluded that both techniques, JESS fixation and PHILOS plating, are equally effective in treating proximal humerus fractures in terms of functional outcome. This study also led us to the conclusion that JESS fixation for proximal humerus fractures is a semi-rigid, inexpensive technique that permits early mobilization, needs few implants, requires a short hospital stay and surgical period, resulting in good to excellent functional results with a minimal risk of complications.

Conflict of interest *The authors have no conflicts of interest to declare.*

Funding source *There is no funding source for the research work.*

Ethics approval *Ethics committee approval was taken from the institutional Ethics committee.*

Consent for publication *Consent was taken from all the participants.*

Availability of data and materials *The datasets used in and/or analyzed in the current study are available from the corresponding author upon reasonable request.*

The manuscript was read and approved by all the authors.

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ACL reconstruction: correlation of the functional outcome with the position of femoral and tibial tunnels

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Abstract

Introduction The anterior cruciate ligament (ACL) is the main ligament that stabilizes the knee and stops anterior translation. It is also essential to the screw-home mechanism and helps resist valgus and rotational stress. For ACL reconstruction, autograft arthroscopic single-bundle surgery is regarded as the "gold standard" procedure. Joint laxity is enhanced and cartilage degradation is avoided with anatomical ACL restoration. Negative results are frequently caused by technical surgical errors, such as improper tunnel placement.

This study **aims** to evaluate the functional outcome in ACL-reconstructed patients when a graft is placed in an anatomical position, as well as to compare it with when a graft is placed in a non-anatomical place.

Methodology This is a 24-month prospective observational study conducted on 44 patients who underwent arthroscopic ACL reconstruction, with post-op CT scans performed after permission from the institutional review board (IRB). The most common mode of injury was sports-related. Thirty patients belonged to the anatomical group, and 14 patients belonged to the non-anatomical group based on inclusion and exclusion criteria. The Lysholm scoring system was used for functional evaluation on follow-up at three, six, and 12 months.

Results The mean Lysholm score was 41.24 before surgery for the entire sample. In the anatomical group, the score improved to 80.91 at three months, 85.91 at six months, and 89.23 at twelve months. In the non-anatomical group, the score was 58.58 at three months, 65.13 at six months, and 58.58 at twelve months. The improvement in Lysholm scores in the anatomical group was statistically significant.

Conclusion This study concludes that the functional outcome of ACL reconstruction is better when the graft is placed in anatomical footprints than when it is placed in non-anatomical footprints.

Keywords: Femoral tunnel, tibial tunnel, ACL reconstruction, anatomical grafting, Lysholm score

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INTRODUCTION

The anterior cruciate ligament (ACL) is the most frequently injured ligament, while the knee is the most frequently injured joint overall. The knee's main stabilizer, the ACL, stops the knee from anterior translation. Additionally, it plays a crucial role in reducing valgus and rotational stress and plays an important role in the screw home mechanism. Depending on the demography, the annual incidence rates of ACL injuries range from 30 to 40 ruptures per 100,000 people [1]. Incidence is more common in sports players. From the initial primary repair to extracapsular augmentation and tendon graft-based ACL reconstructions, surgical treatment of ACL-deficient knees has advanced. For ACL reconstruction, autograft arthroscopic single-bundle surgery is regarded as the "gold standard" [2]. Reconstruction of a ruptured ACL is a well-established procedure [3]. Restoring proper knee joint function and preventing the onset of secondary osteoarthritis are the goals of ACL restoration [4].

Up to 25 % of patients still do not achieve adequate function following an ACL repair, despite advancements in surgical procedures over the previous few decades [5]. One of the main difficulties in reconstructing the anterior cruciate ligament is the placement of anatomical grafts. Joint laxity is enhanced and cartilage degradation is avoided with anatomic ACL restoration [6]. These days, anatomical graft placements should be prioritized in ACL restoration to replicate normal physiologic graft tension and more precise knee kinematics [7]. Technical surgical errors, such as incorrect tunnel placement, are a common cause of poor outcomes [8]. The most frequent technical mistake that results in graft failure is tunnel misplacement; femoral tunnels positioned too anteriorly seem to be the most crucial of these mistakes [9]. It is estimated that up to 80 % of technical failures are based on improper tunnel placement [10]. Currently, the most effective technique to assess the proper positioning of the ACL tunnel and graft is three-dimensional (3D) reconstruction of computed tomography (CT) images [11–12].

Tunnel diameter, tunnel length, femur diaphyseal angle (coronal angle/coronal obliquity), and tunnel position utilizing the Bernard and Hertel grid are the usual anatomical parameters for the femoral tunnel [13]. Tunnel diameter, tunnel length, anteroposterior and mediolateral tunnel position using the quadrant technique, coronal angle, and sagittal angle are among the anatomical factors for a reconstructed tibial tunnel [14].

The Lysholm scoring method is widely used to assess functional results in knee joints [15]. Theoretically, ACL reconstruction with a non-anatomical graft may impair knee joint stability and kinematics. This non-anatomical reconstruction can potentially alter the functional outcome of an ACL reconstructed knee.

This study **aims** to evaluate the functional outcome in ACL-operated patients when a graft is placed in an anatomical position, as well as to compare it with when a graft is placed in a non-anatomical place.

MATERIALS AND METHODS

This is a 24-month prospective observational study of 44 patients with anterior cruciate ligament (ACL) tears that have been identified and operated on. The institutional ethics (Institutional Review Board — IRB) committee provided approval. Data were gathered using the clinical history proforma, and patient information was documented at a tertiary care facility. The study comprised patients who presented to the orthopaedic department using predetermined inclusion and exclusion criteria.

The study comprised patients with solitary ACL injuries, ACL tears with or without accompanying meniscus injuries (single cruciate ligament damage), fused epiphysis, average body mass index (18.5–24.9 kg/m^2) and age ranging from 20 to 50 years. Patients with open injuries, associated posterior cruciate ligament injury, medial or lateral collateral ligament injuries, ACL re-injury, ipsilateral lower limb fractures around the knee, refusal to undergo a postoperative CT scan, and prior surgery on or around the same knee were excluded. Patients who volunteered to participate in the trial provided signed informed consent.

Preoperative evaluation involved an assessment of general health and a thorough examination of the affected knee. Radiographic evaluation included anteroposterior and lateral views as

well as MRI of the affected knee. All patients underwent arthroscopic ACL reconstruction using a hamstring graft, performed by a senior consultant. Careful attention was given to the preparation of the graft, tunnel creation in the tibial and femoral regions, and secure fixation of the graft in the anatomical position. In the postoperative period, a CT scan of the operated limb was performed to check for anatomical graft placement.

The anatomical parameters used to assess graft placement were:

Femur

— Tunnel diameter;

— Tunnel length;

— Femoral diaphyseal angle (coronal angle/coronal obliquity);

— Tunnel position using the Bernard and Hertel grid.

Tibia

— Tunnel diameter;

— Tunnel length;

— Anteroposterior and mediolateral tibial tunnel position using the quadrant approach;

— The coronal and sagittal angles.

Based on these parameters, patients were categorized into two groups: anatomical (femoral and tibial tunnels in the anatomical position) and non-anatomical (femoral or tibial tunnel not in anatomical position). All the patients in both groups had no difference in an average BMI.

Outcome measures: Functional outcomes were assessed using the Lysholm score preoperatively, at three months, six months, and 12 months postoperatively. This scoring mechanism assumed a pivotal role, serving as a critical instrument in providing an intricate and in-depth assessment of the overall knee function and symptomatology experienced by individuals undergoing ACL reconstruction.

Statistical Analysis: A case record (PROFORMA) was filled out by an investigator using the interview technique. The collected data were tabulated in an Excel sheet under the guidance of a statistician. Means and standard deviations of the measurements per group were used for statistical analysis (SPSS 22.00 for Windows; SPSS Inc., Chicago, USA). The difference between the two groups was assessed using the chi-square test, with the level of significance set at $p < 0.05$.

RESULTS

The study included 44 patients of which 36 were male and eight were female. The mean age of participants was 28 years and the right side was more commonly injured than the left. The most common mechanism for the injury was sports-related. Out of 10 patients with meniscus injury, five patients belonged to each group, and there was no statistically significant difference between the groups (Table 1).

In the anatomical group, preoperatively almost all patients had lower Lysholm scores. Post-operatively, the number of patients with improved Lysholm scores increased from 13 patients (43 %) at three months to 26 patients (87 %) at 12 months. None of the patients showed poor scores at 12 months. This improvement was statistically significant (Table 2). Pre-operatively, none of the patients had an excellent Lysholm score. The number of patients with an excellent and good score increased in the postoperative period for the anatomical group while the number of patients with fair and poor scores remained the same even at 12 months post-operatively. This improvement in the number of patients in the anatomical group was statistically significant.

The mean Lysholm score was 41.24 before surgery in the entire sample of patients. In the anatomical group, this score improved significantly at six months, as well as at twelve months. In the non-anatomical group, the score remained the same at twelve months. The improvement in Lysholm scores in the anatomical group was statistically significant (Table 3).

Table 1

Demography

		Group of anatomical graft placement (n = 30)	Group of nonanatomical graft placement (n = 14)	P value	Statistical significance
Age (Mean)		x ± x = 28.2 years	x ± x=27.7 years	0.176	No
Male	*n*	26	10	0.0000243	Yes
	%	87	71		
Female	*n*	4	4		
	%	13	29		
Bone Mass Index (Mean)		23.1± 2.6	23.5± 3.2	0.687	No
Site Right	*n*	23	7	0.0159	Yes
	%	77	50		
Site Left	*n*	7	7		
	%	23	50		
Mechanism of injury — sports	*n*	24	9	0.0000000294	Yes
	%	80	64		
Mechanism of injury — road traffic accidents	*n*	5	2		
	%	17	14		
Other mechanism	*n*	1	3		
	%	3	22		

Table 2

Comparison of Lysholm scores

Lysholm score	Group of anatomical graft placement (n = 30)		Group of nonanatomical graft placement (n = 14)		P value
	n	%	*n*	%	
Pre-op					
Excellent (91–100)	0	0	0	0	0.553
Good (84–90)	2	7	0	0	
Fair (65–83)	10	33	6	43	
Poor (< 65)	18	60	8	57	
3 months					
Excellent (91–100)	4	13	0	0	0.0075
Good (84–90)	9	30	0	0	
Fair (65–83)	15	50	6	43	
Poor (< 65)	2	7	8	57	
6 months					
Excellent (91–100)	12	40	0	0	0.0000247
Good (84–90)	10	33	2	14	
Fair (65–83)	8	27	4	29	
Poor (< 65)	0	0	8	57	
12 months					
Excellent (91–100)	17	57	0	0	0.000000603
Good (84–90)	9	30	0	0	
Fair (65–83)	4	13	8	57	
Poor (< 65)	0	0	6	43	

Table 3

Lysholm score in the groups

Position	Lysholm score			*P* value
	3 months	6 months	12 months	
Anatomical	80.91	85.91	89.23	< 0.05
Non-anatomical	58.58	65.13	58.58	

Only two patients from our study had swelling, one patient had a stiff knee and one patient had infection. The patients with post-op swelling and stiff knees were managed with physiotherapy and infection was treated with antibiotics.

DISCUSSION

These days, ACL tears are frequent injuries due to rising participation in sports and an increase in traffic accidents. Despite debate over whether ligament restoration is necessary for all individuals with ACL injuries, arthroscopic surgical reconstruction has emerged as the preferred course of treatment. Restoring knee stability is the main objective of this surgery, which enables the patient to resume a normal range of motion and engage in sports. Restoring normal knee kinematics and avoiding early arthritic alterations are additional goals. For ACL reconstruction, hamstring (semitendinosus and gracilis) tendon autograft is currently the recommended option. The purpose of our study was to compare the functional results of patients undergoing ACL restoration in anatomical footprints and those in non-anatomical footprints.

The mean age of the patients in our study was 28 years, and it ranged from 20 to 55 years. Most of the patients were between the ages of 25 and 35. Nine female patients and thirty-five male patients participated in this study. The prevalence of ACL injuries in men may be explained by the fact that men participate in sports and outdoor activities at higher rates than women. Patients' age ranged from 17 to 48 years, with a mean age of 26.3 years and a median age of 25.0 years, according to a series of studies by Johnson et al. [16]. The majority of the patients in their study were between the ages of 15 and 25, including 23 (92 %) men and two (8 %) girls.

Sports-related injuries accounted for 33 (75 %) and traffic accidents for seven (15.90 %) cases of the injuries in our study. Football and athletic activities were the most prevalent sports-related injuries. The increased participation in sports activities may be the cause of the variation in the manner of injury. Twenty-five individuals with ACL deficit, ages 17–43, with an average age of 25.8 years, participated in a study by X. Li et al. [17]. It discovered that sports accounted for 68 % of the injuries, falls accounted for 24 %, and motor accidents accounted for 8 % of cases.

Thirteen individuals (31.81 %) in our study had left knee involvement, while thirty patients (68.18 %) had right knee involvement. In their study, Tayeb et al. [18] found that left-sided ACL injuries were less common (37.5 %), right-sided injuries accounted for the majority (62.5 %).

ACL tears were the most frequent main diagnosis in our study. Ten instances (22.2 %) had medial meniscus injury, and three cases (6.67 %) had lateral meniscus injury, for a total of thirteen patients (28.89 %) with combined meniscal injury and ACL tear. If a meniscal tear was discovered during surgery, a meniscectomy was carried out. ACL injuries were isolated in the 32 individuals (71.11 %) that remained. In their analysis of 107 patients, Kruger-Franke et al. [19] discovered that ACL ruptures were linked to 45 % of medial meniscus ruptures and 55 % of lateral meniscus tears.

Of 44 patients, 30 had anatomical graft placement (68.18 %), while 14 had non-anatomical graft placement (31.81 %). We used a 3D CT scan to check the post-operative anatomic placement of the reconstructed ACL. Kim et al. [5] and Parker et al. [20] also used a CT scan to check the anatomical placement. Femoral and tibial tunnel length and diameter, femoral diaphyseal angle, tunnel, and tunnel position using the Bernard and Hertel grid (femur) and quadrant method (tibia), as well as coronal and sagittal angles for the tibia, were the methods used for anatomical graft

placement. In 2015, Vermersch et al. [21] did a study on CT assessment of femoral tunnel placement and found 124 femoral tunnels (68.9 %) were in the optimal position and 56 (31.1 %) were not. A radiologic evaluation of the femoral and tibial tunnel placement based on anatomic landmarks in arthroscopic single-bundle anterior cruciate ligament restoration was conducted in 2017 by Nema et al. [22]. Patel et al. [23] conducted a study on the tibial tunnel position of 39 patients using the above parameters and concluded that a CT scan is an imaging modality to study tunnel position after ACL reconstruction.

In our study, we used the Lysholm scoring system functional outcome evaluation. The scores improved from 80.91 at three months to 89.23 at 12 months in the anatomical group, while in the non-anatomical group, they remained the same (58.58) even at 12 months' follow-up. Of 30 patients from the anatomical group, 28 patients showed either excellent or good scores and only two patients had fair and poor scores. This is statistically significant. Wang et al. [24] in their study showed that the Lysholm scoring questionnaire is reliable, valid, and responsible for the evaluation of patients with ACL injuries and it would be an effective evaluation tool. Mashreghi et al. [25] used the Lysholm scoring system for the functional evaluation of ACL reconstruction in 140 operated cases with the hamstring graft.

In our study only two patients had swelling and one patient had a stiff knee which was managed with physiotherapy. One patient developed infection that was managed with antibiotics.

CONCLUSION

This study concludes that the functional outcome after arthroscopic anterior cruciate ligament reconstruction is better when the graft is placed in an anatomical footprint of native ACL for both femoral and tibial tunnels. Also, the functional scores in the anatomical group of patients improved after the surgery and at follow-ups.

Conflict of interest *There is no conflicts of interest.*

Funding *None.*

Ethics approval and consent to participate *The study was approval by the institutional review board (IRB).*

Consent for publication *Consent was taken from all the participants.*

Availability of data and materials *The datasets used in and/or analyzed in the current study are available from the corresponding author upon reasonable request.*

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Comparative analysis of femoro-tibial synostosis results in periprosthetic infection

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Abstract

Introduction Periprosthetic infection (PJI) after total knee arthroplasty remains a serious challenge for orthopedic surgeons and requires radical treatment methods. Femoro-tibial synostosis (FTS) is one of the last salvage operations if revision arthroplasty fails or impossible. However, there is currently no consensus on a rational technology that would provide an optimal anatomical and functional result of surgical rehabilitation.

The **aim** of the work was to analyze clinical outcomes of surgical treatment performing FTS of the knee joint in the patients with PPI using an intramedullary nail (IN) versus the Ilizarov apparatus (IA).

Materials and methods A comparative analysis of 46 patients with PPI who underwent arthrodesis of the knee joint (AKJ) was performed. The patients were divided into two groups depending on the osteosynthesis technology for bone fusion between the femur and tibia: 25 patients in group 1 (IN) and 21 in group 2 (IA). The clinical characteristics of the patients, comorbid background, type of bone defects and microbiological profile were assessed. Statistical analysis of the comparison of functional results, timing of ankylosis, limb shortening, recurrent infections and complications was performed using the Jamovi software (version 2.6.17).

Results The average time of bone fusion was significantly shorter in group 1 (IN), 4.5 months versus seven months in group 2 (IA), $p = 0.027$. Functional results of the groups were comparable ($p = 0.075$). In defects with significant bone loss (AORI type III), patients in group 2 (AI) demonstrated better LEFS indicators ($p = 0.018$). The infection recurrence rate was 13 % in group 1 (IN) and 4.8 % in group 2 (IA), $p = 0.609$. Systemic complications (6.5 %) were detected only in group 1 (IN). Adverse events were considered using the unified classification of complications.

Discussion The obtained results indicate that IN and IA provide comparable treatment efficacy in patients with PPI with differences in the timing of bone fusion and functional indicators in significant bone defects. The increasing prevalence of multiresistant microflora and the frequency of complications require a careful and individual approach to the choice of the FTS technique.

Conclusion The results of the study demonstrate the effectiveness of both techniques: the use of IN contributes to a more rapid bone fusion between the femur and tibia, while IA provides better anatomical and functional results in patients with significant bone loss.

Keywords: femorotibial synostosis, knee arthrodesis, periprosthetic infection, intramedullary nail, Ilizarov apparatus, clinical outcome, recurrent infection, arthrodesis complications

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INTRODUCTION

Femorotibial synostosis (FTS) in periprosthetic infection (PJI) remains one of the most controversial and demanded salvage operations nowadays. Despite significant progress in the field of joint arthroplasty and improvement of algorithms for the prevention of infectious complications, the development of PJI after primary total knee arthroplasty remains a significant problem. According to current literature data, the incidence of PJI after primary total knee arthroplasty ranges from 0.2 % to 2 %, and after revision interventions reaches 28 % [1]. Moreover, the risk of recurrent infection increases with each sanitizing operation, significantly affecting the quality of life of patients and increasing the medical and social burden on the society [2].

The current treatment tactics for PJI, proposed by A.F. Chen, include long-term use of antibacterial therapy, surgical treatment with retention of the implant or one-/two-stage revision arthroplasty, along with salvage operations of joint arthrodesis, resection arthroplasty and limb amputation [3]. Two-stage revision arthroplasty with a cement spacer impregnated with antibiotics is recognized as the “gold standard”. This approach, first described by Insall et al. [4], allows for eradication of infection in 88–96 % of cases [5, 6].

In clinical practice, one can encounter a situation in which revision arthroplasty cannot be performed. The reasons for this are total and subtotal defects of the bones that form the knee joint, severe insufficiency or absence of the knee joint extensor apparatus, as well as the presence of multi-resistant microflora causing chronic bone infection with persistent relapses and fistula formation. The combination of the listed above complications in the outcome of arthroplasty is called the "terrible triad" in the literature [7].

Over the past 15 years, the overall rate of arthrodesis operations on the knee joint for PJI has been 0.26 % [8]. However, as noted by domestic authors, the number of such interventions tends to increase [9].

A comparative assessment of the outcomes of salvage operations shows that, despite the remaining risks, arthrodesis of the knee joint allows for more favorable functional results and early rehabilitation compared with amputation, providing patients with not only the ability to self-care, but also socialization. According to a systematic review of Low et al., 86.4 % of patients after FTS retain the ability to move independently and take care of themselves, while the rate is only 54.4 % after limb amputation [10].

Among the known arthrodesis techniques in knee joint PJI, the most widely used methods use are arthrodesis with an intramedullary nail (IN) or the Ilizarov apparatus (IA). The use of bone plates in modern practice is limited due to ambiguous results, a high rate of infection recurrence, and the need for long-term immobilization [11, 12]. However, despite the widespread use of IN and IA, data on the comparative effectiveness of these approaches are scattered and often based on the analysis of limited series of cases. In the domestic literature, there is no comprehensive comparison of clinical outcomes, infection recurrence, and complications after the use of these techniques for PJI, which determines the relevance and scientific novelty of this study.

Purpose The aim of the work was to analyze clinical outcomes of surgical FTS of the knee joint in the patients with PPI using an intramedullary nail (IN) versus the Ilizarov apparatus (IA).

MATERIAL AND METHODS

The study included patients who were treated at the Hospital for War Veterans (Ekaterinburg) in the period from 2016 throughout 2024. Analysis of the results and surgical treatment were performed by one surgical team of researchers.

Inclusion criteria:

— Patients with knee joint PJI in who revision arthroplasty was impossible to perform;

— Patients who underwent two-stage revision knee arthroplasty for PJI and develop infection recurrence;

— Patients who had not fewer that two debridement operations due to PJI;

— Defects of the bones forming the knee joint;

— Detection of multi-resistant microflora according to microbiological tests (MBT);

— Insufficiency/absence of the extensor apparatus of the knee joint (including the patella).

Exclusion criteria:

— FTS operation for other etiological reasons (post-traumatic, osteomyelitic);

— Uncontrolled course of the infectious process, leading to amputation of the limb;

— FTS operation involving various options of bone grafting;

— Conversion to the methods for performing bone transport and reducing limb shortening during synostosis.

Exclusion criterion: rejection of patients to be included in the study.

A total of 46 patients who underwent FTS for PJI after total knee arthroplasty were included in the study: group 1 (IN) of 25 patients, group 2 (IA) of 21 patients. Group 1 (IN) included 12 patients studied prospectively and 13 retrospectively. Group 2 (IA) was formed on the retrospective basis.

The proportion of women in the study sample was 67.4 % (n = 31) and of men 32.6 % (n = 15). The average age of women was (70.2 ± 9.37) years and of men (63.7 ± 14.53) years. The average body mass index (BMI) of patients for both groups was (28.7 ± 3.99) kg/m^2.

Baseline characteristics of patients in the compared groups

The distribution of patients according to the ASA (American Society of Anesthesiologists Physical Status Classification) comorbidity criteria [13], types of infection according to Tsukayama [14] and bone defects according to AORI (Anderson Orthopaedic Research Institute) [15] in both groups is presented in Table 1. The groups were comparable in terms of age, gender and clinical characteristics (p > 0.05).

The time interval from the primary knee joint arthroplasty to the PJI manifestation in both groups was two years (IQR = 1–5; p = 0.821). The duration of the infectious process (including relapses and remissions) in group 1 (IN) averaged three years (IQR = 2–4), and in group 2 (IAI) four years (IQR = 3–4; p = 0.474). The median number of surgical interventions on the studied segment before arthrodesis was 4 (IQR = 3–6) in group 1 (IN) and 4 (IQR = 3–5) in group 2 (IA) (p = 0.659).

The majority of patients in both groups had moderate-sized type II knee joint defects (F2A/T2A and F2B/F2B according to the AORI classification), 23.9 % and 26.0 %, respectively (p = 0.655). Large-sized type III defects (F3/T3) were detected in 19.6 % (n = 9) of patients in group 1 (IN) and in 8.7 % (n = 4) of patients in group 2 (IA) (p=0.346). Late chronic and acute hematogenous types of PJI (according to the Tsukayama classification) prevailed in both groups; no statistically significant differences were found between the groups (p = 0.921). In both groups, the somatically burdened category of patients of ASA class III with several severe concomitant diseases, including those in the decompensation stage, prevailed: 26.1 % (n = 12) in group 1 (IN) and 21.7 % (n = 10) in group 2 (IA); the differences did not reach statistically significant difference (p = 0.812).

Table 1

Distribution of patients according to classification criteria

Parameters		Group 1 (IN), *n* = 25	Group 2 (IA), *n* = 21	*p*-value
ASA				
I	N	1	2	0,812
	%	2.2	4.3	
II	N	12	9	
	%	26.1	19.6	
III	N	12	10	
	%	26.1	21.7	
Time from TKA to PJI onset, years (Me [IQR])		2 [1–5]	2 [1–5]	0.821
PJI duration, years (Me [IQR])		3 [2–4]	4 [3–4]	0.474
Number of debridement operations (Me [IQR])		4 [3–6]	4 [3–5]	0.659
PJI type (Tsukayama)				
I type (acute postoperative)	N	2	3	0.921
	%	4.35	6.52	
II type (late chronic)	N	9	7	
	%	19.57	15.22	
III type (acute hematogenous)	N	9	8	
	%	19.57	17.39	
IV type (intraoperative culture)	N	5	3	
	%	10.87	6.52	
AORI defects types				
I type (F1/T1)	N	5	5	0.655
	%	10.87	10.87	
II type (F2A/T2A)	N	5	6	
	%	10.87	13.04	
II type (F2B/T2B)	N	6	6	
	%	13.04	13.04	
III type (F3/T3)	N	9	4	
	%	19.57	8.70	

Notes: M — mean value; SD — standard deviation; Me — median; IQR — interquatile range; ASA — American Society of Anesthesiologists Physical Status Classification; TKA — total knee artthroplasty; Tsukayama classification of periprosthetic infection; AORI — classification of defects of the bones forming the knee joint

The patients underwent standard examination procedure: clinical, laboratory, radiological and microbiological studies to confirm the infectious process and clarify the nature of its course. Two weeks before hospitalization, patients of group 1 (IN) took CT (Siemens SOMATOM, Germany) of the lower extremities for planning and ordering an individual long femoral rod (CITO, Russia). It is worth noting that all patients had undergone previous two-stage revision arthroplasty before arthrodesis surgery.

The surgical field was treated with the patient in the supine position. If a fistula was present, a coloring indicator (brilliant green solution with 3 % hydrogen peroxide) was introduced into its canal to determine the affected bone areas and to detect hidden leaks. Surgical approach was performed along the previous postoperative scar with its excision. Whenever possible, the components of the cement spacer were removed in a minimally invasive manner. Tissue biopsy samples were collected for microbiological and histological studies. Then, radical surgical treatment of the infection site within healthy tissues was performed, and intramedullary canals were opened.

The external fixation device was sequentially mounted on the femur and tibia in a wire or hybrid (wire/half-pin) version for performing arthrodesis using the Ilizarov method. The number of external supports depended on the size of the bone defect and the contact area of the femoral and tibial

ends. For small defects (AORI type I), three ring were mounted; for larger, asymmetrical or subtotal defects (AORI types II and III), four rings were mounted.

In case of using an intramedullary rod for knee arthrodesis, the entry point at the level of the pyriform fossa was formed retrograde using a titanium reamer, and the intramedullary rod was inserted in an antegrade manner [16]. After distal locking, the rod was reversely pinned until the ends of the femur and tibia fragments were in full contact. Proximal locking was performed using a dynamic scheme with one screw for small defect sizes (AORI type I) and good contact of the surfaces, or using a static scheme with the possibility of dynamization with two screws for large defects (AORI types II and III). Active drainage was installed. The wound was sutured layer by layer.

In the postoperative period, all patients received antibacterial therapy. If bacteriological cultures and identification of the pathogen at the previous stages of treatment were availavle, it was etiotropic, if there were none it was empirical (Vancomycin + Cefoperazone/sulbactam). Based on the results of MBT of intraoperative material, antimicrobial (antibacterial or antifungal) therapy was adjusted. Patients also received anti-inflammatory, analgesic, symptomatic and vascular therapy. Dressings were changed once every two days. Drains were removed on the second to fourth day. Sutures were removed on the 14th to 16th day. Training under the guidance of a physical therapy specialist was initiated on the second day after surgery.

Supportive compression was applied at the junction of the fragments with the Ilizarov apparatus, which was maintained throughout the period of external fixation. All patients were supervised up by traumatologists at their place of residence and were invited for a follow-up once every two to three months until the appearance of radiographic signs of bone fusion between the femur and tibia. In slow formation of bone callus, interfragmentary compression with the Ilizarov apparatus was enhanced.

In the static intramedullary nail locking, the patient was hospitalized after two to three months for nail dynamization. Upon achieving bone fusion, a clinical test for bone fusion strength (lack of mobility) was performed in hospital conditions, after which the fixator was dismantled. In none of the cases was the nail removed upon achieving bone ankylosis. The shortening of the limb was compensated by orthopedic footwear. Subsequently, patients were called for a control follow-up to assess the results of dynamic observation at long term.

The functional outcome was assessed using the Lower Extremity Functional Scale (LEFS) questionnaire four to six months after surgery (upon achieveing ankylosis). A score of less than 19 points was considered minimal or no function; 20–39 points was significant limitation of function; 40–59 points was moderate limitation, 60–79 points means minor limitation. A score of 80 points was considered the maximum and full function [17].

Limb shortening was determined using a tape measure at the final follow-up in comparison with the contralateral limb. The endpoint for determining the FTS period was bone fusion in radiographs, clinical test adequacy for group 2 (IA), and full weight-bearing walking on the affected limb for both groups of patients.

At present, there is no classification standardizing the recording of complications for both methods. In this regard, we propose a unified classification for recording and analyzing complications after FTS surgery:

— **Category 0. No complications:**

- ✦ none.

— **Category 1. Mild complications**:

- ✦ 1.1 mild contractures in the adjacent joints;
- ✦ 1.2 mild soft-tissue inflammation (treated conservatively);

- ✦ 1.3 mild residual deformities that do not impair functions;
- ✦ 1.4 traction neuropathy (treated conservatively).

— **Category 2. Complications that require additional procedures that did not worsen the outcomes**:

- ✦ 2.1 soft-tissue inflammation that required repeated interventions;
- ✦ 2.2 fractures at the regeneration level that are eliminated conservatively or minimal invasively;
- ✦ 2.3 subluxation/contractures of moderate severity that require interventions;
- ✦ 2.4 instability of the fixation elements that require intervention.

— **Category 3. Significant complications that affect the outcome**:

- ✦ 3.1 ankylosis failure/fracture of the regenerate;
- ✦ 3.2 re-infection;
- ✦ 3.3 severe contractures that restrict functions;
- ✦ 3.4 persistent neurological disorders in the limb;
- ✦ 3.5 metal implant or fixation failure.

— **Category 4. Systemic complications:**

- ✦ 4.1 pulmonary embolism;
- ✦ 4.2 fatty embolism;
- ✦ 4.3 acute cerebrovascular accident;
- ✦ 4.4 other systemic complications.

— **Category 5. Other complications:**

- ✦ 5.0 other complications, not included in the classification.

It is important to note that during the study, the clinical outcome data of two patients in Group 1 (IN) were not taken into account due to their death in the early postoperative period and were designated as NA (not available). However, these cases were included in the analysis of postoperative complications, which allowed us to estimate the overall frequency of critical events associated with the method. The exclusion of functional indicators is due to the impossibility of their assessment, but the inclusion of deaths in the complications section ensures the completeness of the data and transparency of the methodology.

The study was approved by the local ethics committee of the War Veterans Hospital (Ekaterinburg, protocol dated 14.12.2023 No. 12/2023) and was conducted in accordance with the 1975 Helsinki Declaration (revised 2008). All patients gave written informed consent to participate in the study and publish the data. There is no detailed information that would help to personalize the patients included in the study.

Statistical analysis was performed using Jamovi software (version 2.6.17, Australia) and Microsoft Excel (version 16.75.2, USA). The mean and standard deviation (M ± SD) were used to describe quantitative data with a normal distribution, and the median and interquartile range (IQR) corresponding to the lower (Q1) and upper (Q3) quartiles (Me [IQR]) were used for non-normal data. The normality of data distribution was tested using the Shapiro–Wilk test. Categorical data were described by indicating absolute values and percentages (n, %). Comparison of groups by a quantitative indicator with a normal data distribution was performed using Student's t-test or the Mann–Whitney U-test for a non-normal distribution. Analysis of qualitative (nominal) features was performed using Pearson's χ^2 test (with expected values in each cell greater than 5) or Fisher's exact test (with expected values in each cell less than 5). Statistical significance of differences between groups was accepted at $p < 0.05$.

RESULTS

Functional parameters, limb shortening and terms of bone fusion

The functional indices according to the LEFS scale in group 2 (IA) were (38.3 ± 5.9) %, while in group 1 (IN) they were (34.4 ± 8.1) % ($p = 0.075$), and indicate comparable functional efficiency of the methods.

In type III defects, significant differences in functional indices were revealed according to AORI: in group 2 (IA), the average LEFS value was (31.56 ± 2.14) %, while in group 1 (IN) it was (25.71 ± 2.69) % ($p = 0.018$), which indicates better functional results with the use of the Ilizarov apparatus in significant bone defects (Fig. 1).

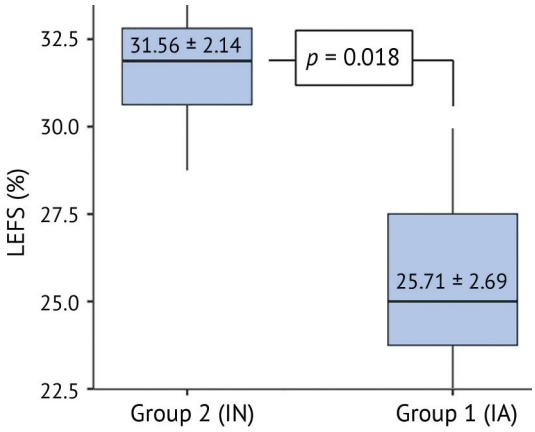

Fig. 1 Comparison of functional indices (LEFS, %) between the groups in type III bone defects

The median of limb shortening in group 1 (IN) was 4.0 cm (IQR = 3.0–5.0), in group 2 (IA) 3.0 cm (IQR = 3.0–4.0). The differences are not statistically significant ($p = 0.338$), indicating a comparable effect of the methods on limb length.

Statistically significant differences were found in the timing of knee joint ankylosis: in group 2 (AI), the median term was 7 months (IQR = 6.0–8.0), in group 1 (IN) the median was 4.5 months (IQR = 3.5–7.5; $p = 0.027$), indicating a more rapid bone fusion with the use of intramedullary rods.

Microbiological profile of infection agents and infection recurrence analysis

Recurrence of infection was recorded in three (13 %) patients of group 1 (IN) and in one (4.8 %) patient of group 2 (IA). No statistical difference was found between the groups ($p = 0.609$), indicating the absence of a significant effect of the fixation method on re-infection (Fig. 2).

Microbiological analysis revealed prevalence o gram-positive microorganisms, 54.3 % ($n = 25$), while gram-negative bacteria accounted for 34.8 % ($n = 16$). In 8.7 % ($n = 4$) of cases, microbial associations were detected, and fungal flora was encountered also, 2 % ($n = 1$). The most common pathogen was *Staphylococcus aureus*, detected in 32.6 % of cases ($n = 15$). *Pseudomonas aeruginosa* was found in 10.9 % ($n = 5$), *Enterococcus faecalis*, MRSA, *Enterobacter cloacae* and other microorganisms were detected altogether in no more than 8.7 % of cases (Fig. 3).

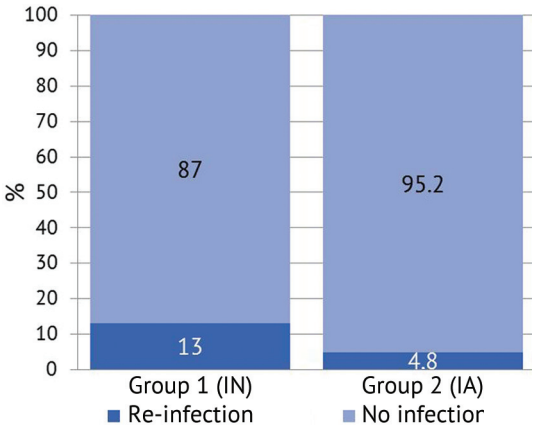

Fig. 2 Rates of re-infection in the groups

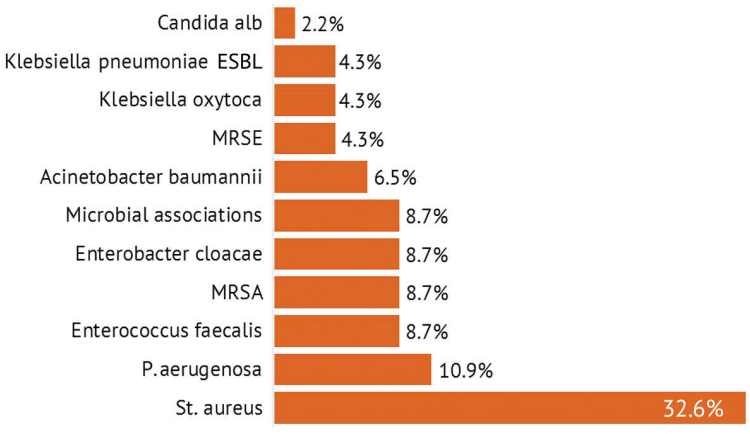

Fig. 3 Rates of PJI agents encountered in the whole sample

Complications

Complications in the compared groups according to the unified classification and analysis of FTS complications are presented in Table 2.

Table 2

Complications encountered in the studied groups

Category / Subcategorуя	Group 1 (IN)		Group 2 (IA)	
	n	%	*n*	%
Category 0. No complications				
0.0 none	15	32.6	11	23.9
Category 1. Mild complications:	1	2.2	5	10.9
1.1 mild contractures in the adjacent joints	NA		NA	
1.2 mild soft-tissue inflammation (treated conservatively)	0	0	5	10.9
1.3 mild residual deformities that do not impair functions	NA		NA	
1.4 traction neuropathy (treated conservatively)	1	2.2	0	0
Category 2. Complications that require additional procedures that did not worsen the outcomes:	1	2.2	2	4.3
2.1 soft-tissue inflammation that required repeated interventions	0	0	1	2.2
2.2 fractures at the regeneration level that are eliminated conservatively or minimal invasively	NA		NA	
2.3 subluxation/contractures of moderate severity that require interventions	NA		NA	
2.4 instability of the fixation elements that require intervention	1	2.2	1	2.2
Category 3. Significant complications that affect the outcome:	5	10.9	3	6.5
3.1 ankylosis failure/fracture of the regenerate	0	0	2	4.3
3.2 re-infection;	3	6.5	1	2.2
3.3 severe contractures that restrict functions	NA		NA	
3.4 persistent neurological disorders in the limb	NA		NA	
3.5 metal implant or fixation failure	2	4.3	0	0
Category 4. Systemic complications:	3	6.5	0	0
4.1 pulmonary embolism	2	4.3	0	0
4.2 fatty embolism	NA		NA	
4.3 acute cerebrovascular accident	1	2.2	0	0
4.4 other systemic complications	NA		NA	
Category 5. ПОther complications:				
5.0 other complications, not included in the classification	0	0	0	0
p-value	0.022			

Note: NA — not available; differences are considered significant at $p < 0.05$ (очный тест Фишера).

Category 1 complications that did not affect the treatment outcome were observed mainly in group 2 (IA) and were 10.9 % ($n = 5$) compared to 2.2 % ($n = 1$) in group 1 (IN).

Complications that required additional interventions (category 2) were recorded in 4.3 % ($n = 2$) of patients in group 2 (IA) and in 2.2 % ($n = 1$) in group 1 (IN).

Significant complications (category 3) that had a negative impact on the treatment outcome were noted in 10.9 % ($n = 5$) of patients in group 1 (IN) and in 6.5 % ($n = 3$) of patients in group 2 (IA).

Systemic complications (category 4) were registered only in group 1 (IN) and were 6.5 % ($n = 3$), including two fatal outcomes caused by pulmonary embolism (category 4.1) and one case of acute cerebrovascular accident (category 4.3). In group 2 (IA) systemic complications were not recoreded.

Statistical analysis revealed significant differences between the groups ($p = 0.022$), indicating the influence of the chosen method on the rate and nature of complications (Fig. 4).

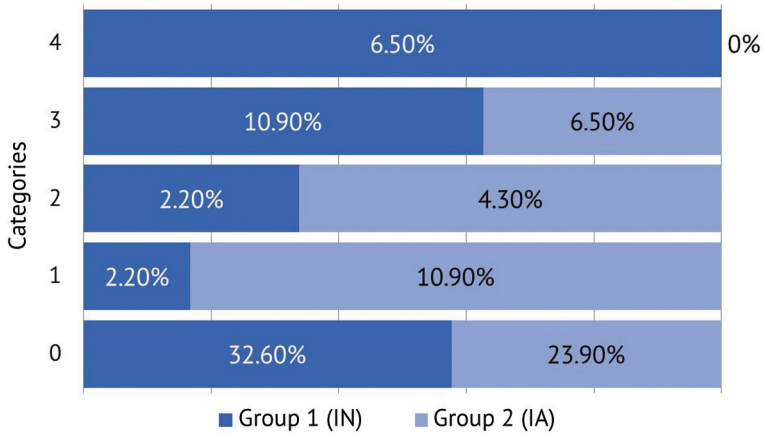

Fig. 4 Diagram of complications according to categories

DISCUSSION

The authors of this work opine that there is a certain terminological ambiguity in the designation of surgical intervention aimed at creating a fixed knee joint by fusion of articulating surfaces. Traditionally, such an operation is called "arthrodesis of the joint", and in English-language sources one can find the names "knee fusion" and "knee arthrodesis". From our point of view, the term used is not fully suitable for designating the surgical technology and reflecting the anatomical and functional picture observed in failures of total arthroplasty in the conditions of purulent infection. Anatomical and functional changes are represented by a tissue defect formed after resection of the articular ends, sequestered areas of the epimetaphyseal zone, an unstable implant and, in fact, the absence of the joint [18]. We believe that a more suitable formulation of the goal of surgical intervention is to achieve consolidation (synostosis) between two long bones, which is more correctly characterized by the term “femorotibial synostosis” (FTS).

Functional outcomes after knee arthrodesis should be assessed based on the function of the entire lower limb and its weight-bearing capacity as a whole. It is equally important to consider the patient’s quality of life. Separate assessment of knee joint function is inappropriate due to the joint being locked in a functionally advantageous position. Authors of other studies use different versions of questionnaires: SF-12 [19], SF-36 [16], WOMAC [20], KSS [21, 22]. Some authors assess the weight-bearing capacity of the limb, lameness, and pain syndrome [23]. However, this approach does not reflect the patient’s quality of life after surgery. Functional outcomes should also include assessment of the level of daily activity and quality of life. In our opinion, the LEFS questionnaire meets the stated requirements for assessing functional outcomes after knee arthrodesis. In the literature, we found only one study whose authors used the LEFS questionnaire to determine the functional outcomes of knee arthrodesis. The work of Zajonz et al. reported the median LEFS of 26 % (IQR = 15–51) in a small sample of 25 patients operated on using an intramedullary nail [24]. In our study, the average LEFS in Group 1 (IN) was (34.4 ± 8.1) %. We did not find any targeted studies assessing limb function with LEFS (%) after knee arthrodesis implemented with the Ilizarov apparatus. Analysis of functional outcomes according to the LEFS scale showed comparable results in regard to significant limitation of function after both methods (p = 0.075); however, in AORI type III defects, the Ilizarov apparatus method demonstrates statistically significant advantages. The obtained data indicate that it is precisely in the case of large bone defects that the use of IA provides a better functional outcome: (31.56 ± 2.14) points in group 2 (IA) versus (25.71 ± 2.69) points in group 1 (IN), p = 0.018.

Based on these results, we recommend the Ilizarov apparatus for patients with large bone defects (AORI type III). Further studies using standardized instruments for assessing the functional knee arthrodesis results based on uniform questionnaires and scales are probably needed. Such an approach would provide more objective and comparable data, deepen the understanding of the impact of different techniques on the functional status and quality of life of patients, and would contribute to the development of clearer and more substantiated recommendations for clinical practice.

An important factor that has an impact on the patient's functional results and quality of life after knee arthrodesis is residual shortening of the limb. Specialists involved in joint arthroplasty and reconstruction of long bones consider limb discrepancy of up to 2 cm to be acceptable, having no significant impact on quality of life and not requiring the use of additional support [25]. However, in practice, even such a shortening can affect the patient's walking and daily life. It should also be considered that equal leg length after knee joint fusion does not always provide comfort and can create inconvenience for the patient. Residual shortening depends on the size and nature of the defects in the bones that form the knee joint. Each sanitizing operation aimed at eliminating the source of infection is associated with osteonecrectomy and, as a consequence, bone loss. For producing arthrodesis of the knee joint, it is necessary to achieve the maximum contact area of the ends of the fragments by means of modeling resection. It also reduces the length of the lower limb. The timing of bone fusion directly affects the functional results and the possibility of rapid rehabilitation of the patient. However, methods that provide faster ankylosis may be accompanied by increased shortening of the limb [12], which requires a balanced approach when choosing treatment tactics and consider both the timing of bone fusion and the possible consequences of residual shortening.

We found that the time to achieve a bone fusion had significant differences and depended on the surgical technology used. In the group of an intramedullary rod, bone fusion occurred faster due to periosteal hyperplastic bone formation (median 4.5 months) compared to the Ilizarov apparatus (median 7 months), $p = 0.027$. These data demonstrate the advantage of the IN method in terms of bone fusion formation time in type I and II defects according to the AORI classification. In addition, the use of the IN method reduces the burden on outpatient medical services, minimizes the need for regular dressings and significantly facilitates patients care and self-care, improving their quality of life. The results obtained in our study correlate with the findings of Balato et al., presented in a large meta-analysis that included 26 studies and 422 patients [26]. The authors note that the duration of knee joint ankylosis formation was statistically significantly shorter ($p = 0.031$) with the use of an intramedullary rod, 5.78 months (IQR = 3.6–8.0) compared to 7.19 months with the Ilizarov apparatus (IQR = 6.3–10.3). The average limb shortening in the IN group was (2.4 ± 1.5) cm, while in the IA group it was (4.0 ± 0.7) cm ($p = 0.005$), indicating a significant impact of the chosen method on the magnitude of residual shortening. It should be emphasized that in the aforementioned meta-analysis, the IN group included modular implants capable of compensating for limb shortening within 2–4 cm, but not providing the formation of bone ankylosis. This circumstance explains the statistically lower shortening rates in the IN group. A similar tendency is reflected in other foreign publications studying the use of modular intramedullary implants for knee arthrodesis [27, 28].

However, we believe that the FTS technique itself is not a determining factor in residual limb shortening. This statement is confirmed by the results of our study, where the median limb shortening in group 1 (IN) was 4.0 cm (IQR = 3.0–5.0), and in group 2 (IA) it was 3.0 cm (IQR = 3.0–4.0), while no statistical differences were found between the groups ($p = 0.338$). Thus, the effect of the techniques used on the limb length can be considered comparable. The issue of eliminating the difference in the length of the lower limbs to improve the functional results and quality of life of patients remains relevant. Of course, the priority in equalizing the length of the limbs is the use of Ilizarov transosseous distraction osteosynthesis technologies.

Recurrent infection is one of the key problems in lower limb reconstruction. One of the most important mutual expectations of the doctor and the patient when deciding on knee arthrodesis is complete suppression of the infection focus and elimination of the risks of recurrence. The following factors are known to influence the success of infection eradication: radical surgical debridement, restoration of the osseous integrity the limb, and targeted antimicrobial therapy. Radicality of the surgical debridement of the infection focus is a key factor not only in the treatment of patients with PJI, but also in the prevention of recurrent infection [29]. There is no clear opinion in the literature on which of the arthrodesis techniques is most effective in preventing recurrent infection. In this context, a thorough analysis of the microbial landscape is especially important.

The increase in the multiresistant microflora and its widespread worldwide significantly affect the choice of antibacterial drugs, complicating the selection of effective therapy and increasing the risk of recurrent infection. Moreover, some gram-negative pathogens, in particular *P. aeruginosa*, *K. pneumoniae* and *A. baumannii*, are associated with a mortality risk of up to 10 % [30].

The data of domestic authors reflect the high level of complexity of managing PJI requiring arthrodesis of the knee joint. Thus, Prokhorenko et al. reported that the use of the Ilizarov apparatus in 34 patients provided persistent relief of infection in 85.29 % of cases, respectively, relapse of infection was observed in 14–15 % [31]. Aother study of Klyushin et al. reported 27 % (n = 17) of relapses of infection during arthrodesis using the Ilizarov apparatus in a sample of 63 patients. The authors also noted the dominance of gram-positive microflora (68 %, n = 43), where the most common pathogen was *Staphylococcus aureus* (n = 32/64) [32]. In our study, recurrence of infection was observed in three (13 %) patients in group 1 (IN) and in one (4.8 %) patient in group 2 (IA), but these differences were not statistically significant (p = 0.609), indicating comparable effectiveness of both methods in infection arrest. Moreover, in our sample, and consistent with the literature, the most frequently detected pathogen was *Staphylococcus aureus*, 32.6 % of cases (n = 15). These findings are supported by the meta-analysis of White et al., including 12 original studies (a total of 456 patients), which did not reveal statistically significant differences in the rates of infection recurrence between the intramedullary nail and the Ilizarov apparatus groups (OR = 0.91; 95 % CI: 0.38–2.15; p = 0.83) [33]. In recurrent infection cases, we performed another debridement of the infection focus and re-arthrodesis. For patients in group 1 (IN), the intramedullary rod was removed and treated in an ultrasonic bath, then re-installed. In group 2 (IA), partial reassembly of the fixator and change of transosseous elements was performed. It should be noted that in this clinical sample we did not perform conversion of osteosynthesis methods.

The most popular and practically applicable classification of complications is the one developed by D. Paley. It clearly distinguishes between the concepts of “a problem”, “an obstacle” and “a complication”. It is widely used in assessing the outcomes of transosseous osteosynthesis with the Ilizarov apparatus in limb reconstruction [34]. There is currently no similar standardized system for assessing complications after knee arthrodesis with the use of intramedullary fixation. In the available literature, complications associated with the techniques of intramedullary nailing and the Ilizarov external fixation are considered separately [16], which complicates a comprehensive analysis of the differences in adverse events associated with bone fusion in PJI. Based on the interpretation of the above concepts by D. Paley, we have developed a unified classification of complications that covers all negative outcomes of both techniques. For ease of analysis, complications are divided into categories and detailed in subcategories. It allows for a more complete and structured evaluation of the problems that arise (Table 2).

The highest number of complications that did not have impact on the outcome of surgical rehabilitation (categories 1 and 2) were recorded in group 2 (15.2 %, n = 7), they are associated mainly with inflammation of the soft tissues in the area of the transosseous elements. The inflammatory process was stopped with local injections of antibiotics in soft tissues and dressings with Levomekol, and in case of persistent wire-tract infection with re-insertion of the fixation elements. It is also worth noting a case of postoperative neuropathy of the peroneal nerve in group 1 (IN), which resolved within 30 days with measures of neurotropic therapy and soft tissue edema subsided. Similar results are presented in the work of Leroux et al., where two cases (13.3 %) ended with complete recovery of sensitivity within six months after surgery [35].

More severe complications that affect the treatment outcome (categories 3 and 4) were more common in group 1 (IN), 10.9 % (n = 5). Thus, two cases (4.3 %) of intramedullary nail failure required repeated surgical intervention, nail removal followed by re-arthrodesis using the same technique but with a nail of a larger diameter nail. Group 2 (IA) patients had fractures at the level of femorotibial synostosis (4.3 %, n = 2), although the test for bone fusion was positive but refractures occurred within two to three weeks after dismantling the Ilizarov apparatus. In both cases, repeated hospitalization

and re-osteosynthesis were required. Bruno et al. encountered a similar problem. Two of 15 patients had a fracture in the synostosis zone after dismantling the external fixator. The authors implemented external immobilization of the limb until complete bone fusion [15]. Systemic complications were noted in three cases (6.5 %) in the intramedullary nail group, two of them resulted in death. The events may indicate a potentially higher risk of critical outcomes with this technique.

Limitations of the study

This study has several limitations. First, there was no randomization and blinding of either patients or surgeons making the decision on the choice of the FTS technique. Second, the sample of patients was relatively small. It should be clarified that knee arthrodesis in PJI is an exceptional and rarely used, rather than routine, intervention. Finally, the exclusion of two patients in Group 1 (IN) from the analysis of clinical outcomes due to death in the early postoperative period limits the completeness of the result assessment in this group, but their inclusion in the analysis of complications reduces the risk of systematic error and allows for a more objective assessment of the safety of the method.

CONCLUSION

Femorotibial synostosis in patients with PJI remains the only possible operation that provides acceptable anatomical and functional results of surgical rehabilitation and stable arrest of infection. The results of treatment of patients with PJI show that the terms of bone fusion with an intramedullary rod were shorter. The best anatomical and functional results were recorded in patients with subtotal and total bone defects treated with external fixation. Analysis of the infection recurrence did not reveal a statistically significant difference between the groups. The rates and nature of complications differed significantly between the groups, while systemic complications were observed only in the intramedullary fixation group.

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Ethical statement *The study was approved by the local ethics committee of the War Veterans Hospital (Ekaterinburg, protocol dated 12/14/2023 No. 12/2023).*

Informed consent *All patients gave written informed consent to participate in the study and publish the data. There is no detailed information that would help to personalize the patients included in the study.*

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Antibiotic therapy for orthopedic infections caused by gram-negative pathogens over a 12-year observation period

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Abstract

Introduction Treatment of patients with orthopedic infection includes a combination of the optimal surgical debridement and adequate antibacterial therapy. Gram-negative bacteria are encountered in 13–28 % of orthopedic infections, and *A. baumannii, K. pneumoniae, P. aeruginosa* are significant bacteria notorious for its high and intrinsic antibiotic resistance and can be associated with worse outcomes.

The **objective** was to substantiate the choice of drug for targeted empirical and etiotropic antibacterial therapy based on the analysis of antibiotic resistance in leading gram-negative bacteria (*A. baumannii, K. pneumoniae, P. aeruginosa*) isolated from patients with orthopedic infection.

Material and methods Antibiotic sensitivity of leading Gram(–) microorganisms isolated from patients with orthopedic infection was retrospectively examined between 01.01.2011 and 31.12.2022. The average frequency of isolated resistant strains was examined and resistance trends of leading Gram(–) pathogens to various antimicrobialbacterial drugs (fluoroquinolones, co-trimoxazole, cephalosporins, carbapenems, monobactams, aminoglycosides, fosfomycin, colistin) determined.

Results Over a 12-year period, statistically significant trends were revealed towards an increase in the proportion of *A. baumannii* strains resistant to ciprofloxacin ($p = 0.024$) and levofloxacin ($p = 0.012$), and *P. aeruginosa* ($p = 0.018$) and *K. pneumoniae* ($p = 0.018$) strains resistant to ciprofloxacin. The predicted proportion of *A. baumannii* strains resistant to fluoroquinolones tends to 100 %. There was a significant increase in *A. baumannii* and *P. aeruginosa* strains resistant to cefoperazone+[sulbactam] ($p = 0.027$ and $p = 0.010$, respectively), *K. pneumoniae* strains resistant to meropenem and imipenem ($p = 0.037$ and $p = 0.003$, respectively), and *P. aeruginosa* strains resistant to imipenem ($p = 0.001$). No statistically significant trends were found for the remaining antibiotics; drug resistance of the pathogens remained stable or had a wave-like course over the 12-year period. Cefoperazone+[sulbactam] was the optimal drug active against Gram(–) bacteria.

Discussion There is an authoritative list of antimicrobiall drugs active against *A. baumannii, K. pneumoniae, P. aeruginosa* strains, mainly containing drugs for parenteral administration. The list is limited to one or two groups for resistant strains, and there are no drugs available in oral form. This causes difficulties in the infection control and a high rate of relapses. The negative dynamics in increasing antibiotic resistance of leading Gram(–) pathogens to fluoroquinolones, cephalosporins and carbapenems is a global problem necessitating the use of reserve antibiotics.

Conclusion Protected cephalosporin is more practical for targeted empirical initial antimicrobial therapy due to the lower risk of selected resistant strains. Fluoroquinolones and carbapenems can be used with the sensitivity known. Polymyxin B and fosfomycin should be considered as reserve drugs for the treatment of infections caused by strains resistant to other AB, and prescribed as part of combination therapy. Aminoglycosides and unprotected cephalosporins can be an alternative due to the pharmacokinetic characteristics and high level of resistance when more active drugs cannot be administered.

Keywords: implant-associated infection, orthopedic infection, periprosthetic joint infection, *Pseudomonas aeruginosa, Klebsiella pneumoniae, Acinetobacter baumannii*, antibacterial therapy, antibiotic resistance, empirical therapy, etiotropic therapy

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INTRODUCTION

Peri-implant joint infections are among the most severe complications of musculoskeletal surgeries [1]. Gram(+) bacteria *S. aureus* and *S. epidermidis* are common pathogens causing orthopedic infections (OI), and gram-negative bacteria are encountered in 13–28 % [2, 3]. There may be specific local prevalence of the pathogens; microorganisms are reported to be as high as 61 % in some countries [4]. Gram-negative aerobes being most frequently isolated are the *Enterobacteriaceae* family (*K. pneumoniae* and E. coli) and non-fermenting bacteria (*P. aeruginosa, A. baumannii*).

Gram(–) bacteria *K. pneumoniae, P. aeruginosa* and *A. baumannii* are a group of common pathogens with documented critical and severe levels of antibiotic resistance designated as ESKAPE pathogens by the Infectious Diseases Society of America. Resistance to fluoroquinolones (FQ) antibiotics including cephalosporins (CS) and carbapenems (CP), which have traditionally been considered the drugs of choice, is a significant problem.

The involvement of Gram(–) bacteria in the etiology of implant-associated infection (IAI) is a poor prognostic sign. Relapses of the infections caused by Gram(–) bacteria are recorded in 50–60 % of patients with IAI during the first two years after debridement surgery [5, 6]. Researchers suggest a direct correlation between the antibiotic resistance of bacteria isolated from patients and the frequency of adverse outcomes [7]. The data substantiate the need for continuous local monitoring of the sensitivity of the microorganisms to antibacterial drugs to facilitate review of the options for initial empirical and etiotropic antibiotic therapy in hospital and at the outpatient stage.

Fluoroquinolones, unprotected and protected cephalosporins of the third and fourth generations, carbapenems, monobactams, aminoglycosides, fosfomycin, colistin and co-trimoxazole atr the main drugs with the spectrum of action including Gram(–) bacteria. The practical use of drugs of the groups has advantages and disadvantages, which will be discussed in this paper.

The **objective** was to substantiate the choice of drug for targeted empirical and etiotropic antibacterial therapy based on the analysis of antibiotic resistance in leading gram-negative bacteria (*A. baumannii, K. pneumoniae, P. aeruginosa*) isolated from patients with orthopedic infection.

MATERIAL AND METHODS

A retrospective study of data on antibacterial resistance of common Gram(–) pathogens isolated from patients with OI was performed between January 1, 2011 to December 31, 2022. Common pathogens included microorganisms with prevalence exceeding 3.5 % in the total spectrum of OI pathogens according to previously published central monitoring [8].

Data on antibiotic resistance were obtained from the Microbiological Monitoring System Mikrob-2 program (MedProject-3, 2002–2020) and from the Across-Engineering laboratory information system (2021–2022). Bacteriological analysis of biomaterials obtained from patients was performed in accordance with accepted international standards of microbiological research (UK SMI). Species identification of grown cultures was produced with the biochemical method on Microlatest panels (Erba Lachema) using iEMS Reader MF (Labsistems, Finland) until 2021 and by the MALDI-TOF mass spectrometry method since 2021.

The sensitivity of the isolated strains of Gram(–) bacteria was determined to antimicrobial drugs included in the center's formulary list:

— *A. Baumannii*: to ciprofloxacin, levofloxacin, co-trimoxazole, cefoperazone+[sulbactam] (determined by cefoperazone), imipenem, meropenem, amikacin, gentamicin, colistin;

— *K. pneumoniae*: to ciprofloxacin, co-trimoxazole, ceftriaxone, cefoperazone+[sulbactam] (determined by cefoperazone), cefepime, imipenem, meropenem, aztreonam, colistin, fosfomycin (since 2017);

— *P. Aeruginosa*: to ciprofloxacin, levofloxacin, ceftazidime, ceftazidime+[avibactam], cefoperazone+[sulbactam] (determined by cefoperazone), cefepime, imipenem, meropenem, aztreonam, amikacin, gentamicin, colistin.

Throughout the 12-year period, susceptibility of strains was determined according to the breakpoints in the current version of EUCAST at the time of the initial microbiological study.

Absolute values and proportions of the whole (*n*, %) were used to describe categorical variables. Variables with a continuous distribution were described by the mean and standard deviation (M ± σ), discrete variables and ordered data were described by the median, 1–3 quartiles (Md [Q1; Q3]). The minimum and maximum values (|min; max|) were calculated.

The main trends in antibiotic resistance for the pathogens were presented by antibiotic groups including fluoroquinolones, co-trimoxazole, cephalosporins, carbapenems, monobactams, aminoglycosides, fosfomycin, polymyxin E (colistin). The resistance-time curve was modeled using the `mgcv` library. The proportion of resistant strains per year was used as the dependent variable, and time and bacterial species were used as independent variables. The nonlinear dependence was modeled using the cubic spline transformation method from time with the effect of interaction with group affiliation.

The beta distribution model was used with the dependent variable being in the range (0, 1). To exclude extreme values (0 and 1), the following transformation of the dependent variable was performed ($y \times (n - 1) + 0.5) / n$, where y is the dependent variable, n is the number of observations. The syntax of the model was as follows:

gam (y ~ s(time, bs = 'cr', k = 5) + name + s(time, by = name, bs = 'cr', k = 5), family = betar()).

The model was characterized by the pseudo-determination coefficient R2, normalized root of the mean square error (nRMSE), and degrees of freedom. the Linear trend hypotheses were tested to specify data with the models obtained. The average false discovery rate (FDR) was used to correct multiple hypothesis testing. All calculations were performed in the R v4.4.0 programming language.

RESULTS

Fluoroquinolones (ciprofloxacin, levofloxacin)

The mean resistance rate of A. baumannii, K. pneumoniae and P. aeruginosa strains was 83.7 % for ciprofloxacin [62.5–98.7], and 87.6 % for levofloxacin [50–98.6]. A statistically significant increase in the resistance rate of ciprofloxacin-resistant strains was observed for most common Gram(–) bacteria ($p = 0.024$) throughout the period. The proportion of resistant strains increased by 36.2 %, 25 % and 33.4 %, respectively, for *A. baumannii* ($p = 0.024$) (Fig. 1A), *K. pneumoniae* ($p = 0.018$) (Fig. 1B) and *P. aeruginosa* ($p = 0.018$) (Fig. 1C) between 2011 and 2022, and reached 98.7 %, 98.2 % and 66.7 %, respectively, by the end of the observation period.

A similar picture was observed with respect to levofloxacin. The general trend was characterized by a statistically significant increase in the proportion of *A. baumannii* strains resistant to the drug ($p = 0.012$). However, the isolation of levofloxacin-resistant *P. aeruginosa* strains had a wave-like pattern despite the predicted increase in the proportion of resistant isolates with no clear trend identified ($p = 0.461$).

The predicted isolation rate of fluoroquinolone-resistant *A. baumannii* will reach 100 % in the coming years. The level of 100 % will not be reached for *K. pneumoniae* and *P. aeruginosa* despite the obvious increase in resistance to fluoroquinolones.

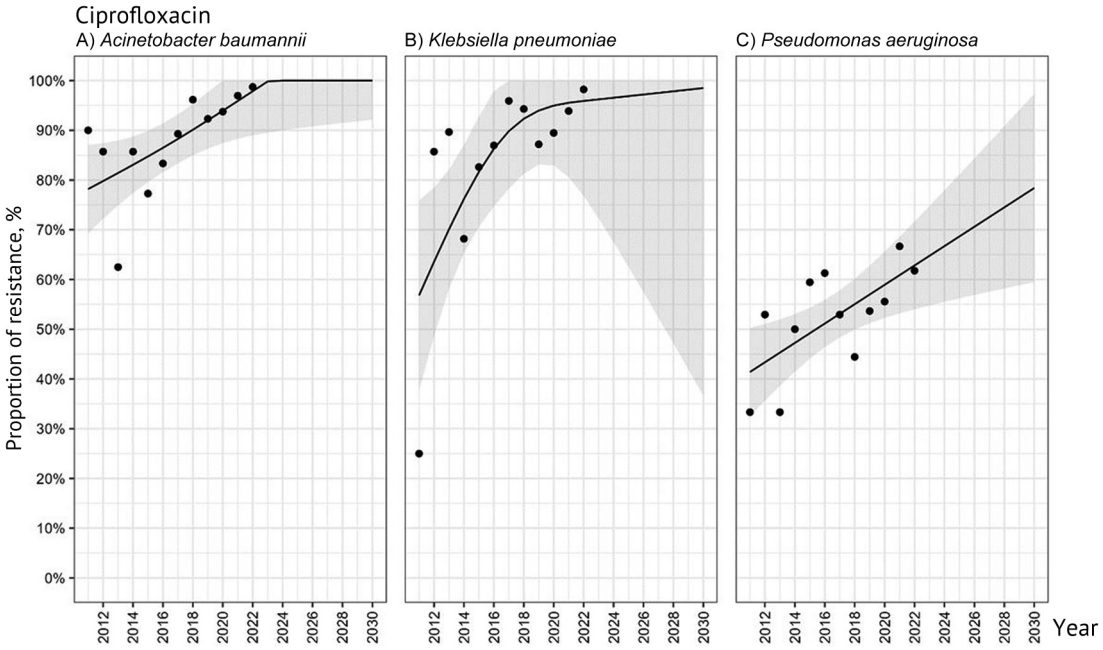


Fig. 1 Prediction of resistance of *A. baumannii* (A), *K. pneumoniae* (B) and *P. aeruginosa* (C) to ciprofloxacin

Sulfamethoxazole-trimethoprim (co-trimoxazole)

On average, 74.8 % [47.1–92.6] of *A. baumannii* strains were resistant to co-trimoxazole. There were two main trends in the dynamics of the isolation of resistant strains: the proportion of resistant isolates decreased by 38.9 % between 2011 and 2016 and increased by 45.5 % (Fig. 2A) between 2017 and 2022. Despite the predicted increase in the frequency of isolated resistant strains, a clear trend could not be identified ($p = 0.978$).

On average 81.9 % [52.4–97.1] strains demonstrated resistance to this antibiotic among *K. pneumoniae*. The frequency of isolation of co-trimoxazole-resistant *K. pneumoniae* strains was characterized by constant fluctuations. Despite a decrease in this indicator in the last three years of observation, the overall trend shows a statistically insignificant increase in the proportion of resistant strains ($p = 0.195$), which is likely to reach 100 % by 2030 (Fig. 2B).

Protected and unprotected cephalosporins

The average proportion of *A. baumannii* strains resistant to cefoperazone+[sulbactam] was 53.3 % [18.8–83.3]. There was nonlinear dynamics in the indicator throughout the observation period (Fig. 3A); however, the overall trend over 12 years was characterized by a steady increase in the proportion of resistant strains ($p = 0.027$), which is predicted to reach 100 % by 2026. The frequency of isolation of *K. pneumoniae* strains resistant to cefepime and ceftriaxone remained almost steady over 12 years of observation and averaged to 86.3 % [76.2–97.4] and 85.0 % [76.9–96.4], respectively. The predicted frequency of isolation of resistant strains was close to average.

The dynamics in the isolated *K. pneumoniae* strains resistant to cefoperazone+[sulbactam] had a wave-like pattern; a decrease in this indicator was recorded between 2015 and 2017 (Fig. 3B). However, the overall trend demonstrated a statistically insignificant increase in resistance ($p = 0.225$). Against, Cefoperazone+[sulbactam] was most effective for *P. aeruginosa*, with 32.8 % [7.8–60.3] of the strains included in the study being resistant.

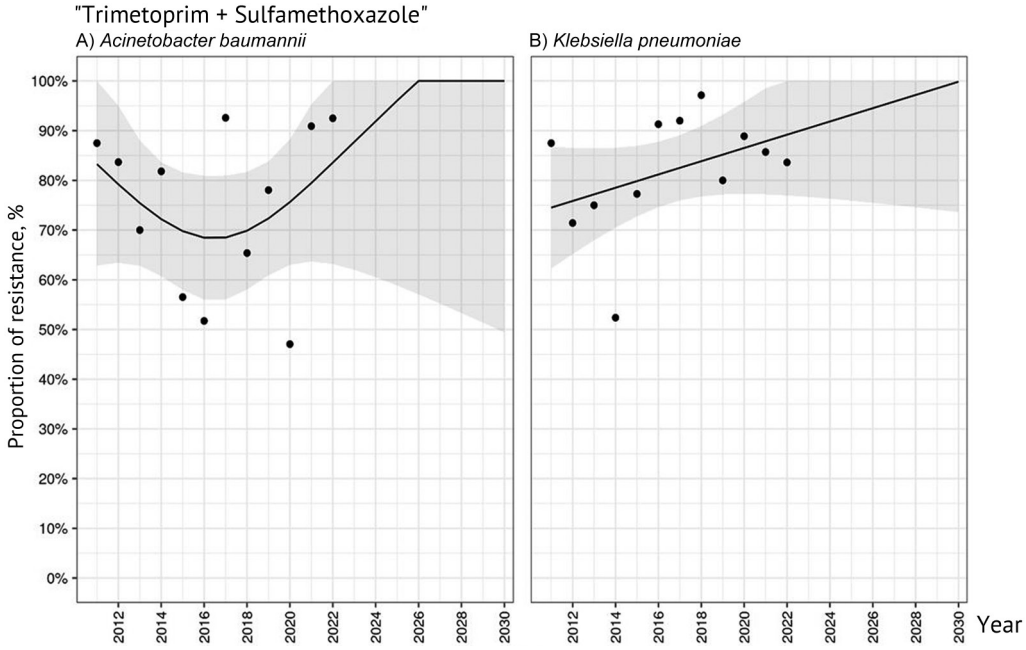


Fig. 2 Predicted resistance of *A. baumannii* (A) and *K. pneumoniae* (B) for co-trimoxazole

For comparison, the average proportion of strains resistant to ceftazidime+[avibactam] was 41.2 % [25.4–50.0]; to ceftazidime, 45.9 % [17.3–75.0]; to cefepime, 49.1 % [19.2–75.0]. A negative trend of an increased proportion of resistant *P. aeruginosa* strains was revealed for cefoperazone+[sulbactam] ($p = 0.010$) (Fig. 3C). A minor increase in the proportion of resistant *P. aeruginosa* strains is predicted for ceftazidime, with no increase in the proportion of resistant *P. aeruginosa* strains predicted for cefepime.

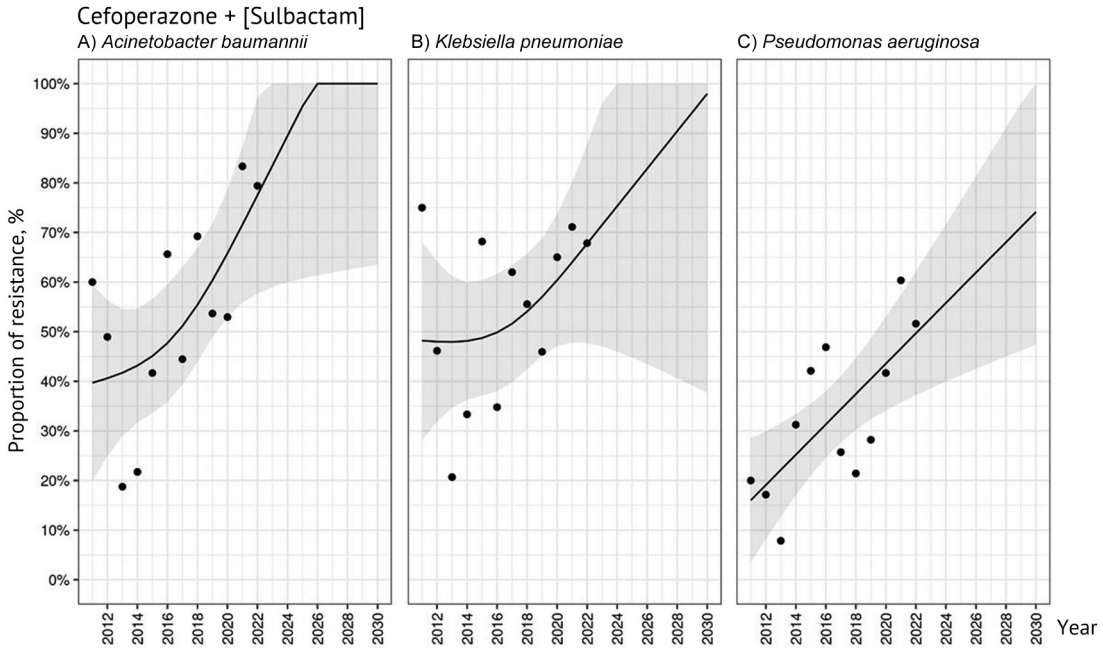


Fig. 3 Predicted resistance of *A. baumannii* (A), *K. pneumoniae* (B) and *P. aeruginosa* (C) for Cefaperazone+[Sulbactam]

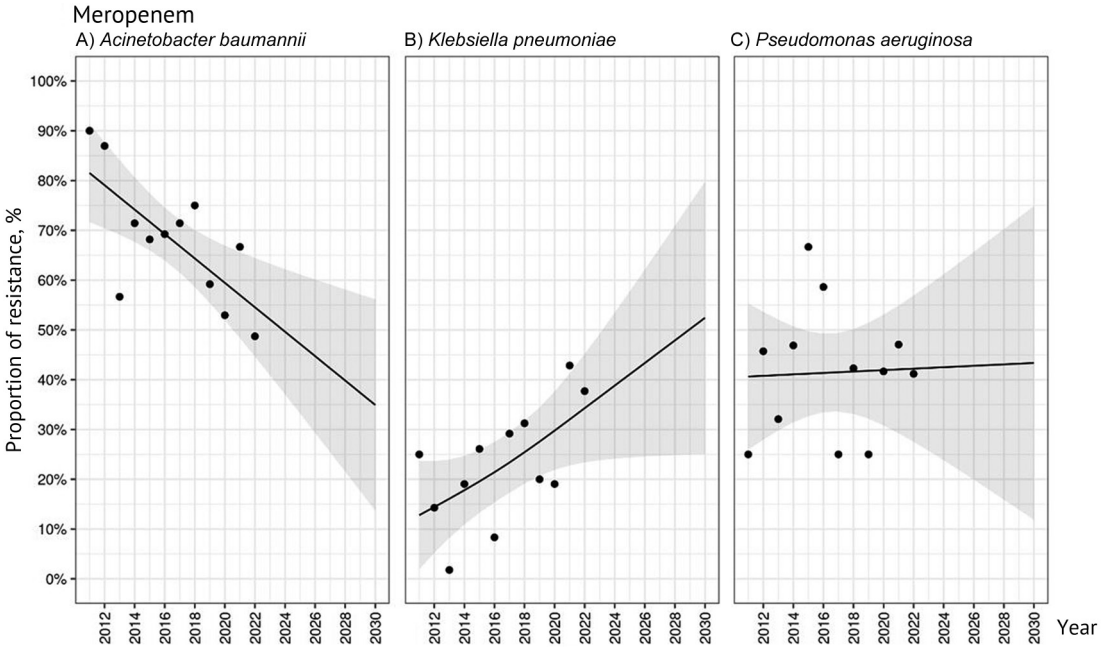
Carbapenems

The average frequency of isolated imipenem-resistant *A. baumannii* was 56.7 % [33.3–75.0] with wave-like dynamics and no trend identified ($p = 0.877$). The predicted frequency of isolated resistant strains in the coming years will remain close to the average value. Despite the higher average proportion of meropenem-resistant *A. baumannii* strains compared to imipenem (68.0 %

[48.7–90.0]), the indicator decreased by 41.3 % during the observation period (Fig. 4A). A statistically significant decrease in the frequency of isolated meropenem-resistant strains was established (p = 0.010) which is projected to decrease to 35 % by 2030.

The average resistance level of *K. pneumoniae* strains to imipenem and meropenem was identical and amounted to 23.0 % [3.6–42.9] and 22.9 % [1.8–42.9], respectively. The trends were comparable and characterized by a stable, statistically significant increase in the prevalence of *K. pneumoniae* strains resistant to imipenem (p = 0.003) and meropenem (p = 0.037) despite the wave-like course. More than 50 % of strains of the species will be resistant to CP by 2030 according to the forecast (Fig. 4B). The proportion of imipenem-sensitive *P. aeruginosa* strains decreased over 12 years of observation. The average proportion of resistant strains was 34.3 % [9.6–56.1] despite the lack of a linear trend. The overall trend can be characterized as a significant increase in the frequency of resistant strains (p = 0.001), which was 50 % by 2022. About 75 % of *P. aeruginosa* strains are predicted to be resistant to imipenem by 2030. For meropenem, the mean proportion of resistant strains was 41.4 % [25.0–66.7], and the predicted isolation rate will be comparable at 45 % by 2030 (Fig. 4C).

Fig. 4 Predicted resistance of *A. baumannii* (a), *K. pneumoniae* (b) и *P. aeruginosa* (c) for meropenem



Monobactams

No dynamics in the level of resistance to aztreonam in *P. aeruginosa* and *K. pneumoniae* strains was identified. The average frequency of isolated aztreonam-resistant *P. aeruginosa* strains was 48 % [29.4–62.5], *K. pneumoniae* measuring 85.7 % [75–96.9]. No statistically significant trends in changes in the sensitivity of the pathogens to aztreonam were found.

Aminoglycosides (gentamicin, amikacin, tobramycin)

The average frequency of isolated *A. baumannii* strains resistant to amikacin and gentamicin was similar and amounted to 78.1 % [40.0–97.4] and 78.2 % [50.0–98.1], respectively. The general trends were characterized by an increase in the proportion of resistant strains, which was statistically significant for amikacin (p = 0.091) and insignificant for gentamicin (p = 0.869). The predicted frequency of isolated *A. baumannii* strains resistant to aminoglycosides will reach 100 % by 2025–2026 (Fig. 5A).

On average, 52.5 % [13.0–87.5] of *K. pneumoniae* strains were resistant to amikacin. A steady decrease by 74.5 % was observed in the proportion of resistant strains between 2011 and 2016, and the opposite trend was observed between 2017 and 2021 (Fig. 5B). Despite a slight decrease in the resistant strains in 2022 compared to 2021, the overall trend can be characterized as an increase in the proportion of resistant strains ($p = 0.481$).

The dynamics in isolated amikacin-resistant *P. aeruginosa* showed less variability (Fig. 5C) than for *A. baumannii* and *K. pneumoniae*. On average, only 35 % [19.1–58.3] of cases of *P. aeruginosa* strains were resistant to it. The overall trend showed a decrease in the frequency of isolated resistant strains with low statistical significance of the prediction ($p = 0.762$). A persistent increase in resistant *P. aeruginosa* strains for gentamicin from 25 % to 83 % was identified between 2011 and 2017 with the average of 41.0 % [25.0–83.0]. The sensitivity of *P. aeruginosa* to gentamicin has not been determined since 2019.

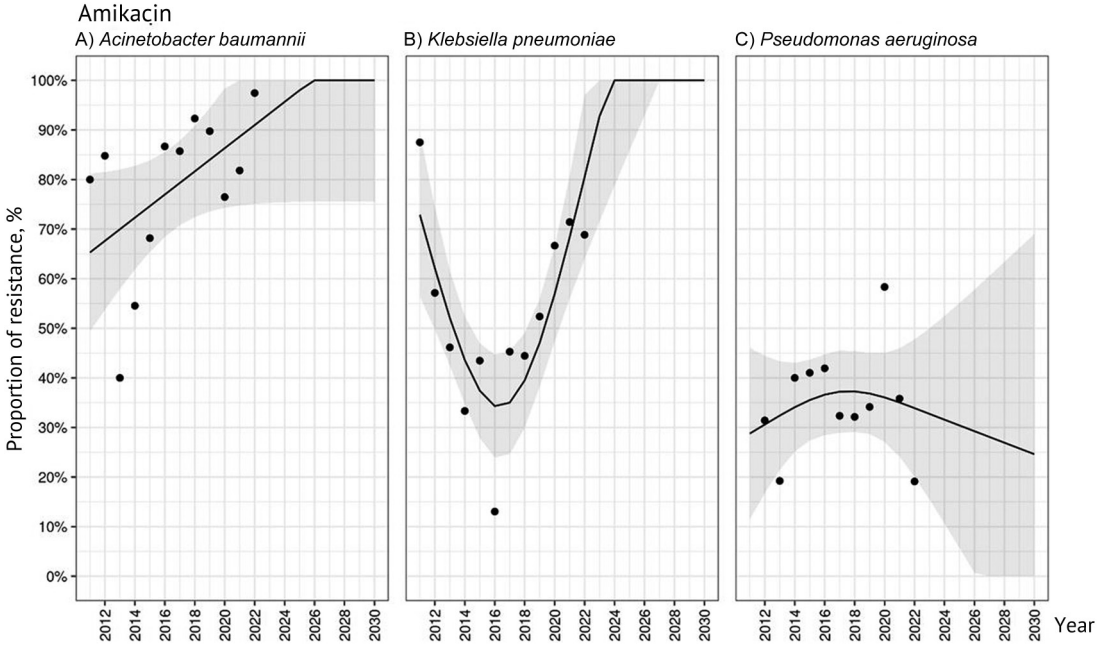


Fig. 5 Predicted resistance of *A. baumannii* (A), *K. pneumoniae* (B) and *P. aeruginosa* (C) for amikacin

Polymyxin E (colistin)

The average frequency of isolated colistin-resistant *A. baumannii* strains was 11.4 % [1.6–25]; *K. pneumoniae*, 13.2 % [6.7–30.8]; *P. aeruginosa*, 15.3 % [1.2–50].

There was a nonlinear frequency of isolated resistant *A. baumannii* strains between 2012 and 2015 with an increase in the proportion noted and the opposite trend observed in the following four years (Fig. 6A). The overall trend could be characterized as the absence of pronounced dynamics with the expected frequency of isolated colistin-resistant *A. baumannii* being close to the average ($p = 0.390$). The susceptibility of *K. pneumoniae* to colistin was determined since 2017. The nonlinear incidence of resistant strains was observed over the six years of observation (Fig. 6B) with a trend toward a statistically insignificant decrease in the resistance rate ($p = 0.151$). The proportion of colistin-resistant *P. aeruginosa* strains decreased throughout the observation period (Fig. 6C) reaching 1.2 % by 2022 ($p = 0.054$).

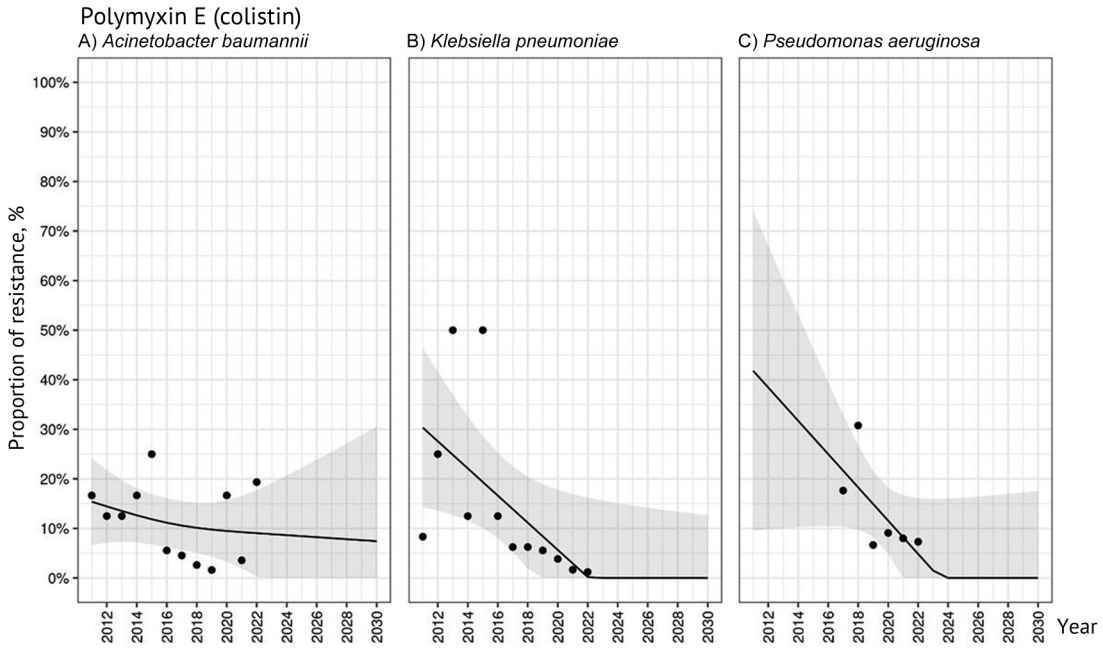


Fig. 6 Predicted resistance of *A. baumannii* (A), *K. pneumoniae* (B) and *P. aeruginosa* (C) to polymyxin E (colistin)

Fosfomycin

Fosfomycin susceptibility was determined only for *K. pneumoniae* starting from 2017. The average level of fosfomycin resistance of *K. pneumoniae* strains was 22.4 % over six years [3.6–48.7]. The incidence of fosfomycin-resistant strains decreased from 30 % to 5 % between 2017 and 2020 with a subsequent increase to 10 % by 2022. A trend could not be established due to the small number of observations.

DISCUSSION

Infection associated with orthopedic implants requires a comprehensive approach including radical surgical treatment of the purulent focus, removal of the infected metal construct combined with etiotropic anti-inflammatory therapy. A prolonged antibiotic therapy for IAI would include a course of parenteral administration of drugs (7–14 days) and a course of oral administration (4–8 weeks). Treatment of patients with IAI caused by Gram(–) bacteria with MDR (multidrug-resistant) and XDR (extensively drug-resistant) susceptibility phenotypes can be associated with the limited choice of drugs that are active against pathogens. Antibiotics administered parenterally include CS, KP, monobactams, aminoglycosides, tigecycline, fosfomycin, polymyxin B, dioxidine and a list of oral drugs for stepwise ABT at the outpatient stage is limited to include FQ, co-trimoxazole, minocycline and cefixime.

The frequency of Gram(–) microorganisms with MDR and XDR phenotypes of antibiotic susceptibility reported by Benito et al. [9] was in line with that observed with our series. Our findings for the 12-year period 2011–2022 indicated Gram(–) pathogens including *K. pneumoniae* (4.78 %), *P. aeruginosa* (3.88 %) and *A. baumannii* (3.65 %) as most common [8]. Our data are generally comparable with the results reported by the Russian [2] and foreign [10] colleagues.

Fluoroquinolones (ciprofloxacin, levofloxacin)

FH, cipro- and levofloxacin are drugs that are commonly used in the treatment of patients with OI. Ciprofloxacin is the drug of choice in the treatment of patients with IAI caused by Gram(–) bacteria including *P. aeruginosa*. The drug provides high concentrations in the bone having antibiofilm

activity (Table 1) with oral antibiotics being characterized by high bioavailability [12]. Step therapy is another positive aspect. Despite the fact that levofloxacin is slightly inferior to ciprofloxacin in terms of penetration into the bone [16], the concentration of levofloxacin in synovial fluid exceeds serum concentrations and ciprofloxacin and levofloxacin are characterized by similar levels of activity according to scientific publications. The pharmacokinetic features result in the widespread use of FQ in the treatment of patients with IAI caused by Gram(–) pathogens. Given the need to prescribe AB therapy for a long period the cardio- and neurotoxicity [13] of FQ are to be considered with a greater risk of tendon rupture, tendonitis, aortic aneurysm and mental disorders [12].

Table 1

Pharmacokinetic parameters of the main groups of antibiotics used in the treatment of patients with IAI

INN	Residual/average concentration in blood (mcg/ml)[1]	Concentration in spongy/cortical bone (μg/ml)	Concentration in synovial fluid (mcg/ml)	Effect on biofilms	Possibility of step-by step ABT	Degree of expression HP[1]	References
Fluoroquinolones	Cipro — 0.2; levo — 0.6	Cipro — 13.8/13.8; levo — 10/4.6	cipro — penetrates well1; levo — 8,9	yes	yes	+	[11–14]
Trimethoprim/ sulfamethoxazole	1.3–2.8/32–63	The serum to bone C ratio is 1.2 for trimethoprim; 0.36 for sulfamethoxazole.		none	yes	++	[15–17]
III generation CA	ceftriaxone — 10.5; ceftazidime — 3	ceftriaxone — ND/10.7; ceftazidime — 32.1/32.1	ceftriaxone 60–100 % of plasma concentrations; ceftazidime — 25.6	none	none	+	[11, 16, 18]
Cefoperazone + [sulbactam]	69.23/6.49	penetrates well[1]	penetrates well[1]	none	none	+	[19, 20]
Cefepime	0.7	67.6/99.8	does not penetrate well	none	none	+	[16, 21]
Carbapenems	meropenem — 8.0; imipenem — 1.0	meropenem — 10.6/10.6; imipenem — 2.6/2.6	meropenem — 12.5; imipenem — 13.8	yes/none	none	+	[16, 22, 23]
Aztreons	does not exist; C max — 90	16 (20 % of C in serum)	83 (95 % of C in serum)	yes	none	+	[16, 24]
Aminoglycosides	gentamicin — 2.0; amikacin — 10	lOW C[1]	25–50 % of C in serum	to immature	none	+++	[16, 25, 26]
Polymyxin B	2.0	ND	does not penetrate well[1]	yes (*in vitro*)	none	+++	[27–31]
Fosfomycin	11.4	penetrates well, bone to plasma C ratio 0.43	penetrates well[1]	yes	none	++	[16, 32–37]

Note: [1] Register of SmPC and LV of the EAEU, State Register of Medicines. Designations: C, concentration; ND, no data; C max, maximum serum concentration

According to the AMRmap platform, 93 % of P. aeruginosa strains isolated from patients with bone and joint infections in Russia between 2012 and 2022 were resistant to ciprofloxacin, which was 37 % higher than in the period between 2002 and 2012. Ciprofloxacin-resistant strains increased for *A. baumannii* and *K. pneumoniae* from 76 % to 93 % and from 66 % to 84 %, respectively [38]. A statistically significant trend towards increased resistance to ciprofloxacin was obtained for all of the above pathogens ($p = 0.025$ for *A. baumannii* and $p = 0.018$ for *K. pneumoniae* and *P. aeruginosa*) in our series. Increased resistance to levofloxacin was detected only for *A. baumannii* ($p = 0.012$). In recent years, the proportion of *A. baumannii* and *K. pneumoniae* strains resistant to ciprofloxacin has approached 100 % with the resistance of P. aeruginosa being 63 % by the end of the study period. The catastrophic growth of resistance to FCh of the main Gram(–) bacteria was reported by foreign researchers [39].

In addition to the high level of resistance there is another difficult question whether FQ can be used as monotherapy in cases where the infection is caused by an antibiotic-resistant strain of Gram(–) bacteria. Attempts to combine FQs with representatives of other groups of antibiotics in the presence of resistance are not convincing. Grossi et al. suggested that the additional administration of oral FQs to prolonged infusion of beta-lactam antibiotics being active against bacteria had no significant effect on the outcome of treatment of patients with IAI caused by strains resistant to FH during the entire treatment period (median 90 days) [40].

Sulfamethoxazole-trimethoprim (co-trimoxazole)

Co-trimoxazole is one of the alternatives to FH from the standpoint of stepwise ABT of OI caused by Gram(–) bacteria (except for naturally resistant *P. aeruginosa*). Co-trimoxazole has a bactericidal effect in relatively low concentrations due to the synergism of the components (trimethoprim and sulfamethoxazole) [41]. The drug penetrates bone tissue well (Table 1) and is indicated for acute and chronic osteomyelitis and can be prescribed as a step therapy. Unlike FQ, co-trimoxazole lacks antibiofilm activity [16].

There is a paucity of literature reporting co-trimoxazole to be used for the treatment of patients with OI caused by Gram(–) pathogens. The largest study of its effectiveness included 51 patients with bone and joint infection. However, the drug was mainly prescribed as part of a combination antibacterial therapy with no possibility to assess an individual contribution [42]. Co-trimoxazole used for treatment of outpatients with IAI caused by *K. pneumoniae* significantly improved the likelihood of a favorable outcome ($p = 0.038$) [43]. There are publications reported the experience with co-trimoxazole used for the treatment of patients with bone and joint infections caused by *E. cloacae, Burkholderia spp*. and *Stenotrophomonas maltophilia*. Long-term therapy with co-trimoxazole can be associated with side effects of varying severity primarily from the hematopoietic system and the skin [15].

According to Russian researchers, more than 70 % of *K. pneumonia*e and *A. baumanni*i strains isolated from OI patients are resistant to co-trimoxazole [2, 44]. According to the AMRmap platform, 50 % and 54 % of *A. baumannii* strains and 61 % and 69 % of representatives of the *Entrobacteriaceae* family isolated from patients with bone and joint infection were resistant to this drug in the periods between 2002 and 2012 and between 2012 and 2022, respectively, in Russia [38]. Our findings showed a more negative picture: resistance of *A. baumannii* to co-trimoxazole was 74.8 %, *K. pneumoniae* being 81.9 %.

Beta-lactam antibiotics

These drugs are generally characterized by good penetration into bone tissue (Table 1) and a varying activity against Gram(–) bacteria.

Cephalosporins

Third- and fourth-generation cefiximes, including inhibitor-protected forms, exhibit potential activity against Gram(–) bacteria. They are officially registered for the treatment of patients with bone and joint infections, with the exception of cefixime, the only orally administered third-generation cefixime. The use of cefixime for stepwise ABT in traumatology and orthopedics is significantly limited by poor penetration into bone tissue and the natural resistance of *P. aeruginosa* and some representatives of the *Enterobacteriaceae* family to the drug. The efficacy of this drug for outpatients with bone and joint infections remains under-explored. The proportion of drug-resistant Gram(–) bacteria strains was not examined in our series.

With the declared activity of ceftriaxone against some Gram(–) bacteria including representatives of the *Enterobactiaceae* family and *A. baumannii*, we did not find any publications devoted to its use in IAI of Gram(–) etiology. This is probably due to the high level of resistance to it (up to 90 % of strains) of A. baumannii and K. pneumoniae and natural resistance of P. aeruginosa. In our series, 85 % of *K. pneumoniae* strains were resistant to this drug by 2020–2022 [76.9–96.4].

For a long time, infection caused by *P. aeruginosa* was the main indication for ceftazidime. According to the ARMmap platform, the proportion of ceftazidime-resistant *P. aeruginosa* strains isolated from patients with bone and joint infection was 33–39 % for the period between 2002 and 2022. The susceptibility of *K. pneumoniae* and *A. baumannii* is not determined [38]. According to our data, resistance to ceftazidime in *P. aeruginosa* strains averaged 45.9 % without a specific trend throughout the observation period, which may be due to the limited use of this drug for the treatment of patients with OI.

The spectrum of action of cefoperazone includes predominantly Gram(–) bacteria, including *P. aeruginosa*, which distinguishes it favorably from ceftriaxone, and the drug penetrates well into the bone and the synovial fluid (Table 1). However, the combination of cefoperazone with the beta-lactamase inhibitor sulbactam is clinically more significant. This combination increases the antimicrobial activity of the drug including some KP-resistant strains of *A. baumannii*, and can be considered as a drug for targeted empirical ABT. Rou-Zhen et al. reported the effectiveness of cefoperazone+[sulbactam] in the treatment of patients with infection caused by Gram(–) bacteria being better in some cases than that with unprotected third-generation CS and carbapenems. The effect may be caused by a slower resistance with a lower risk of selection of resistant strains [17].

According to our data, the antibiotic retains greater activity against *P. aeruginosa*, and somewhat less against *A. baumannii* and *K. pneumoniae*. The statistically significant trend identified with increasing proportion of *A. baumannii* ($p = 0.027$) and *P. aeruginosa* ($p = 0.010$) strains resistant to cefoperazone+[sulbactam] is of concern with the sensitivity being higher than for other CS and comparable to KP. Hypocoagulation is one of the serious side effects that can be associated with the use of cefoperazone+[sulbactam] and must be taken into account with prescription to elderly patients and for a long course [20].

Cefepime is active against most Gram(–) microorganisms, with the exception of *Stenotrophomonas maltophilia*. According to the ARMmap platform, the proportion of *Enterobacteriaceae* strains resistant to this antibiotic isolated from patients with bone and joint infections increased from 43 % to 58 % over 20 years [38]. According to our data, resistance to cefepime was higher for *K. pneumoniae* and amounted to 86.3 % and 49.1 % for *P. aeruginosa* showing no significant changes throughout the observation period. Considering the poor penetration into synovial fluid (Table 1) and relatively high level of resistance of Gram(–) bacteria to the drug, Cefepime has no registered indications and is not indicated for patients with OI.

Carbapenems

CPs have the broadest spectrum of action among β-lactam antibiotics and have long been the antibiotic of choice for the treatment of patients with infections caused by Gram(–) bacteria producing ESBL (extended spectrum β-lactamases). Indications for imipenem+[cilastatin] include bone and joint infection caused only by *P. aeruginosa*, while meropenem does not have such an indication. Both carbapenems are widely used in the treatment of patients with OI caused by FC and CS-resistant Gram(–) bacteria. This is due to the fact that CPs reach sufficiently high concentrations in the bone and the synovial fluid (Table 1), allowing them to exceed the MIC for most Gram(–) bacteria.

In recent years, there is an increasing tendency for the proportion of Gram(–) bacteria demonstrating resistance to the drugs. According to the results of a multicenter study (2000–2015), ESBL-producing bacteria were isolated from 91 patients (72 %) with IAI with the resistance to CP recorded in 12 cases (9 %) [7]. According to the AMRmap platform, 70 % of *A. baumannii*, 25 % of *K. pneumoniae* and 40 % of *P. aeruginosa* strains isolated from patients with bone and joint infection between 2012 and 2022 were resistant to meropenem, with a marked increase in resistance observed for the three pathogens compared to the period 2002–2012. A similar trend was noted for imipenem [38]. A similar statistically significant increase in the proportion of *K. pneumoniae* ($p = 0.003$) and *P. aeruginosa* ($p = 0.001$) strains resistant to imipenem, which was absent for A. baumannii in our series. There was a statistically significant decrease in the proportion of *A. baumannii* strains resistant to meropenem ($p = 0.037$), which is not in line with the results of foreign and Russian authors and is probably a local finding that has no scientific role.

Monobactams

Aztreonam, the only current representative of the group, is naturally active against most Gram(–) bacteria, including ESBL producers, with the exception of *A. baumannii*. According to the ARMmap platform, 66.5 % of *Pseudomonas spp*. strains and 38.5 % of *Enterobacteriaceae* strains isolated from patients with bone and joint infections over the period between 2003 and 2022 retain sensitivity

to the drug, without any specific dynamics [38]. According to our study, 52 % of *P. aeruginosa* and 14.3 % of *K. pneumoniae* strains were susceptible to aztreonam. The resistance level remained stable throughout the observation period.

Aztreonam produces concentrations in synovial fluid comparable to serum concentrations, but penetrates the bone five times less (Table 1). A systematic review by Thabit et al. showed that bolus administration of a loading dose of the drug resulted in its concentration in cancellous bone tissue and synovial fluid exceeding the concentration of meropenem by 1.5 and 6.6 times, respectively [16]. However, the drug does not have a registered indication for the treatment of patients with bone and joint infection, and it is not used in routine clinical practice for the treatment of patients with intraocular infections and osteomyelitis. Existing publications evaluate the combined use of aztreonam with ceftazidime+avibactam in cases of intraocular infections caused by XDR strains of Gram(–) bacteria. Researchers recommend simultaneous, synchronous infusions through different catheter ports or through different venous accesses. This combination helps cover the maximum range of Gram(–) bacteria with extreme and pan-resistant resistance, even in the presence of resistance to each of them [24].

Other reserve antibacterial drugs: aminoglycosides, fosfomycin, polymyxin B

These drugs are not the treatment of choice for patients with acute respiratory infections, and are used in cases of pathogen resistance to fluoroquinolones, β-lactams, and co-trimoxazole as etiotropic antibiotics.

Aminoglycosides are antibacterial agents to which the vast majority of Gram(–) bacteria are naturally susceptible. Gentamicin and amikacin are commonly used for systemic antibiotic therapy in the Russian Federation. Aminoglycosides accumulate well in tissues with an active blood supply and much less so in bone tissue [16]. High doses of these drugs are needed for therapeutic concentrations of bone and synovial fluid increasing the risk of adverse reactions (Table 1), primarily nephro- [25] and ototoxicity [26]. Aminoglycosides are not commonly used in the treatment of patients with OI. According to the ARMmap platform, 76 % of *Acinetobacter spp*. strains and 60 % of *K. pneumoniae* strains isolated from patients with bone and joint infection during the period 2012–2022 were resistant to gentamicin [38]. Identical results were obtained in our series: 78.2 % of *A. baumannii* strains were resistant to gentamicin, with a statistically significant upward trend in the proportion of resistant strains.

Amikacin demonstrated slightly greater activity against the strains than gentamicin. According to the ARMmap platform, 33 % of *Pseudomonas spp.*, 30 % of *K. pneumoniae*, and 84 % of *Acinetobacter spp*. strains isolated from profile patients over the period 2012–2022 were resistant to amikacin, with negative dynamics compared to the period 2002–2012 [38]. According to our data, the level of resistance to amikacin was 78.1 % for *A. baumannii*, 35 % for *P. aeruginosa*, 52.5 % for *K. pneumoniae* which is generally comparable with the all-Russian data, but no specific trend identified.

Fosfomycin is active against a wide range of Gram(–) bacteria, including members of the *Enterobacteriaceae* family and some strains of *P. aeruginosa*, but is naturally inactive against *A. baumannii*. The drug is characterized by a pronounced synergistic effect when combined with beta-lactams, FQs, or aminoglycosides against a wide range of Gram(–) aerobic bacteria. Fosfomycin penetrates bone tissue well and has a registered indication for the treatment of patients with bone and joint infections (Table 1) [34].

The average incidence of fosfomycin-resistant *K. pneumoniae* strains was 22.4 % over 12 years at our center. However, no trend could be established due to the small number of observations: susceptibility to this antibiotic was determined only for strains with extreme resistance at the request of physicians. According to the AMRmap platform, only 14 % of *Enterobacteriaceae* strains isolated from patients with bone and joint infections were resistant to fosfomycin, and for 35 % of *Pseudomonas spp*. strains, the MIC of fosfomycin measured 64 mg/L [38].

Fosfomycin is commonly used for the treatment of patients with OI, but its use in monotherapy is not recommended due to the rapid development of resistance and decreased efficacy in the presence of a large amount of bacterial inoculum, which is typical for bone and joint infections [35]. Pronounced synergism of combined fosfomycin and colistin E in in vitro experiments against *K. pneumoniae* and *P. aeruginosa* in biofilms, with CP in the treatment of patients with infection caused by difficult-to-eradicate P. aeruginosa, is a serious justification for the use of fosfomycin as part of combination therapy [35].

Polymyxin B is active exclusively against Gram-negative bacteria. It cross-resists with colistin (polymyxin E), so susceptibility to polymyxin B is traditionally assessed using colistin. Resistance of Gram(–) bacteria to this drug reaches 10 % in some countries of Southeast Asia and the Mediterranean, however, in most countries, including the Russian Federation, polymyxin B retains its activity against the most problematic Gram(–) bacteria, including producers of various carbapenemases [29]. The frequency of isolated colistin-resistant strains was higher and averaged 11.4 % for *A. baumannii*, 13.2 % for *K. pneumoniae*, and 15.3 % for *P. aeruginosa* in our series. This was due to the determination of susceptibility only for multiresistant and panresistant strains. No significant dynamics in the level of resistance for *A. baumannii* and *K. pneumoniae* were observed due to the small number of observations.

The use of polymyxin B can be associated with the high frequency of adverse reactions including renal and urinary dysfunction, acute renal failure, and neurotoxicity. The drug poorly penetrates bone tissue and SF (Table 1), however, it exhibits pronounced antibiofilm activity due to its effect on metabolically inactive cells within the inner layers of the biofilm. The effect is observed with topical application of polymyxin; it is significantly weaker with systemic administration and higher doses of the antibiotic lead to an increased incidence of adverse reactions. Lora-Tamayo et al. recommend using a combination of colistin with other antibiotics active against Gram(–) bacteria: CS, KP, etc. [30].

The clinical efficacy of colistin has been confirmed by the results of multicenter studies. Papadopoulos et al. (2000–2015) performed a multicenter study and reported the frequency of favorable outcomes among patients with IAI caused by XRD strains, compared with MDR strains of bacteria treated by combination therapy with colistin as high as 66.7 % and 39.1 %, respectively ($p = 0.018$). The authors recommended the use of colistin in the absence of an alternative [7]. Another study demonstrated an advantage of using a combination of intravenous infusions of beta-lactams and polymyxin in the treatment of 44 patients with IAI caused by multidrug-resistant Gram(–) microorganisms, with adverse reactions occurring in 10 % of cases and being completely reversible [31]. Limitations of the study include the retrospective design and the local nature of the data. Predictions of microbial resistance to antibacterial drugs require confirmation in further studies.

CONCLUSION

With negative dynamics in the increased proportion of strains of common Gram(–) bacteria resistant to cefoperazone+[sulbactam], meropenem and imipenem+cilastatin, the use of a protected cephalosporin for targeted empirical initial therapy appeared to be more practical due to the lower risk of selection of strains resistant to it. FH and KP can be used with the susceptibility proved. Polymyxin B and fosfomycin should be considered reserve drugs for the treatment of infections caused by strains resistant to other antibiotics and should only be prescribed as part of combination therapy. Aminoglycosides and unprotected cephalosporins are an alternative due to their pharmacokinetic properties and high levels of resistance when more active drugs cannot be used. The list of drugs (fluoroquinolones, co-trimoxazole) for oral administration remains limited at the outpatient stage; additional studies are needed to evaluate the effectiveness in the treatment of patients with IAI caused by resistant Gram(–) bacteria.

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Original article
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Evolution of gait in preschool and primary school children after multilevel orthopedic surgeries performed to correct orthopedic complications of spastic diplegia

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Abstract

Introduction The optimal age for performing multilevel interventions in patients with cerebral palsy is the period from 10 to 16 years, but indications for eliminating contractures, torsional bone deformities, and foot deformities in children with cerebral palsy of GMFCS level I–III may also occur at an earlier age.

The **aim** of the work is to evaluate changes in the kinematic and kinetic parameters of gait in children with spastic diplegia who underwent multilevel bilateral surgical interventions for orthopedic complications of cerebral palsy that arose before the onset of pubertal growth acceleration.

Material and Methods 63 children with cerebral palsy, I–III GMFCS. Group 1 (n = 50): average age 7.1 years, no orthopedic interventions had been performed previously. Group 2 (n = 513): average age 7.4 years, isolated interventions were performed at the age of up to 4 years.

Results In group 1: after the operation for two years — an increase in the strength of all extensor muscles with a reliable difference compared to the preoperative level; after 4–5 years — stabilization of the achieved improvements in kinematics. In group 2: after the operation for two years — a decrease in the values of the total working power of the lower limb muscles; after 4 years — decompensation of motor capabilities occurred, the working power of the muscles of the hip and ankle joints did not exceed the initial values, and for the knee joint, the decrease in working power was permanent.

Discussion The positive effect of surgical intervention in both groups is similar and consists of improving the synergistic interaction of muscles.

Conclusion Orthopedic multilevel surgeries performed in children for orthopedic complications before prepubertal growth spurt are associated with functional development only in children who did not undergo early Achilles tendon lengthening or percutaneous fibromyotomies. The result remains stable for 4–5 years after surgery. Isolated Achilles tendon lengthening or percutaneous fibrotomies prevent lower limb muscular development in the long-term follow-up period.

Keywords: cerebral palsy, early-age multilevel surgery, instrumented gait analysis, long-term outcomes, children

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INTRODUCTION

Cerebral palsy (CP) is the most common cause of motor disorders in children (1.5–3 cases per 1,000 of pediatric population) [1, 2]. Conservative treatment (physical therapy, spasticity control, orthotic fitting) in children with global motor function impairment level I–III according to the Gross Motor Function Classification System (GMFCS) remains the method of choice until the age of six, when the development of muscle retractions (fixed contractures), bone deformities, and subluxations, as a rule, has not yet occurred [3, 4]. It has been established and repeatedly proven that the development of secondary orthopedic complications leads to both a decrease in motor activity and the loss of previously acquired skills and a significant deterioration in the quality of life, despite the stable nature of encephalopathy [5–10]. For surgical orthopedic correction of contractures, dislocations and bone deformities, the method of choice is simultaneous bilateral (or sequential bilateral with a short time interval) multilevel orthopedic interventions, accompanied by a single rehabilitation period [11–13]. Computer 3D gait analysis is a universal tool for assessing motor disorders, measuring orthopedic deformities and contractures, which are one of the factors in the deterioration of motor activity, quantitative planning of orthopedic intervention elements and the treatment outcome in subsequent years of monitoring the child [7, 14].

The optimal age for performing multilevel interventions is the period from 10 to 16 years old, especially the second half of the pubertal growth acceleration [15–17], when the risk of recurrence of orthopedic problems decreases [18]. However, indications for the elimination of contractures, torsional bone deformities, foot deformities in children with cerebral palsy of GMFCS levels I–III may also arise at an earlier age [5, 6, 9, 10, 19] if conservative therapy fails [20, 21]. Separately, it is necessary to point out the development of iatrogenic orthopedic problems with isolated and/or inadequate lengthening of the triceps surae [22–26]. Percutaneous, so-called minimally invasive fibromyotomies, selective muscle lengthening, especially those performed without correction of foot deformities [27, 28], inevitably lead to the manifestation of muscle weakness and the development of a crouch gait pattern in the medium and especially long term [29–31]. If plantar flexion weakens due to uncorrected foot deformities and contractures of the overlying joints, orthopedic surgery may be indicated.

The **aim** of the work is to evaluate changes in the kinematic and kinetic parameters of gait in children with spastic diplegia who underwent multilevel bilateral surgical interventions for orthopedic complications of cerebral palsy that arose before the onset of pubertal growth acceleration.

MATERIAL AND METHODS

This retrospective study included 63 patients with spastic cerebral palsy who underwent bilateral multilevel intervention to correct orthopedic complications of the underlying disease.

Inclusion criteria were age up to 10 years, the ability to undergo computer gait analysis within the established examination timeframes (before surgery, at intervals of 1–2 years, 2–3 years, 4–5 years after surgery), levels of global motor functions I, II, III GMFCS.

Exclusion criteria were more severe levels of GMFCS, incomplete (in terms of timing) instrumental gait analysis, age at the time of multi-level intervention of 10 years or above, orthopedic surgery performed on one anatomical area.

Out of 511 cases, 63 patients who fully met the inclusion criteria were selected for the study.

Based on surgical history, patients were included in two groups (Table 1):

— Group 1 (n = 50) were patients who had previous surgical intervention on the muscular apparatus of the lower limbs;

— Group 2 (n = 13) were patients who underwent isolated interventions on the triceps of the lower legs (lengthening of the Achilles tendon, so-called “minimally invasive” fibromyotomies).

Table 1

Characteristics of the groups

Group	Number of patients	Age, years	Gender				GMFCS					
			female		male		I		II		III	
			n	%	*n*	%	*n*	%	*n*	%	*n*	%
1	50	7.1 ± 1.57	19	38	31	62	4	8	25	50	21	42
2	13	7.4 ± 0.85	5	38	8	62	3	23	6	46	4	31

Immediately before surgery and during the late postoperative period, patients underwent clinical and radiographic examinations and computer gait analysis. Patients walked barefoot on a seven-meter treadmill at their usual speed, either independently or holding a parent's hand.

Kinematic data were recorded using Qualisys 7+ optical cameras with passive marker video capture technology, synchronized with six KISTLER (Switzerland) dynamometric platforms. The IOR model was used for marker placement. Kinematics and kinetics analysis was performed using QTM (Qualisys) and Visual3D (C-Motion) software with automated value calculation [32]. The functional asymmetry coefficient of symmetrical lower limb kinetic parameters was calculated using the formula: $Kac = (D-S)/(D+S)\times 100\ \%$, where D and S are values for the right and left lower limbs, respectfully.

AtteStat 12.0.5 was used for statistical data processing. The hypothesis of normal distribution was tested using the Shapiro-Wilk test. Given the number of cases in the groups and the lack of confirmation of the hypothesis of normal distribution, nonparametric statistics were used to process the results. Quantitative characteristics of the sample populations are presented in the table as the median with the percentile distribution level (Me 25 % ÷ 75 %) and the number of casess (n). The statistical significance of differences was determined using the unpaired Wilcoxon test, with a significance level of $p \leqslant 0.05$. The relationship between parameters was assessed using the Spearman correlation coefficient.

The research was approved by the Ethics Committee of the Ilizarov National Medical Research Center of Traumatology and Orthopedics. The study was conducted in accordance with the ethical standards of the World Medical Association's Declaration of Helsinki, "Ethical Principles for Medical Research Involving Human Subjects," as amended in 2000, and the "Rules for Clinical Practice in the Russian Federation," approved by Order No. 266 of the Russian Ministry of Health dated June 19, 2003. The parents of the children participating in the study were present during the study and provided informed consent for publication of the study results without identifying their children.

RESULTS

The only fundamental difference between the groups was the attempt to restore active plantar flexion and improve the functioning conditions of the extensor apparatus of the knee joint (Table 2).

The summarized spatiotemporal characteristics and the integral gait index are presented in Table 3. The data allow us to identify a trend toward improvement in the global assessment of kinematic gait parameters in both groups after surgery over a period of at least three years. Within one to two years, a decrease in walking speed and gait cycles per minute was noted. After an obvious period of adaptation of movements to new anatomical parameters, an improvement in the quantitative gait characteristics was noted in both groups within two to three years after surgery: an increase in walking speed and stance period length, a decrease in the duration of the double-support period. However, in Group 2 (triceps lengthening in the early age), decompensation of motor abilities occurred from year four which was manifested by a significant increase in the GPS (gait profile

score), a decrease in walking speed, and an increase in the duration of the double-support period of the gait cycle compared to Group 1. In addition, in Group 2, BMI values significantly increased and exceeded the age norm.

Table 2

Distribution of surgical elements in patient groups

Elements of bilateral interventions	Group 1 (*n* = 50)		Group 2 (*n* = 13)	
	n	%	*n*	%
Aponeurotomy of the lumbar muscles	7	14	2	15
Lengthening of the adductor longus muscle	41	82	13	100
Elongation of the gracilis muscle	35	70	13	100
Lengthening the medial flexors of the knee joint	42	84	4	31
Patellar stabilization	–		3	23
Aponeurotomy of the gastrocnemius muscle (Strayer) with or without aponeurotomy of the soleus muscle	50	100	2	15
Hoke's percutaneous Achilles tendon repair	9	18	2	15
Subtalar arthroereisis according to Grice	32	64	11	85
Lengthening of the lateral column of the foot according to Evans	8	16	2	15
Tenodesis of the posterior tibial muscle	46	92	13	100
Correction of torsion deformity of the hip	10	20	4	31
Derotational varus osteotomy	3	6	2	15
Achilles tendon shortening	–		3	23

Table 3

Spatiotemporal characteristics of gait cycle and body mass index

Parameter	Group	Before surgery	After Surgery		
			1–2 years	2–3 years	4–5 years
Body mass index	1	15.9 (13.9÷17.3)	16.0 (14.4÷17.5)	16.8 (15.8÷18.4)	**16.7 (15.3÷17.6)**
	2	16.7 (13.5÷21.5)	16.3 (13.7÷17.3)	**19.1 (16.2÷23.8)**	**21.5 (18.1÷24.3)*1**
Gait index (GPS), °	1	17.0 (12.9÷21.2)	14.4 (11.6÷16.1)	13.7 (11.3÷14.6)	**11.9 (10.4÷12.6)**
	2	17.6 (14.2÷20.5)	15.6 (12.9÷17.8)	13.2 (11.5÷14.3)	**14.1 (13.4÷15.2)***
Speed, m/sec	1	0.56 (0.39–0.78)	0.53 (0.34–0.68)	0.65 (0.49–0.87)	**0.83 (0.68–1.01)1**
	2	0.71 (0.58÷0.86)	0.61 (0.36÷0.83)	0.71 (0.46÷0.95)	**0.59 (0.52÷0.66)***
Step period length, m	1	0.64 (0.51÷0.79)	0.64 (0.52÷0.71)	0.83 (0.72÷0.95)	0.94 (0.89÷1.07)
	2	0.78 (0.68÷0.88)	0.7 (0.56÷0.78)	0.83 (0.73÷0.96)	0.84 (0.77÷0.98)
Step width, m	1	0.14 (0.11÷0.16)	0.15 (0.12÷0.19)	0.15 (0.13÷0.19)	0.16 (0.13÷0.2)
	2	0.14 (0.11÷0.15)	0.15 (0.1÷0.18)	0.15 (0.12÷0.17)	0.16 (0.13÷0.18)
Gait cycles per min	1	51.3 (42.9÷61.6)	47.7 (37.1÷56.8)	46.3 (42.0÷55.9)	51.0 (45.7÷55.4)
	2	60.6 (52.9÷63.8)	50.7 (42.9÷55.4)	51.1 (38.8÷65.9)	42.2 (39.0÷43.9)
Duration of support period from gait cycle, %	1	67.0 (62.7÷71.2)	69.9 (65.2÷74.2)	66.5 (62.2÷70.3)	67 (62.5÷71.1)
	2	64 (60.8÷67.7)	69.2 (63.4÷74.8)	67.5 (63.4÷68.9)	67. 0 (65.7÷70.2)
Duration of swing period from gait cycle, %	1	33.0 (29.4÷37.3)	29.4 (25.9÷34.9)	33.5 (29.8÷37.9)	33.0 (28.9÷37.6)
	2	36.9 (32.6÷39.8)	30.9 (25.2÷36.6)	32.5 (31.1÷36.7)	30.9 (29.8÷34.2)
Duration of double support period from gait cycle, %	1	33.5 (25.1÷38.5)	39.2 (28.0÷45.3)	31.6 (22.5÷39.6)	30.4 (25.2÷30.5)
	2	28.3 (21.7÷37.8)	39.3 (26.6÷52.6)	36.1 (26.5÷39.5)	**40.0 (31.9÷40.8)***

Note: * — significant differences according to the criterion between groups 1 and 2 at this period of comparison after surgery; 1 — reliable differences within this group compared with the previous study period

Interestingly, a positive significant correlation was observed between BMI and GPS (r = 0.769) from four years after surgery in group 2 (Table 4).

Table 4

Dynamics of several kinematic parameters

Parameter	Group	Before surgery	After surgery		
			1–2 years	2–3 years	4–5 years
Position of foot at initial contact (Г0), °	1	**–9.8 (–20.0÷0.6)**	**0.78 (–3.5÷5.0)[1]**	2.5 (–1.6÷6.8)	3.0 (1.3÷4.8)
	2	**3.0 (–4.0÷10.3)***	0.9 (–3.8÷7.1)	1.49 (–0.2÷3.1)	–0.1 (–2.8÷2.2)
Maximum dorsiflexion in stance(Г2), °	1	**–0.21 (–1.1÷0.0)**	**12.0 (7.7÷16.1)[1]**	17.4 (10.9÷21.3)	12.8 (10.3÷17.2)
	2	**17.4 (12.4÷24.1)***	11.9 (7.2÷16.8)	15.8 (8.2÷23.9)	13.1 (3.4÷24.3)
Position of foot in swing phase (Г4), °	1	**–4.5 (–13.3÷–6.9)**	**9.8 (5.6÷15.5)[1]**	10.5 (4.8÷15.6)	10.0 (9.8÷13.2)
	2	**11.5 (5.2÷17.8)***	9.8 (5.7÷14.4)	14.2 (7.4÷19.7)	11.2 (6.5÷14.2)
Clearance (forefoot tip), cm	1	4.6 (3.2÷5.5)	5.1 (3.9÷5.7)	5.7 (4.5÷5.6)	6.1 (5.5÷6.9)
	2	6.3 (4.8÷5.9)	4.8 (3.6÷6.0)	6.2 (4.3÷8.1)	6.2 (4.8÷8.1)
Knee position at initial contact (K0),°	1	27.0 (19.5÷35.5)	17.5 (10.9÷23.8)	20.9 (15.3÷28.9)	17.8 (11.9÷20.3)
	2	36.5 (20.8÷48.5)	17.9 (4.4÷28.8)	17.5 (1.3÷31.5)	18.9 (6.7÷32.8)
Extension range in stance (K1–K2), °	1	26.6 (14.7÷28.8)	18.4 (12.2÷24.8)	18.1 (10.3÷22.1)	15 (11.6÷18.9)
	2	18.3 (16.3÷24.7)	16.2 (7.5÷28.9)	14.5 (5.8÷21.1)	20.2 (17.0÷24.1)
Maximum knee extension in stance (K2), °	1	8.5 (0.9÷19.5)	0.52 (–9.4÷9.6)	5.3 (–3.9÷12.7)	3.2 (2.6÷8.0)
	2	16.2 (8.9÷36.6)	2.1 (–5.6÷9.2)	6.6 (–5.5÷14.0)	5.2 (–6.6÷13.3)
Maximum knee flexion in swing phase (K3), °	1	61.5 (54.5÷69.7)	52.7 (44.2÷62.6)	51.2 (44.1÷56.1)	52.6 (47.8÷61.5)
	2	71.5 (59.6÷86.1)	50.8 (44.1÷60.3)	55.9 (47.5÷61.5)	57.9 (46.5÷72.1)
Hip position at initial contact (T0), °	1	35.4 (28.3÷42.8)	36.6 (28.0÷44.9)	38.1 (33.5÷41.2)	36.1 (31.2÷40.1)
	2	42.4 (38.7÷48.9)	35.2 (29.8÷37.2)	38.0 (23.2÷49.3)	34.9 (28.4÷43.7)
Maximum hip extension (T2), °	1	1.8 (–6.5÷6.8)	1.3 (–7.8÷10.3)	–2.0 (–5.4÷0.08)	**–3.1 (–7.5÷–0.85)**
	2	9.1 (3.9÷11.5)	0.13 (–4.2÷7.9)	3.6 (–8.7÷12.2)	**9.8 (5.2÷16.1)***
Hip range of motion in sagittal plane, °	1	9.2 (7.4÷11)	9.1 (7.05÷11.2)	10.1 (7.3÷11.2)	12.8 (8.6÷13.8)
	2	10.6 (10.1÷11.3)	11.2 (10.1÷12.9)	9.5 (7.9÷10.8)	9.3 (7.1÷10.1)
Hip rotation range, °	1	24.3 (19.7÷29)	25.0 (18.9÷32.4)	27.4 (18.8÷33.7)	29.5 (19.1÷38.6)
	2	33.2 (18.9÷49.3)	28.2 (23.5÷35.5)	27.4 (21.2÷32.5)	27.4 (24.7÷29.3)
Femur rotation range, °	1	19.5 (14.9÷22.7)	20.9 (15.6÷26.0)	22.5 (16.5÷29.2)	22.5 (17.7÷24.4)
	2	25.7 (16.5÷32.5)	28.0 (24.8÷32.5)	18.8 (14.5÷23.2)	21.4 (14.2÷24.7)
Knee motion range, °	1	54.0 (45.7÷64.0)	53.4 (47.9÷59.1)	49.9 (37.5÷52.4)	50.5 (43.3÷59.5)
	2	53.8 (28.8÷70.2)	50.6 (37.6÷59.3)	51.1 (44.9÷59.0)	53.0 (45.3÷56.0)
Foot motion range in the satittal plane, °	1	25.9 (16.7÷34.2)	23.0 (19.1÷27.7)	27.4 (22.6÷31.8)	25.2 (19.5÷29.4)
	2	30.5 (24.3÷37.4)	26.5 (22.4÷30.9)	25.4 (18.2÷31.3)	25.4 (18.1÷25.7)

Note: * — significant differences according to the criterion between groups 1 and 2 at this period of comparison after surgery;
[1] — reliable differences within this group compared with the previous study period

The key differences in kinematic parameters between the groups before multilevel surgeries were in range of motion and foot position. In group 1, passive dorsiflexion was significantly limited due to triceps contracture. Furthermore, the increase in knee extension range during the stance phase in group 1 naturally reflects the jump knee gait pattern, typical for this age group. No significant differences were found between the groups after surgery, although by the end of the follow-up, group 2 showed a trend toward increased knee flexion range during the stance phase, accompanied by full extension by mid-stance. This trend, combined with a clear limitation of maximum hip extension, significantly different from group 1, which is adaptive in nature at this stage, reflects the onset of the crouch gait pattern. This observation logically correlates with a decrease in Gait Profile Score values. It should be noted that no differences were found between the groups at the end of the follow-up in the parameter of maximum pelvic tilt in the sagittal plane: 14.8° (10.2÷18.8) in group 1 and 17.5° (13.8÷21.4) in group 2.

Table 5

Dynamics of several kinetic parameters

Parameter	Group	Before surgery	After surgery		
			1–2 years	2–3 years	4–5 years
Hip extension power, Nm/kg	1	**0.62 (0.45÷0.72)**	0.64 (0.48÷0.74)	0.72 (0.59÷0.84)	**0.89 (0.77÷1.0)**[1]
	2	**1.08 (0.79÷1.43)***	0.89 (0.63÷0.94)	0.89 (0.73÷1.08)	0.87 (0.76÷0.96)
Knee extension power, Nm/kg	1	0.4 (0.25÷0.53)	0.33 (0.17÷0.43)	0.6 (0.36÷0.82)	**0.62 (0.54÷0.64)**[1]
	2	0.53 (0.28÷0.75)	0.39 (0.12÷0.59)	0.51 (0.17÷0.64)	0.41 (0.16÷0.62)
Plantar flexion power, Nm/kg	1	0.66 (0.5÷0.86)	0.65 (0.39÷0.79)	0.79 (0.66÷0.95)	**1.12 (0.94÷1.19)**[1]
	2	0.62 (0.56÷0.81)	0.68 (0.49÷0.89)	0.78 (0.61÷0.97)	0.95 (0.81÷1.09)
Total power generated at the hip joint level, W/kg	1	**1.51 (0.96÷1.75)**	1.43 (1.0÷1.67)	1.61 (1.14÷1.63)	1.75 (1.29÷2.03)
	2	**2.93 (1.82÷4.11)***	0.98 (0.3÷1.31)	1.95 (1.39÷2.18)	2.03 (1.39÷2.37)
Efficiency of muscle contractions at the hip joint level, %	1	70.6 (63.4÷78.6)	72.2 (64.0÷80.2)	73.1 (64.2÷76.1)	70.3 (64.6÷73.7)
	2	68.8 (62.8÷72.4)	70.2 (64.5÷78.8)	69.1 (63.2÷75.7)	66.4 (56.3÷74.6)
Total power generated at the knee joint level, W/kg	1	1.7 (0.96÷2.18)	1.56 (0.99÷2.14)	2.1 (1.11÷3.04)	2.15 (1.43÷2.46)
	2	2.5 (1.46÷3.13)	2.1 (0.97÷2.57)	1.89 (1.29÷2.34)	1.69 (1.26÷2.1)
Efficiency of muscle contractions at the knee joint level, %	1	39.0 (26.5÷52.5)	39.1 (31.2÷46.1)	40.3 (31.9÷50.0)	**41.9 (35.8÷48.9)**
	2	38.3 (32.3÷37.0)	39.0 (31.1÷47.1)	33.2 (23.6÷41.2)	**30.7 (21.9÷35.3)***
Total power generated at the ankle joint level, W/kg	1	1.46 (0.66÷2.01)	1.17 (0.58÷1.39)	1.66 (0.98÷2.05)	**2.39 (1.51÷2.75)**
	2	1.64 (1.05÷2.13)	1.28 (0.71÷1.83)	1.39 (0.99÷1.63)	**1.5 (0.93÷1.66)***
Efficiency of muscle contractions at the ankle joint level, %	1	53.7 (44.1÷63.7)	48.4 (35.0÷61.5)	56.9 (48.9÷64.9)	61.1 (52.2÷68.0)
	2	52.2 (47.4÷55.2)	48.5 (41.2÷57.7)	50.9 (42.4÷59.8)	53.9 (49.2÷63.2)
Total power of the lower limb muscles, W/kg	1	4.64 (2.81÷6.42)	4.15 (2.77÷5.28)	5.39 (3.59÷7.36)	6.26 (4.78÷7.14)
	2	6.08 (4.98÷7.02)	4.36 (3.11÷6.31)	5.22 (4.1÷5.91)	5.23 (3.93÷7.1)
The effectiveness of the total power of the lower limb muscles, %	1	55.1 (51.1÷61.5)	54.4 (50.5÷58.3)	53.5 (50.3÷59.1)	58.9 (57.7÷60.2)
	2	54.9 (47.2÷60.7)	54.0 (49.7÷58.2)	52.9 (46.3÷58.7)	51.6 (46.3÷57.2)
Functional asymmetry of the total power of the lower limb muscles, %	1	19.7 (12.9÷25.7)	14.6 (5.2÷22.1)	21.1 (10.9÷27.0)	**20.4 (11.6÷28.9)**
	2	18.3 (11.6÷24.9)	19.8 (8.6÷24.2)	12.2 (6.85÷17.4)	**5.8 (4.67÷7.85)***
Functional asymmetry of the total efficiency of the lower limb muscles, %	1	6.8 (2.2÷9.7)	6.6 (4.5÷8.7)	8.6 (6.3÷10.7)	4.0 (2.3÷3.9)
	2	10.9 (4.6÷15.8)	7.3 (3.4÷4.1)	7.95 (5.0÷7.7)	4.4 (2.5÷6.28)

Note: * — significant differences according to the criterion between groups 1 and 2 at this period of comparison after surgery;
[1] — reliable differences within this group compared with the previous study period

Several significant findings can be highlighted. Significantly higher power characteristics of hip joint movements in group 2 before multilevel interventions reflect the dominance of these locomotion patterns in gait generation, while the role of plantar flexion remains diminished. In group 1 up to two years after surgery, an increase in the force of extension contractions was observed at all levels of the lower extremity biomechanic chain; significant differences emerged after four years compared to preoperative levels. In group 2, normalized muscle contraction force at the hip and knee extension level did not reach preoperative levels at any time point. However, at the ankle joint, an increase in plantar flexion torque values was observed in both groups.

More significant differences relate to the total generated contraction power. While a decrease in this indicator can be noted in both groups for all three joints within one to two years postoperatively, an increase exceeding baseline values was observed in the long-term follow-up only in group 1. In group 2, the increase in total power did not exceed baseline values for the hip and ankle joints, while for the knee joint, the decrease in extension power was constant throughout the follow-up period, becoming significantly lower than group 1 values after four years.

Absence of a decrease in contraction power efficiency in both groups during the observation period and a decrease in the asymmetry of power efficiency compared to the asymmetry of total power indicators at each study period for both groups should be noted. It reflects the synergistic interaction of muscles (adherence to the "optimal gait" rule) while maintaining compensation for motor impairments [34].

The results of the study of the dynamics in the total power of movements at the level of the knee and ankle joints are presented in Figure 1 and Figure 2.

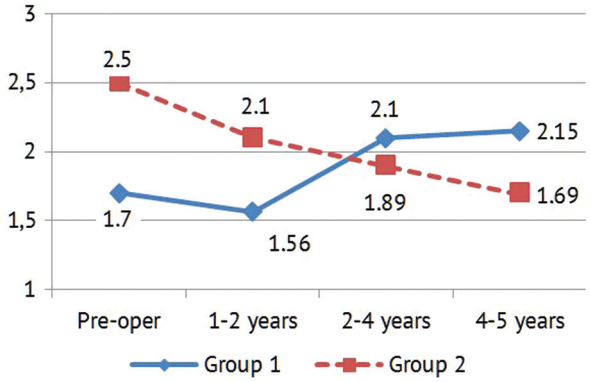

Fig. 1 Average values of total movement power at the knee joint level (W/kg) during follow-ups

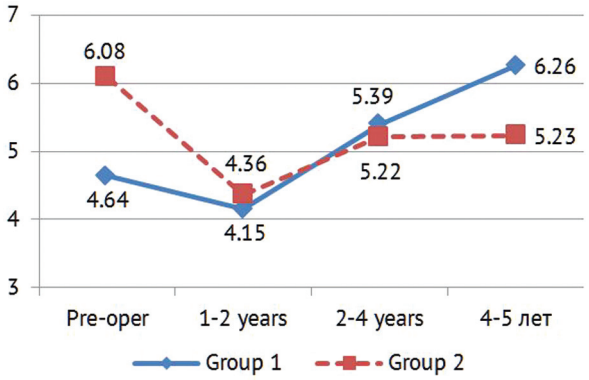

Fig. 2 Average values of total movement power at the ankle joint level (W/kg) during follow-ups

Finally, we would like to highlight the high positive correlation in group 1 between the "knee extension range of motion in the stance phase" and "knee extension power" parameters at two to three years and four to five years postoperatively: Spearman's coefficient was 0.600 and 0.691, respectively. For the "knee extension range of motion in the stance phase" and "knee extension power generation efficiency" pair, r = 0.501 and r = 0.483, respectively. This corresponds to sufficient functional capacity of the limb extension function. In group 2, the correlation coefficients for these pairs of parameters changed from positive (r = 0.115 and r = 0.430) to negative (r = –0.592 and r = –0.370) at two to three years postoperatively, reflecting a decrease in efforts and their efficiency for knee extension at the stance phase with an increase in the knee flexion range of motion. It is at this point that increased flexion in the hip joint becomes a compensatory mechanism at the onset of decompensation of the interconnected paired function of “knee extension” and “plantar flexion”.

The additional surgeries performed during the follow-up period were nine cases (18 %) in group 1, which included various combinations of the following:

— Repeated triceps surae lengthening (*n* = 2);

— Posterior tibial muscle tenodesis (*n* = 3);

— Evans foot reconstruction (*n* = 2);

— Adductor lengthening (*n* = 4);

— Patellar stabilization (*n* = 1);

— Correction of torsional deformities of the femurs (*n* = 3).

In Group 2, the following surgical procedures were performed on four patients:

— talonavicular arthrodeses (*n* = 3);

— posterior tibial muscle tenodeses (*n* = 3);

— correction of torsional deformities of the femurs (*n* = 1).

In most cases, the above-mentioned additional procedures were combined with the planned removal of osteosynthesis materials.

DISCUSSION

Multilevel bilateral orthopedic interventions in children with spastic diplegia who are able to walk independently (with or without assistive devices) are justified by the systemic nature of the disease, close timing of development of true orthopedic complications (contractures, bone deformities, dislocations/subluxations) and an integrated rehabilitation period [17, 33–35]. Baird et al. showed high correlation between the loss of achieved gait characteristics and the development of orthopedic deformities [5].

Graham et al. [6] distinguish two periods, coinciding in age (4–12 years) when orthopedic surgery becomes appropriate: the period of contractures and the period of bone deformations. During these periods, surgery is reconstructive in nature; it is possible to restore the anatomical parameters of the musculoskeletal system without performing elements of palliative interventions (arthrodesis).

It should be noted that before the development of orthopedic complications, treatment efforts in patients with cerebral palsy are aimed at developing their own motor abilities through the combined use of physical therapy [3], spasticity control, including botulinum therapy and selective dorsal rhizotomy [36, 37], and conservative methods for preventing contractures [38]. Unjustified premature orthopedic interventions on non-retracted muscles, even by increasing the passive range of motion in the joints, leads to their excessive weakening which is manifested by early functional decompensation and the development of iatrogenic crouch gait. A characteristic feature of iatrogenic crouch gait is its early age occurrence, even in the absence of torsional deformities [24, 31].

Multilevel interventions are usually performed at the age of 11–15 years (after pubertal growth acceleration) to achieve a stable surgical result [8, 17, 39, 40]. However, the authors note that in children over 12 years of age, it is often no longer possible to achieve complete anatomical restoration of the structures and relationships between limb segments and muscle proportions, and often the only solution is palliative orthopedic surgery for crouch gait [6]. Currently, there are conflicting recommendations regarding the optimal age of patients for reconstructive orthopedic interventions [3, 41, 42]. Svehlík et al. consider pubertal acceleration of lower limb growth as a factor in decompensation of motor capabilities and the development of the crouch gait pattern [18].

Performing orthopedic surgeries at an early age before the prepubertal growth spurt in children with cerebral palsy of GMFCS levels I–III is indicated in the case of early development of orthopedic complications of cerebral palsy (contractures of the ankle and knee joints, foot deformities, torsional deformities), which negatively affect the implementation of rehabilitation measures and orthotics, reducing the child's motor abilities. The average age of performing early interventions in various series was: six years [40], 6.4 [43], 8.6 [6], 9.7 [44]. It is in the period from four to 12 years that a gradual decrease in the range of motion in the joints occurs and the role of muscle retraction increases compared to spasticity, the level of which gradually decreases [6]. Hägglund and Wagner found that 47 % of four-year-old children had spasticity of the gastrocnemius muscle of levels II–IV according to the Modified Ashworth Scale [45]. However, only 23 % of children at 12 years of age had their previous level of spasticity.

In our study, indications for multilevel interventions are due to both the early development of true orthopedic complications of cerebral palsy and the negative impact of isolated lengthening of the Achilles tendons or so-called "minimally invasive" early interventions, referred to as fibromyotomies, the negative effect of which is explained by a significant weakening of the strength of the plantar flexors of the foot with an increase in the amplitude of passive dorsiflexion [24, 31].

The positive impact of multilevel interventions on the kinematic and kinetic parameters of gait was discussed by many authors. The key effects in the immediate and mid-term postoperative periods are increases in step length, walking speed, and knee extension in the support phase, as well as a decrease in pelvic tilt and normalization and/or improvement of foot kinematics at each moment of the gait cycle. Rutz et al. note a change in GPS from 20.7° to 11.1° (by 47 %) towards gait normalization in the period from one to three years after surgery [17]. Dreher et al. state the maintenance of a significantly improved integral GPS indicator in the long-term period in 77 % of patients (177 out of 231 patients) and, at the same time, a decrease in GPS values in the first year after multilevel interventions [7].

Many researchers agree that the period of maintaining the positive effect of multilevel interventions is quite long. Godwin et al. [40], Thomason et al. [44] and Terjesen [8] describe the maintenance of the positive effect on gait parameters and the overall functional outcome in children with GMFCS levels II–III five years after bilateral intervention. In a multicenter retrospective study, Dreher et al. showed the maintenance of the achieved improved kinematic parameters nine years after multilevel interventions, when the age of the patients at the time of the last instrumental gait analysis was 19 years 8 months [7].

Our results are similar to those of the studies presented above. Orthopedic surgery improved ranges of motion in all planes in both groups throughout the entire follow-up period. Importantly, a temporary deterioration in kinematic parameters after surgery within one to two years was followed by a progressive improvement toward normalization. Differences between the groups were revealed four to five years after surgery when previously compromised plantar flexion in group 2 manifested itself as a significant increase in GPS, combined with a decrease in gait speed and an increase in BMI. In our study, we merely observed a correlation between these parameters without establishing a cause-and-effect relationship: movement impairment leads to a decrease in gait speed and an increase in body weight, or vice versa. We also note a significant restriction in maximum hip extension in group 2; this observation is interpreted in the discussion of kinetic parameters.

The authors note the need to perform individual additional surgeries (often combined with the removal of osteosynthesis material) to preserve the result of the primary intervention: Dreher et al. [7] in 39 % of cases, Tejersen et al. [8] in 48.3 %, Rutz et al. in 64.3 % [17]. At the same time, no statistically significant relationship was found between the incidence of additional interventions and parameters of gender, GMFCS level, previous surgeries, or age at surgery. In our series, the rate of unplanned surgeries aimed at preserving the results of the primary intervention is comparable to literature data.

The comprehensive treatment strategy for patients with cerebral palsy is based on the development of motor skills, functions, and improvement of gait parameters, as well as the prevention of secondary orthopedic complications, including walking with flexed knee joints (flexed-knee gait) which is a precursor to the crouch knee gait pattern when reconstructive treatment is impossible [3, 6, 10]. Moreover, the development or non-development of this pattern is considered a criterion for the effectiveness of the treatment [7, 8].

Therefore, we examine the results specifically from the perspective of identifying early signs of extension decompensation in the late period following surgical treatment that was necessarily performed at an early age in children with cerebral palsy of GMFCS levels I–III. It is important to emphasize the fundamental principle that improving motor abilities and gait parameters does not affect the GMFCS level caused by static encephalopathy [46].

We agree with the opinion of Hua et al. about the lack of studies that fully reflect the dynamics of kinetic parameters of gait after surgery, as well as the dynamics of kinematic data [47], given

that the efficiency of energy expenditure for generating movements in children with cerebral palsy is 28 % lower than in healthy peers. The study of Van Rossom et al. confirms that multilevel interventions improve kinematic parameters, normalize moments of force at the level of the involved joints and improve the parameters of generated power of movements [48]. Considering the natural evolution of movement disorders in the direction of the crouch gait pattern [6, 9, 10], accompanied by extreme inefficiency of energy supply of gait, it is necessary to choose the methods for performing orthopedic interventions and subsequent rehabilitation that prevent such development of movement disorders. An obvious predictor of this unfavorable evolution, as clearly demonstrated by Pilloni et al., is the surgical weakening of the plantar flexors. Thereby, the first sign is an increase in the minimal flexion of the knee joint in the support phase [24].

Our results confirm the improvement in kinetic gait parameters after multilevel interventions in previously surgically intact patients: normalized hip, knee, and ankle extension moments increase, accompanied by an increase in the total power generated at these joints. In the long-term follow-up, total power exceeds baseline levels without losing its effectiveness. However, we observed a progressive decrease in knee and hip extension power in patients who underwent early triceps surae lengthening even if there was a progressive increase in plantar flexion power. Consequently, the total power generated at the knee and ankle joints was significantly higher in group 1 than in group 2. Similar to GPS values, a decrease in kinematic parameters was observed in both groups during a one- to two-year follow-up period. Another important difference is that while total power in group 1 was higher than preoperative after four to five years postoperatively, it never reached preoperative values in group 2. We also point to the predictor of extensor mechanism failure (hip extension deficit combined with excessive pelvic tilt in the sagittal plane), identified in our study and interpreted as a compensatory mechanism for the anterior displacement of the center of mass from the axis of knee joint motion. Nevertheless, the positive effect of surgery in both groups is similar and consists of a reduction in the asymmetry of total effectiveness relative to the asymmetry of total power. However, this is insufficient to maintain stable treatment results in patients predisposed to the development of the iatrogenic crouch gait pattern (group 2).

Limitations of our study are its retrospective nature and a relatively small number of patients in group 2. To obtain a comprehensive conclusion on the effect of multilevel interventions performed in children before the prepubertal growth acceleration, it is necessary to follow the dynamics of kinematic and kinetic data until the completion of their natural growth.

CONCLUSION

Multilevel orthopedic surgeries performed in children due to orthopedic complications before the prepubertal growth spurt are effective in improving kinematic parameters, accompanied by the development of functional abilities and increased strength characteristics of movement, only in children who did not undergo early Achilles tendon lengthening or percutaneous fibromyotomies. The results remain stable for four to five years after surgery.

Isolated Achilles tendon lengthening, or percutaneous fibrotomies, performed at an early age, hinder improvement and development of lower extremity muscles, increases in torques, and increases in muscle contraction power at long-term follow-up, even if multilevel interventions corrected bone deformities and contractures of the knee and hip joints. In the fibrotomies and early isolated Achilles tendon lengthening group, GPS parameters and gait speed worsen, and BMI increases four to five years after multilevel procedures.

Restricted hip extension with increased pelvic tilt in the sagittal plane during the support phase is a compensatory mechanism for the deficit in knee extension strength and can serve as a predictor of the development of the crouch gait pattern.

Conflict of interests None.

Funding None.

Ethical approval Approval to conduct the research was obtained from the Ethics Committee of the Ilizarov National Medical Research Center of Traumatology and Orthopedics.

Informed consent Parents of the children participating in the study were present during the analysis and confirmed their informed consent for the publication of the study results without identification.

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Methodology of gait assessment for identifying mechanisms of decompensatory musculoskeletal fatigue in patients with hip arthritis

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Abstract

Introduction Gait analysis is an objective tool for assessing treatment results and musculoskeletal function in patients with orthopedic pathology. Safety of compensatory mechanisms and the fatigue component seen with repeated measurements and being dependent on the clinical situation are essential for the patients.

The **objective** was to develop a methodology of gait assessment for identifying mechanisms of decompensatory musculoskeletal fatigue in patients with hip arthritis including those with THA of the contralateral limb.

Material and methods The study included 41 patients with Kellgren – Lawrence grade III and IV hips. Gait analysis was performed using the Stedis-Step treadmill and five Neurosens inertial sensors (Neurosoft LLC, Ivanovo, Russia), recording the spatiotemporal and kinematic characteristics of movements in the lumbosacral spine, hip and knee joints being synchronized with the step cycle. Patients were divided into two groups according to gait assessment protocol including Group 1 (n = 26) with three series of two-minute tests with a break of at least 20 minutes; Group 2 (n = 15) with three series of two-minute walks without a break with the total length of six minutes.

Results A 20-minute rest was enough to reproduce baseline gait parameters. Walking parameters including maximum flexion phase, stance period and range of motion could serve as markers for early detection of mechanisms of decompensatory muscle fatigue. The total hip arthroplasty on the contralateral side significantly affected the gait parameters.

Discussion New methods of no-break gait assessment facilitated decompensation and fatigue mechanisms identified in patients with hip arthritis. Reduced movement amplitude during short-term load indicated increasing fatigue even over a brief period (6 minutes).

Conclusion The methodology allowed for the identification of mechanisms of decompensatory musculoskeletal fatigue in patients with hip arthritis including those with THA of the contralateral limb, early diagnosis, improved monitoring and rehabilitation.

Keywords: gait analysis, decompensatory reaction, fatigue, hip arthritis, methodology, Stedis

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INTRODUCTION

Hip arthritis (HA) is a serious medical condition which can lead to significant medical and social challenges including impaired daily-life gait and quality of life [1, 2]. The incidence of osteoarthritis of the hip is constantly increasing and can be associated with increased life expectancy and a sedentary lifestyle [3]. Expanding surgical indications may be associated with the improved safety and technical variety that would improve quality of life and neuropsychological status of patients [4, 5]. The number of patients requiring revision total hip replacement (THR) who had undergone primary THR some 10–15 years ago is growing progressively. There are non-standardized approaches to diagnosis, selection of the optimal time for surgical treatment and objectification of the effectiveness of rehabilitation of this cohort of patients. Gait analysis is one of the most accurate and objective tools for assessing treatment results and an integral characteristic of function and activity for orthopedic patients [6, 7, 8].

Modern studies demonstrate that a multidisciplinary approach to the management of hip arthritis provides significant clinical results [9, 10]. The effectiveness would depend on the accurate assessment of individual compensatory capabilities of the musculoskeletal system and the reproducibility in multicenter, multidisciplinary management of the patient. The analysis of biomechanical disorders is essential for patients with HA and combined pathology, in the presence of the contralateral THR, in particular. Despite the available publications on gait analysis, clinical recommendations (Objective assessment of walking function: clinical guidelines https://rehabrus.ru/Docs/2017/02/Hodba_met_rek_pr_fin.pdf) and theoretical developments of the main biomechanical phenomena [11, 12], there are several fundamental problems:

— lack of uniform standards for conducting load tests;

— significant influence of fatigue factor on the results of repeated measurements of the gait biomechanics;

— insufficiently considered role of adjacent segments (pelvis, spine, knee joints) in compensating for the motor deficit of the hip.

The safety margin of compensatory mechanisms and the fatigue component are important for repeated measurements, which can vary significantly depending on the clinical situation. Traditional assessment methods may not allow for a quantification of the critical parameter, which significantly influences the effectiveness and volume of medical interventions, the process of patient recovery, his/her personalized biomechanical portrait and prognosis for recovery [13]. Restoration of the walking function, as a key goal of orthopedic interventions, requires objective criteria of effectiveness. Technologies that would facilitate structural and functional restoration without formation of pathological motor compensations are essential to pursue the goal. Inertial sensor technology as one of the ways of objective gait assessment can be introduced into clinical practice. The method suggests the use of static parameters and dynamics in changed motor stereotypes under weight-bearing, treatment and correction in real time, which is especially important for predicting the effectiveness, timeliness and optimal volume of treatment and rehabilitation. In this case, the use of inertial sensors plays a key role, allowing us to identify movement patterns in HA patients providing a more accurate assessment of the functionality [14, 15, 16].

The **objective** was to develop a methodology of gait assessment for identifying mechanisms of decompensatory musculoskeletal fatigue in patients with hip arthritis including those with THA of the contralateral limb.

MATERIAL AND METHODS

The study was conducted between January and March 2025 at the Pirogov Clinic of High Medical Technologies, St. Petersburg State University. The walking pattern was assessed using the Steadis-Step walking simulator and biofeedback (Neurosoft LLC, Ivanovo) in the Assessment configuration (RU No. RZN 2018/7458 dated 07.08.2018). Five Neurosens inertial sensors were used to be placed on the lumbosacral spine and on symmetrical areas of the middle third of the femurs and tibiae 2 cm above the lateral ankles (Fig. 1). The patient was asked to walk on a flat surface for two minutes at a comfortable pace.

Fig. 1 An instance of inertial sensors placed for patient examination

The analysis of standard parameters automatically entered into the gait analysis protocol with the software included:

— temporal parameters of walking (step cycle (SC), step, step frequency); (цикл шага (ЦШ), шаг, частота шага);

— phases of the gait (support period, single support, double support, first double support, second double support, beginning of second double support, stride time);

— spatial parameters of the gait (height of the foot rise, circumduction — the distance from the central line of the walking direction to identical points of the foot in the frontal plane, half of the step base);

— hip flexion/extension (flexion/extension range, maximum extension phase, maximum extension, maximum flexion phase, maximum flexion);

— adduction/abduction in the hip joint (amplitude of adduction/abduction, phase of maximum abduction, maximum abduction, phase of maximum adduction, maximum adduction);

— hip rotation (rotation amplitude, phase of maximum external rotation, maximum external rotation, phase of maximum internal rotation, maximum internal rotation);

— kinematic parameters of the pelvis: adduction/abduction, flexion/extension, rotation.

Considering the significance of the decreased support function of the hip joint with degenerative changes in the joint, goniograms and kinematic parameters synchronized with the walking pattern of the hip joint (the diseased and intact sides) were additionally analyzed during the support period (up to 50 % of the SC with a measurement step of 5 % of the SC). The study included 41 patients with Kellgren–Lawrence grade III and IV hips admitted to the trauma and orthopaedic department for elective treatment using THR. Preoperative examination was performed for the patients. Radiographs were provided using a digital radiography system with automatic image stitching SG Jumong retro (Korea). Exclusion criteria included patients with acute and/or chronic diseases of various etiologies in the acute stage. A comprehensive prospective examination was performed for THR patients using an objective gait function assessment technology based on inertial sensors.

A method of interval and continuous testing lasting six minutes was used to analyze the biomechanical aspects of the gait and identify the presence of specific fatigue changes in movement. The effect of THR on biomechanical indicators in hip arthritis was assessed. The patients were randomly divided into two groups. The gait analysis was performed in three series in group 1 (n = 26) with a standard protocol of two minutes each with a break between tests (rest) of at least 20 minutes. The gait analysis was also performed in three series in group 2 (n = 15) with a standard protocol of two minutes each, with a total examination time of six minutes. The groups were comparable in terms of gender and age composition, which allowed comparison of the data obtained (Table 1).

Table 1

Characteristics of study groups

Description		Values by groups	
		Group 1 (n = 26)	Group 2 (n = 15)
Mean age, years		58.23 ± 14.78	59.93 ± 14.85
Males	abs.	15	6
	%	58	40
Females	abs.	11	9
	%	42	60
Unilateral HA	abs.	15	10
	%	58	67
Bilateral HA	abs.	5	1
	%	19	6
Presence of contralateral THR	abs.	6	4
	%	23	27

Statistical processing of the variables was performed using the IBM SPSS Statistics v/23.0 program. The Shapiro – Wilk test was used to identify normal distribution of the quantitative data. The results showed that all data arrays corresponded to the normal distribution, which allowed the parameters to be used for further analysis. The reliability of differences was assessed using the Student's t-test (for independent and dependent groups) and the Spearman's rank correlation test was employed to identify correlation relationships between the parameters. The reliability level was taken as $\alpha = 0.05$. The results were presented as $M \pm \sigma$, where M was the arithmetic mean with σ being the standard deviation of the sample.

The study was performed in accordance with ethical principles for medical research involving human subjects stated in the Declaration of Helsinki developed by the World Medical Association in 1964, Federal Law dated 21.11.2011, No. 323 “On the Fundamentals of Health Protection of Citizens in the Russian Federation”, Federal Law dated 27.07.2006 No. 152 “On Personal Data”.

RESULTS

The spatial-temporal parameters of gait showed no significant differences in non-weight-bearing parameters for the patients in the series (Table 2), which is consistent with the previous assumption about a good compensatory adaptation corridor in trauma and orthopedic patients. Significant differences in the support period were determined due to single support, a decrease in rotation on the side of the involved joint and an earlier phase of maximum flexion, which generally reflect the mechanisms of compensatory unloading of the involved limb to reduce the support load on it.

Table 2

Spatiotemporal parameters of the step cycle and hip joint kinematics

Spatiotemporal parameters	Inlolved limb	Intact limb
Step cycle, s (SC)	1.24 ± 0.16	
Step, s	0.63 ± 0.09	0.61 ± 0.08
Step frequency, s/min	49.20 ± 0.05	
Support period, % SC	63.79 ± 3.87**	66.77 ± 3.71
Single support, % SC	33.17 ± 3.66**	36.13 ± 3.81
Double support, % SC	3.63 ± 6.73	30.63 ± 6.75
Beginning of the second double support, % SC	48.98 ± 2.43	50.95 ± 2.43
Height of foot rise, cm	11.20 ± 2.60	11.83 ± 2.19
Circumduction, cm	3.02 ± 1.39	3.24 ± 1.39
Flexion/extension range, °	54.15 ± 8.05	55.00 ± 9.32
Maximum extension phase, % SC	89.17 ± 21.71	89.20 ± 23.23
Maximum extension, °	7.41 ± 5.01	6.44 ± 5.27
Maximum flexion phase, % SC	69.34 ± 3.54**	72.76 ± 2.99
Adduction/abduction amplitude, °	8.85 ± 3.71	10.10 ± 3.29
Maximum adduction/abduction phase, % SC	66.46 ± 19.85	64.32 ± 21.30
Rotation amplitude, °	11.29 ± 3.52*	13.39 ± 4.91

Note: the reliability of differences between the involved and intact limbs demonstrated: * $p \leq 0.05$, ** $p \leq 0.01$

The analysis of the kinematic measurements of the hip flexion/extension in group 2 (without an interval between examinations) on the side of the hip arthritis, the flexion significantly decreased from the first to the third measurement suggesting progressive fatigue or pain. The indicators on the contralateral side, being primarily higher, also decrease by the third measurement, which might be a manifestation of compensatory overload (Fig. 2a). The initial flexion values on the involved side were higher in group 1 (interval walking with rest) with the hip extension increased by the third measurement suggesting that rest was ineffective as a long-term restorative measure for walking function. The decrease in the initial amplitude on the contralateral side was not accompanied by significant fatigue manifestations similar to those identified in the previous group, that is, a slowdown in the progression of fatigue was noted (Fig. 2b).

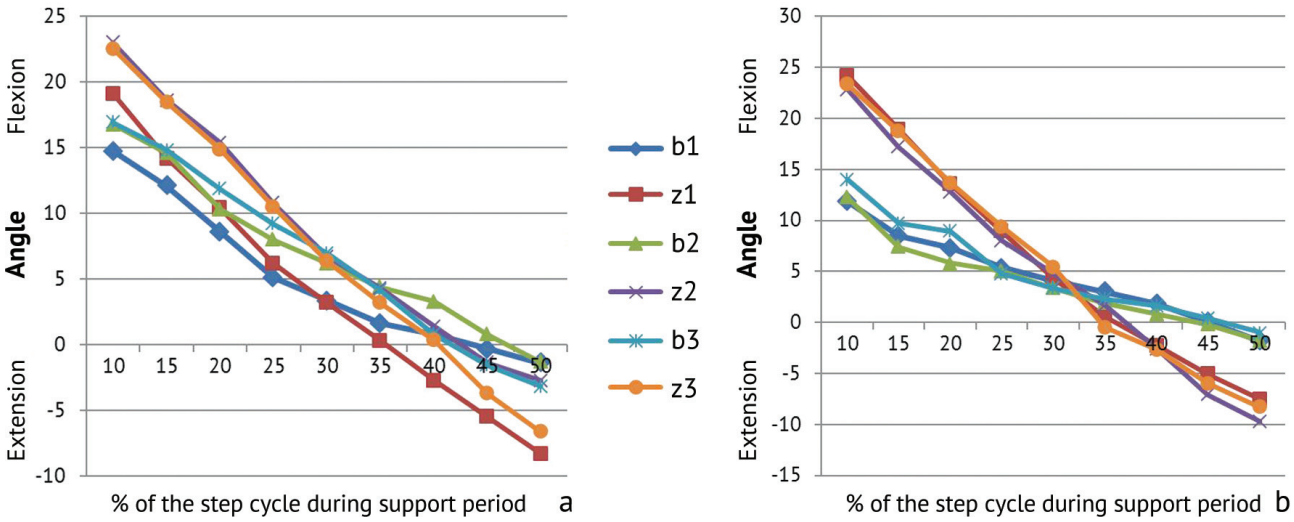

Fig. 2 Dynamics in flexion (positive values) and extension (negative values) values in the step cycle: (a) in group 2; (b) in group 1. Note: b1, b2, b3 are values for the involved lower limb for the first, second and third examinations; z1, z2, z3 are values for the intact lower limb for the first, second and third examinations

The analysis of the kinematic parameter adduction/abduction in group 2 (without interval rest) showed a progressive increase in the amplitude on the side of the involved joint (b1 = 3.70; b3 = 6.65; $p < 0.05$) suggesting compensatory hypermobility. A decrease in values could be observed on the intact side (z1 = 3.90; z3 = 1.65; $p < 0.05$), reflecting adaptive mechanisms for gait stabilization (Fig. 3a). In group 1 (interval rest), on the painful side the range of motion increases, possibly due to a temporary decrease in pain intensity, while on the contralateral side we observe a decrease in values. The range of motion increased on the involved side in group 1 (interval rest), possibly due to a temporary decrease in pain intensity and decreased values were noted on the contralateral side. This might indicate a redistribution of the load to symmetrize the walking pattern, which indicated a universal "rule of optimal gait" with synergistic interaction of muscles (Fig. 3b).

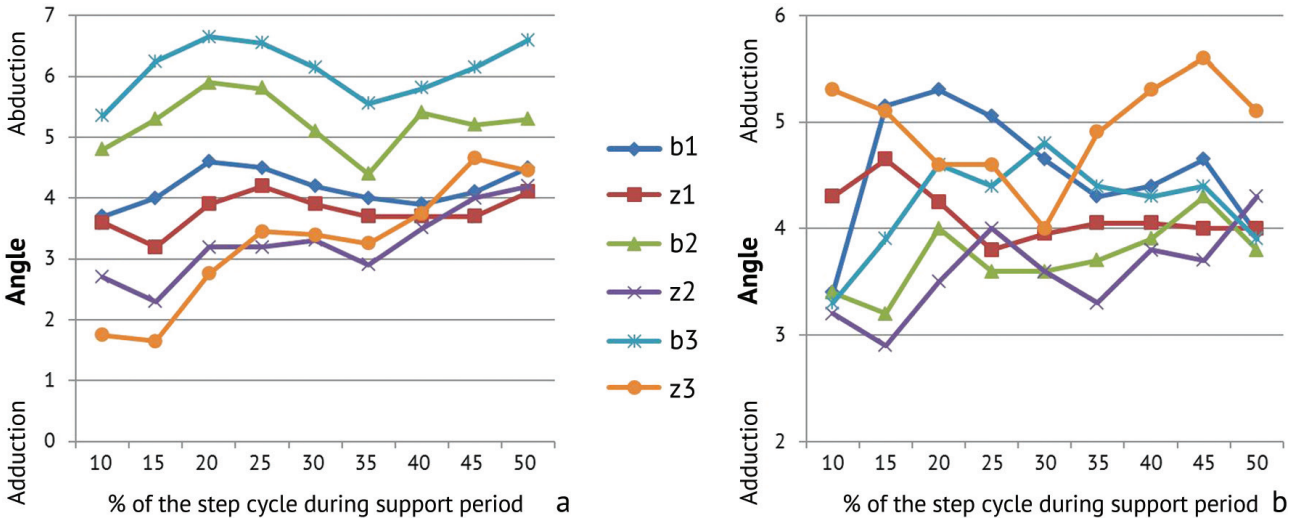

Fig. 3 Dynamics in adduction (positive values) / abduction (negative values) values in the step cycle: (a) in group 2; (b) in group 1. Note: b1, b2, b3 are values for the involved lower limb for the first, second and third examinations; z1, z2, z3 are values for the intact lower limb for the first, second and third examinations

Thus, the presence of interval rest did not allow us to identify subtle compensation mechanisms and the fatigue contribution of ultimate stress in hip arthritis. Walking parameters were compared in group 2 (without interval rest) separately in patients with and without contralateral THR to identify fatigue decompensation, additionally dividing the group into two subgroups: with contralateral THR ($n = 4$) and without contralateral THR ($n = 10$) (Table 3).

The analysis of the results showed the decreased support period in the subgroup of THR patients, while the pelvic flexion/extension indices (the higher hierarchical level of compensation) remained stable indicating a more uniform distribution of the load. The amplitude of adduction/abduction during walking remained unchanged, which indicated stability of movements. The support period increased in the subgroup without contralateral THR with no changes in the amplitude of flexion/extension of the pelvis during movement, which might indicate compensatory overload of the musculoskeletal system with repeated loads. Adaptive patterns were manifested in the increased phase of maximum flexion. It was suggested that the revealed phenomena were a manifestation of the systemic nature of the hip arthritis and limited compensation reserves of the contralateral limb. Additionally, flexion/extension, abduction/adduction and rotation of the hip joint were analyzed in patients with and without contralateral THR based on the results of the analysis of the walking in group 2 (without interval rest) (Fig. 4). Lower values of flexion/extension amplitude were observed during walking in the presence of the contralateral THR.

Table 3

Gait parameters in patients of group 2 (without interval rest) depending on the presence of THR on the contralateral side

Parameters of the automatic gait analysis protocol	Measurement 1			Measurement 2			Measurement 3		
	With THR (n = 4)	Without THR (n = 10)	p < 0,05	With THR (n = 4)	Without THR (n = 10)	p < 0,05	With THR (n = 4)	Without THR (n = 10)	p < 0,05
Support period, difference, %	1.88	3.43	–	1.73	4.21	+	1.50	3.25	+
Single support, difference, %	1.75	3.52	+	1.38	4.10	+	1.53	3.25	–
Double support, difference, %	1.28	3.11	–	1.30	2.96	+	1.20	2.25	+
Stride period, difference, %	1.88	3.43	–	1.73	4.16	+	1.50	3.25	+
Maximum flexion phase, difference, %	2.00	3.50	+	1.75	4.20	+	1.75	3.00	+
Pelvis (involved side), flexion/extension, °	5.00	9.10	+	4.75	9.70	+	4.50	9.00	+
Pelvis (contralateral side), flexion/extension, °	5.00	8.80	+	4.50	9.40	+	4.50	9.00	+
Adduction/abduction, difference, °	0.00	0.50	+	0.25	0.20	–	0.00	0.00	–

Note: difference, between the right and left lower limbs; %, of the step cycle duration.

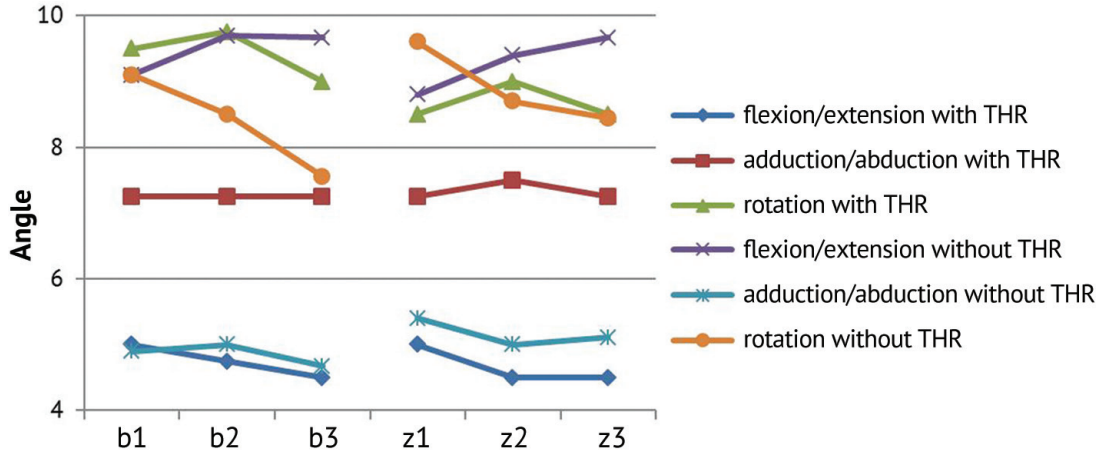

Fig. 4 Dynamics in the hip flexion/extension, adduction/abduction and rotation in the step cycle without interval rest between examinations: b1, b2, b3 are values for the involved lower limb for the first, second and third examinations; z1, z2, z3 are values for the intact lower limb for the first, second and third examinations

DISCUSSION

New treatment methods being developed and introduced into clinical practice are increasing the importance of the search and innovative means to be applied for objective outcome evaluation. Visualization of the dynamics and objective analysis of the walking function allows for a more accurate assessment of the impaired movement function in the dynamics using different technologies for conservative and orthopedic treatment of patients with HA, starting from the early stages of the disease [17, 18].

Ibara et al. suggested that objective assessment of movement function in patients with hip osteoarthritis could be produced without wearable sensors using only force platform data [14]. This approach is simple and fast, but it is limited to measuring reactive forces only and does not allow obtaining information about the kinematics of movements in the musculoskeletal system

as a whole, in all the variety of compensatory mechanisms included, in changes in joint angles, speeds and trajectories of limb movements, and inclusions of higher hierarchical levels. The use of wearable sensors facilitates simultaneous measurements of the kinematics and spatiotemporal parameters of walking providing a more complete understanding of gait patterns and allows for a more accurate analysis of motor functions. Therefore, wearable/inertial sensors are preferable for a comprehensive assessment of motor activity.

The findings suggest that gait analysis using inertial sensor technology is reproducible in multicenter studies, and the presence of rest between individual examinations does not affect the objective biomechanical parameters of the gait pattern with the rest of at least 20 min. The reproducibility of gait parameters using inertial sensor technology was reported in other studies of healthy people and patients with mobility impairments [12, 19, 20]. The methodology used in the study for assessing gait without interval rest with three series of walking analysis allows us to identify key features of decompensatory and fatigue mechanisms in patients suffering from hip arthritis. The use of multiple inertial sensors in combination with the proper placement is a promising approach for fatigue recognition and movement safety monitoring [21]. The available machine learning models can detect fatigue-related changes in gait, for example, based on ground reaction data from young healthy individuals running [22]. However, such models, trained on small samples and in narrow conditions, are not suitable for patients with hip osteoarthritis, as movements can vary greatly. Studies on larger samples are required to allow the use of the models in a clinic, taking into account all input parameters, that is, the models should be refined and retrained in groups of such patients. The promising approach is confirmed by the use of machine learning for the diagnosis of hip osteoarthritis using gait parameters [23]. A decreased amplitude of motion in the joints during the analysis of walking without rest between measurements indicates an increase in fatigue compensatory processes of the musculoskeletal system, even with short-term (six minutes in total) loads, sufficient to detect the depletion of the body's resources and requiring compensation.

Davis-Wilson et al. reported “an increase in forward trunk tilt on the side of osteoarthritis and a bilateral reduction in step length” detected with a six-minute walk test which was associated with compensatory mechanisms caused by pain, while the authors did not mention fatigue mechanisms of influence [24]. The authors reported the decreased walking speed being associated with pain, without the possibility to assess the fatigue component [25]. The contralateral limb with an intact joint, being an equivalent part of the single biomechanical chain of the musculoskeletal system of the lower limbs, is also involved in the compensation process, which manifests itself in signs of functional overload with a “vicious circle” being launched, increasing the asymmetry of the gait and reducing the effectiveness of the compensatory mechanisms. Hulet et al. reported the use of an optoelectronic system to identify gait asymmetry and compensatory mechanisms to be associated with pain in the involved joint and limited movement in the patient’s hip joint and in the ipsilateral knee and ankle joints [26]. Van Rossom et al. reported no overload of the contralateral joint and ipsilateral knee joint in patients with hip osteoarthritis walking up stairs suggesting the specificity of compensatory strategies in different conditions and types of activities [27]. Adaptation of movements associated with fear of movement due to pain during walking can help patients reduce pain that can lead to restructuring of the entire pattern due to other levels of the musculoskeletal system [27, 28]. Maezawa et al. suggested that a difference in the lower limb length of 20 mm has little effect on walking patterns indicating the presence of universal

working compensatory mechanisms in the absence of severe deformity [29]. Compensation for leg length discrepancy occurs because the shortened lower limb is lengthened by “greater hip and knee extension, hip abduction, ankle plantar flexion, and less hip adduction”, and the other lower limb is shortened “due to higher flexion at the hip and knee joints, higher adduction of the hip, dorsiflexion and lower adduction of the ankle joint” [30]. We found no studies reporting the effect of THR on fatigue mechanisms during walking. Langley et al. showed that normal motor activity can be restored in patients with THR with high function [31].

We report lower values of the flexion/extension amplitude during walking in our series in the presence of the contralateral THR. Such indicators rather reflect the stabilization of biomechanics, the stability, rather than deterioration of function. In our opinion, the presence of the contralateral THR can limit excessive movements, preventing hypermobility and overload on the involved and intact sides in the presence of THR without the inclusion of the higher level of compensation of the musculoskeletal system (lumbosacral spine). If the reduced flexion and extension range of motion during walking had been caused by ineffective rehabilitation, the rotation and adduction/abduction range of motion would also change, but according to our data, they remain stable. The results obtained indicate the importance of integrating the proposed dynamic gait assessment methodology into clinical practice for personalizing rehabilitation programs and early diagnosis of hidden disorders. However, limitations related to sample size require further studies including additional assessment methods (quality of life questionnaires, electromyography) in an expanded cohort of patients. Algorithms for predicting decompensation based on biomechanical markers and machine learning are to be devised to optimize treatment and improve the quality of life of patients with hip arthritis.

CONCLUSION

A rest period of at least 20 minutes between individual series of walking studies was found to be sufficient to reproduce the initial data of walking parameters and can be used in multicenter, multidisciplinary patient care. In the continuous walking group, reliable differences were obtained in the dynamics of flexion/extension in the hip joint on the intact side increasing to 35 % of the step cycle from the first to the third measurement and to 45 % of the step cycle from the first to the second measurement. No identical measurements of the manifested fatigue component were obtained in the group of patients with rest between series of passes. The analysis of continuous walking revealed the stress of the musculoskeletal compensation to achieve the optimum, while better functioning provided for the involved limb due to the greater load borne by the healthy side. The presence of the contralateral THR significantly affects the walking pattern of a patient suffering from unilateral hip arthritis: lower values of the hip flexion/extension amplitude were recorded in the presence of THR restricting excessive movements and preventing hypermobility and overload on the involved and intact sides.

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Ethical standards. *The study was conducted in accordance with the ethical standards of the Helsinki Declaration of the World Medical Association.*

Informed consent. *All patients participating in the study voluntarily signed informed consent for the publication of personal medical information in an anonymous form.*

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Evaluation of sclerostin as a new biomarker in the diagnosis of osteoporosis

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Abstract

Background Sclerostin is a glycoprotein mostly produced by osteocytes; it has a key function in bone metabolism and the pathophysiology of osteoporosis.

Objectives The aim of this study is to evaluate the potential use of sclerostin as a new biomarker in the diagnosis of osteoporosis.

Methods This case-control cross-sectional study was carried in Najaf, in Iraq. Seventy patients diagnosed with osteoporosis were involved in the study. The control group consisted of 40 apparently healthy persons identified during the same period. Body Mass Index (BMI) categories were classified according to the world health organization classification. Serum sclerostin levels were determined by a sandwich ELISA technique.

Results The mean sclerostin concentration in patients was 7.9 ± 2.3 ng/mL, much greater than that measured in the control group 2.88 ± 1.22 ng/mL. The univariate logistic regression analysis shows a significant association between high sclerostin levels and the likelihood of having osteoporosis, with an odds ratio of 1.66 and a *p*-value of < 0.034. The results also indicated that sclerostin reported a sensitivity of 78 % and specificity of 82 % (*p*-value 0.029).

Conclusions This study indicated a strong association between high serum sclerostin levels and having osteoporosis risk, suggesting its potential as a bone health biomarker. Further research on larger sample is required to confirm its diagnostic value.

Keywords: sclerostin, osteoporosis, body mass index, receiver operating characteristics, area under the curve

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INTRODUCTION

Sclerostin is a glycoprotein mostly produced by osteocytes; it has a key function in bone metabolism. As such, sclerostin holds critical assumptions for the understanding and treatment of diseases related to bone. The pathway involves Wnt/β-catenin and the regulation by micro RNAs that sclerostin has to create in itself an interaction, therefore creating complexity which needs future attention [1]. Further studies on the structure and physiology of sclerostin will not only deepen the knowledge about bone but also help in creating new ways of treating issues related to bones, like osteoporosis. It works as an inhibitor for the growing process of bones by blocking a certain type of signaling linked to Wnt/β-catenin that is very important for producing new bone cells [2]. The implementation of sclerostin measurement in clinical practice comes with various benefits. It permits better patient stratification according to their fracture risk, which can consequently inform more individualized treatment strategies. For instance, the level of sclerostin could direct the choice of pharmacologic therapies that work by enhancing bone density and lowering fracture risk [3]. These individualized treatment plans are most important in postmenopausal women, where there is a higher prevalence of fractures related to osteoporosis [4]. Besides, the levels of sclerostin give judgments about bone formation over resorption; thus, it has potential as a monitoring biomarker for treatment. By evaluating changes in sclerostin levels over time, it can help at least for sure interventions and hence improve indexing treatments [5]. J. Delgado-Calle et al. highlighted the role of the sclerostin–LRP4 interaction in bone metabolism, suggesting that sclerostin suppresses Wnt/β-catenin signaling through this pathway. This mechanism is crucial for understanding the way by which sclerostin controls bone remodeling and demonstrates that therapeutic modulation of this pathway may offer novel strategies for the treatment of osteoporosis [6]. Regulatory micro RNAs can also be one of the routes through which miR-218 influences sclerostin, hence affecting the differentiation of osteoblasts. Therefore it shows the subtle intricate role sclerostin plays within the larger parameters of bone biology. A study by M.Q. Hassan et al. reported that miR-218 enhances osteoblast differentiation through down-regulation of sclerostin, therefore promoting Wnt signaling pathway activity [1]. The cross-talk between miR-218 and sclerostin not only gives a greater insight into osteobiology but indeed opens up prospective pharmacological targets for driving bone formation processes in pathological states characterized by reduced bone mass [7]. The bone formation effects of sclerostin are just one small aspect of its physiology. High levels of sclerostin, and therefore low skeletal mass, are often seen in postmenopausal women and so underscore the involvement of sclerostin in osteoporosis [8]. This was one of the objectives tested clinically in a trial like that of R.R. Recker et al., which checked whether blosozumab, an anti-sclerostin monoclonal antibody, could increase bone mineral density in such patients. The findings revealed that at both the spine and hip, blosozumab substantially increased bone mineral density maturing the concept of sclerostin as a negative regulator of bone formation with an optimistic therapeutic approach for managing osteoporosis [9]. The various signaling pathways that involve sclerostin also point to its multiple roles in maintaining healthy bones. Those are the interactions from which one might derive insight aimed at crafting fresh intervention strategies leveraging targets on sclerostin to boost bone mass and reduce osteoporotic infection dangers [10]. There remains a gap in knowledge of the role of sclerostin in bone biology. Thus, till now, the exact molecular mechanisms that govern the regulation of sclerostin expression under different physiological conditions have not been fully clarified. Also, though well established, the contribution of other potential interacting partners to the sclerostin-LRP4 interaction should

also be explored [11]. The future should bring studies that uncover new microRNAs and signaling pathways involved in regulating networks for controlling sclerostin expression and activity. Longitudinal studies on bone health after treatment with anti-sclerostin therapies like blosozumab in varied populations would help fill this gap. Studies outside osteoporosis, like metastatic bone disease, will give us broader information on the role of sclerostin in skeletal health [9].

The **aim** of this work is to evaluate the potential use of sclerostin as a new biomarker in the diagnosis of osteoporosis.

MATERIALS AND METHODS

Patients and data collection

This case-control cross-sectional study was carried out at Al-Najaf General Hospital, in Najaf, in Iraq, from February 2024 to September 2024. Seventy patients diagnosed with osteoporosis were involved in the study. The control group consisted of 40 apparently healthy persons identified during the same period. Information about the age and body mass index (BMI) was collected directly from the patients. BMI categories were classified according to the World Health Organization (WHO) classification [12]. Serum sclerostin levels were determined by a technique of sandwich ELISA using the Human SOST Quantikine Immunoassay kit (Rand D, USA). Human SOST Quantikine Immunoassay Kit is a sandwich ELISA for the quantitative determination of sclerostin (SOST) in human serum or plasma. Samples were added to microplate wells that had been pre-coated with capture antibody to ensure attachment of sclerostin from the samples followed by detection with enzyme-linked antibodies. After washing away unbound components, color substrate was added and color development was observed; intensity of color is proportional to concentration of sclerostin in the sample. Finally, the reaction was stopped and the absorbance was measured at 450 nm standard curve used to determine levels in tested samples.

Statistical Analysis

Data was analyzed using SPSS Statistics software, version 25.0 (SPSS, Chicago). The Kolmogorov – Smirnov test was utilized to check the normality of parametric data. Those data that demonstrated normal distribution were expressed as mean ± standard deviation and were subjected to the independent t-test for comparison. The predictive ability of sclerostin in predicting relapses among patients with osteoporosis can be tested by applying the receiver operating characteristic (ROC) curve. A p-value of less than 0.05 was considered statistically significant.

RESULTS

The demographic comparison as shown in Table 1 indicates that there was no statistical difference between the two groups of patients and controls with regard to age ($\chi^2 = 4.79$, $p = 0.18$) or gender distribution ($\chi^2 = 0.33$, $p = 0.56$), meaning that these variables were well matched between the two samples. However, there was a very marked difference in the classification of BMI $\chi^2 = 19.04$, $p = 0.000$ with underweight participants significantly more in number in the study group; this accounted for about 37 % of the osteoporosis patients and only about 5 % of the controls

Table 1

Distribution of patients (osteoporosis) and control groups by their demographic data

Items	Rating	Patient (n = 70)		Control (n = 40)		Chi Square (p-value)
		Freq.	%	Freq.	%	
Age	21–30	14	20.00	13	32.5	4.79 (0.18)
	31–40	25	35.71	17	42.5	
	41–50	16	22.86	4	10	
	52–60	15	21.43	6	15	
Mean ± SD	46.33 ± 12.47					
Gender	Male	31	44.29	20	50	0.33 (0.56)
	Female	39	55.71	20	50	
BMI	Underweight	26	37.14	2	5	19.04 (0.000)
	Normal	22	31.43	28	70	
	Overweight	18	25.71	8	20	
	Obese	4	5.71	2	5	

As shown in Figure 1, it was found that the patients' group had a significantly raised level of serum sclerostin as compared to the controls (p < 0.000). The mean sclerostin concentration in the patients was 7.9 ± 2.3 ng/mL, much greater than that measured in the control group (2.88 ± 1.22 ng/mL). This striking difference indicates that increased expression of sclerostin may be intimately linked with the pathophysiology of the disease under study; perhaps it reflects altered bone metabolism or impaired osteogenic signaling among the patients of this group.

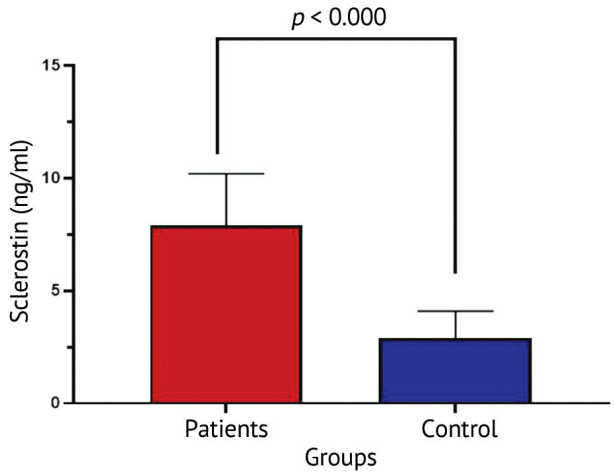

Fig. 1 Measurement of serum sclerostin (ng/mL) between patients and control groups

The univariate logistic regression analysis shows a significant association between high sclerostin levels and the likelihood of having osteoporosis, with an odds ratio (OR) of 1.66 and a p-value of < 0.034; 95 % confidence interval (CI) just includes 1.0 (0.92–1.79), the p-value appears to be statistically significant. So, it allows us to conclude sclerostin is relevant as a possible risk factor. From these results, we can infer that increased sclerostin levels may lead to osteoporosis, underlining its potential role in risk prediction and clinical evaluation.

The analysis of diagnostic performance has revealed sclerostin to have a strong potential as a biomarker for osteoporosis with an area under the curve (AUC) of 0.82 which is fairly good. At a cut-off value of 5.8 sclerostin reported a sensitivity of 78 % and specificity of 82 % which means it can fairly well identify those individuals who have osteoporosis from those who do not. The p-value obtained (0.029) also adds to the evidence in favor of the reliability of sclerostin

in this case. These findings strengthen the potential clinical application of sclerostin evaluation as a non-invasive biomarker in the future for detecting and assessing the risk of osteoporosis at an early stage (Fig. 2).

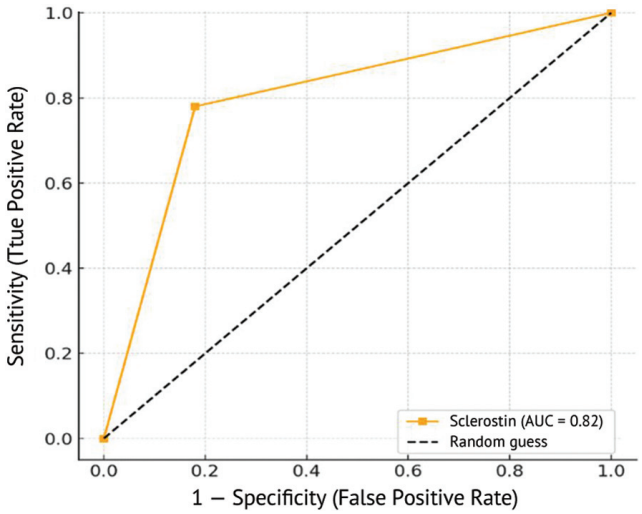

Fig. 2 ROC curve for sclerostin in the diagnosis of osteoporosis

DISCUSSION

The present study findings resonate well with the strong association between low BMI and osteoporosis; thus, in this specific population, low BMI could potentially be considered a risk factor when assessed clinically for bone health [12]. Many previous studies have associated BMI with osteoporosis. Thus, J.S. Walsh et al. reported significant correlation between BMI and osteoporosis, suggesting possible causes like increased loading and higher aromatase activity [13]. Another study conducted by J.T. Lloyd et al. in the USA showed that every unit of increase in BMI was associated with 0.0082 g/cm^2 increase in BMD [14]. Also, D.T. Felson et al. showed the guarding effect of elevated body weight on bone mineral density (BMD) values in different places, mainly in bones that bear weight [15]. In a likely manner, an Asian study found good links between body weight, BMI, height, and being osteoporotic at various anatomical sites [16]. The potential of sclerostin as an osteoporosis biomarker has been discussed in several scenarios. Studies report that the sclerostin level has positive correlation with BMD in postmenopausal women, implying its relevance in assessing fracture risk [17]. Also, the link of sclerostin with metabolic disease markers makes it plausible that it could be a dual biomarker for bone and metabolic diseases in postmenopausal women [18–19]. The only real action that sclerostin performs is to primarily inhibit the Wnt signaling pathway, essential for bone formation. High sclerostin levels have then been associated with low osteoblastic activity and defective bone formation; thus, they are useful towards evaluating severity of osteoporosis [10]. Sclerostin's involvement in bone metabolism highlights its possible application as a diagnostic tool, more so in postmenopausal women, who are about to develop an increased risk of osteoporosis because of estrogen deficiency [20]. Osteoporosis has a very complicated pathophysiology, involves processes at the level of bone remodeling which are controlled by several molecular factors on the activity of sclerostin. Sclerostin is an inhibitor of bone formation which is a glycoprotein produced by osteocytes, it exerts its actions by blocking Wnt signaling pathway, one of the most important regulators of metabolism in bones [21]. The regulation of sclerostin should be very important concerning the maintenance of bone density; high levels have been associated with osteoporosis; elevated sclerostin is also involved in repression of bone formation what makes it an attractive potential therapeutic target for anti-sclerostin therapy

that has currently emerged as a very promising novel interdisciplinary approach targeted toward enhancement of bone formation treatment for osteoporosis [10]. The UK National Osteoporosis Guideline Group (NOGG) recommended the incorporation of sclerostin in clinical practice as a biomarker for the diagnosis and management of osteoporosis. The measurement of sclerostin may improve understanding of individual bone health, that is, BMD assessed conventionally [22]. In this way, treatment could be tailored more on an individual basis for specific high-risk postmenopausal women [23]. Evidence shows that a combined assessment of sclerostin and BMD can give a holistic view regarding the diagnosis and treatment of osteoporosis [10]. Sclerostin assessment will not replace conventional BMD measurements as a linchpin for diagnosing osteoporotic disease but can be added as a biomarker to refine diagnosis and monitoring of treatment [2]. The possible role of sclerostin in guiding clinical choices gets more backing from studies that link its levels to how patients with osteoporosis respond to treatment [21]. The combined use of sclerostin and BMD measurements is likely to provide a comprehensive view in osteoporosis diagnosis and management evaluation [10]. BMD is one essential component in diagnosing osteoporosis, and the incorporation of biomarkers like sclerostin may refine diagnostic precision as well as treatment monitoring [24]. Further, the implied clinical utility of sclerostin based on its level studies relating to treatment response in osteoporotic patients has been underscored by investigations [21]. The importance of sclerostin does not limit its involvement merely to the diagnostic aspect but rather plays a pivotal role in mechanistic understanding related to the coupling within bone remodeling between osteoclasts and osteoblasts. Sclerostin inhibition will be a completely new way that could stimulate bone formation specifically without influencing resorption [25]. Study of the Sirt1-sclerostin route further underlines sclerostin's role as a likely marker and target, implying that changes in this pathway might allow new methods for osteoporosis treatment [26].

CONCLUSION

This study indicates that high serum sclerostin levels are greatly linked to higher risk of osteoporosis, underlining its possible role as a beacon for bone health check. Sclerostin also showed a near link, hinting at a likely tie between metabolic state and bone density. These findings need more investigation in bigger varied studies to confirm the real importance of this biomarker in osteoporosis diagnosis and care.

Ethics approval *The protocol in this study was approved by the ethical committee of the Medical College at the University of Kufa (No. 188 in 2025).*

Consent to participate *Before collection of samples, the patients involved in the protocol were asked to sign consent for their participation.*

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Specific features of orthopedic pathology in neurofibromatosis type I patients of the Republic of Bashkortostan

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Abstract

Background Neurofibromatosis type 1 (NF-1) is a hereditary tumor syndrome characterized by cutaneous, subcutaneous and plexiform neurofibromas, optic nerve gliomas, cognitive disorders and can be associated with orthopedic pathology. Clinical manifestations of NF-1 include skeletal abnormalities requiring a specific approach to treatment of the tumor-like processes in the involved bones and joints.

The **objective** was to determine the frequency of orthopedic pathology and clinical manifestations of the disease in NF-1 patients seen in the Republic of Bashkortostan (RB) and make international comparisons.

Material and methods Outpatient records of patients with a clinical diagnosis of NF-I, the results of laboratory and instrumentation studies were examined. A retrospective analysis of the frequency of occurrence of the main clinical manifestations of NF-1 and orthopedic pathology was conducted. An interactive 2 × 2 contingency table was used for calculation of association statistics (Pearson χ^2 criterion) with the Yates correction for continuity developed by V.P. Leonov and four-field contingency tables were analyzed.

Results and discussion The incidence rate of NF-1 was 1:7407 by 2024 in the RB, which is 2.3 times less than the world average (1:3000 people). Associated malformations included scoliosis seen in 17.4 %, chest deformity observed in 5.3 %, pseudoarthrosis in 3 %, facial dysmorphism in 9 %, short stature in 13.8 % of patients. Osteoporosis, facial asymmetry and sphenoid wing dysplasia were not observed in NF-1 patients in the region. A statistically significant difference in the frequency of occurrence of orthopedic pathology was determined in patients with NF-1 from the RB using four-field contingency tables. A retrospective analysis showed a statistically lower incidence of orthopedic pathology in NF-1 patients of RB as compared to the world average which indicated the need to include orthopedic consultation in medical and economic standards for the timely detection of pathology and treatment.

Conclusion Analysis of orthopedic pathology in NF-1 patients from RB showed the occurrence of chest deformity, scoliosis, short stature and pseudoarthrosis being comparable with world data. Skeletal anomalies, facial dysmorphism and macrocephaly were not common for NF-1 patients of RB. No cases of osteoporosis, facial asymmetry and sphenoid wing dysplasia being characteristic of NF-1 patients were detected in the patients. Learning difficulties were more common for NF-1 patients with orthopedic pathology as compared to NF-1 patients of RB.

Keywords: chest wall deformity, neurofibromatosis type 1, osteoporosis, pseudoarthrosis, scoliosis, frequency of occurrence

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INTRODUCTION

Neurofibromatosis includes three main types which are distinct genetic disorders: neurofibromatosis type 1 (NF-1), neurofibromatosis type 2 and schwannomatosis. NF-1 is a monogenic disease caused by heterozygous mutations in the *NF1* tumor suppressor gene located on the long-arm 17 chromosomes (17q11.2) [1]. According to meta-analysis [2], NF-1 occurs with an average frequency of 1:3,164 of the population worldwide, varying from 1 in 2,020 to 1 in 4,329 in different populations. NF-1 pooled birth incidence was 1 in 2,662 (1 in 1,968-1 in 3,601). About half of NF-1 cases are familial, due to transmission of the disease to the next generation in an autosomal dominant manner. The other half of NF1 cases arise from a new, spontaneous mutation (a de novo mutations) in the *NF1* gene [3]. NF-1 is a hereditary tumor syndrome characterized by multiple café-au-lait macules (CALM) with a diameter of more than 5 mm in prepuberty and more than 15 mm in postpuberty with 99 % being melanocyte tumor growths in the skin due to loss of heterozygosity in the *NF1* gene [4], iris hamartomas (Lisch nodules), cutaneous and subcutaneous neurofibromas, optic gliomas, and plexiform neurofibromas. NF-1-specific bone dysplasias include congenital pseudoarthrosis and/or cortical thinning of long bones, sphenoid dysplasia, spinal deformity (scoliosis/kyphoscoliosis) and chest deformity (pectus excavatum/keeled chest) [5]. According to the criteria developed by the National Institutes of Health (NIH) the diagnosis of NF-1 can be established clinically with both of the signs detected. One sign of the disease would be sufficient in the presence of a confirmed case of NF-1 in genetic relatives [6].

Tumor manifestations are most common manifestations in patients. CALM is detected in 96.5 % of NF-1 patients, freckling of the axillary and inguinal areas is observed in 90 % [7]. Cutaneous and/or subcutaneous neurofibromas are detected in more than 99 %, hamartomas of the iris seen in 70 %, plexiform neurofibromas observed in half of NF-1 patients [6]. Brain damage is also characteristic for NF-1 with optic nerve gliomas seen in 27 % of the cases, brain tumors in 10 %, hydrocephalus in 7.7 % [8], and epilepsy in 8.1 % [9]. Severe complications of NF-1 include malignant peripheral nerve sheath tumors (MPNST) seen in 13 % of NF-1 patients as a result of the degeneration of plexiform neurofibromas; the patients are characterized by high mortality [10].

In addition to the tumor manifestations of NF-1, all patients experience diffuse, lifelong cognitive impairment, leading to learning difficulties in 40 % of cases [3], and common injury to the musculoskeletal system (MSS). According to a meta-analysis [11], approximately 26.6 % of NF-1 patients have scoliosis that usually develops in early childhood affecting the thoracic spine. No reliable correlation has been found between scoliosis and the NF-1 genotype. On average, 24 % of NF-1 patients have short stature [12], and 5 % have pseudoarthrosis [6] which results from fibrous hamartomas of long bones with the lost heterozygosity of the *NF1* gene in the tissues [13]. In total, skeletal anomalies are observed in at least 60 % of NF-1 patients with severe cases requiring surgical treatment [14]. Treatment of pseudoarthrosis in NF-1 would include excision of fibrous hamartoma tissues and subsequent correction using the Ilizarov external fixation [13]. Spondylodesis and the growing rods were practical for treatment of scoliosis in NF-1 patients [11].

Sphenoid wing dysplasia characteristic of NF-1 can be detected in 9 % of the patients, facial asymmetry in 10 %, macrocephaly in 25 % [15], and skull anomalies leading to facial dysmorphism in 53 % of NF-1 patients [16]. Chest deformity is detected in 3.5 % of NF-1 patients, which is significantly higher than in the general population (0.3 %) [17]. A meta-analysis [18] showed that NF-1 can be associated with decreased bone mineral density in the lumbar spine and femur and an increase levels of parathyroid hormone and C-telopeptide of type I collagen in the blood, a decrease in alkaline phosphatase, calcium, vitamin D, osteocalcin, and markers of bone formation

as compared to normal individuals. Half of the patients are diagnosed with osteoporosis [19]. The study of orthopedic pathology is essential for NF-1 patients due to the need to systematize data on the prevalence of skeletal anomalies in patients from different regions and identify shortcomings in the medical care in order to correct them.

The **objective** was to determine the frequency of orthopedic pathology and clinical manifestations of the disease in NF-1 patients seen in the Republic of Bashkortostan and make international comparisons.

MATERIAL AND METHODS

An orthopedic pathology was evaluated in patients from the Republic of Bashkortostan (RB), registered with an established diagnosis of "neurofibromatosis type I" with a geneticist at the Republican Medical Genetic Center. A total of 543 NF-1 patients from 433 families from the RB were examined including 259 (48 %) male and 284 (52 %) female patients aged 1 to 85 years with the mean of 30 years and 7 months. MRI and CT were performed for 60 patients and 28 patients, respectively; radiography and densitometry findings were not presented in the outpatient records. Of all the patients, four NF-1 patients received treatment with a mitogen-activated protein kinase inhibitor (selumetinib or coselugo). The examination were conducted in compliance with biomedical ethics and Good Clinical Practice (GCP). Specific clinical manifestations of NF-1 were examined in patients from the RB, the findings were compared with global data, and the frequency of occurrence and severity of tumor in patients with skeletal anomalies were compared with the general group of NF-1 patients from the RB.

Statistical processing was performed to obtain high-quality binary data using an interactive 2×2 contingency table with the calculation of association statistics (Pearson χ^2 criterion) with the Yates correction for continuity developed by Leonov (http://www.biometrica.tomsk.ru/freq2.htm), and an analysis of four-field contingency tables on the website https://medstatistic.ru/calculators/calchi.html. In addition to statistical analysis, a molecular genetic examination of DNA samples from patients was performed that resulted in mutations in the *NF1* gene identified in 20 samples. Of the 544 NF-1 patients, eight were thoroughly examined by an ophthalmologist using a slit lamp to detect iris hamartomas.

RESULTS AND DISCUSSION

NF-1 was diagnosed in 543 patients from 433 families in the RB. Taking into account the population of the republic, the prevalence of the condition was 1:7,407 people, which is more than twice the global rate (1 in 3,164 [2]). Of the 543 patients, 245 (45 %) were found to have inherited the disease from one of the parents, while 299 (55 %) were sporadic cases without a family history, which is consistent with the data of other researchers [3]. The male to female ratio was approximately 1:1.

Pigment spots were identified in 100 % of NF-1 patients and the criterion was the main one for makingthe diagnosis. Identical skin spots similar to those seen in NF-1 can occur in other hereditary tumor syndromes including tuberous sclerosis [20], Leopard [21], Noonan and Costello [22], Cowden [23], Peutz-Jeghers [24], Legius [25] syndromes, and neurofibromatosis type II [22]. Therefore, at least two criteria established by the NIH [6] are used to diagnose NF-1. Only 314 patients (58 %) out of 543 were found to have cutaneous or subcutaneous neurofibromas, which is significantly lower than the global average (99 %) [6].

No data were found on malignant MPNST tumors in NF-1 patients from the RB, which occur in 13 % of NF-1 patients [10]. Cognitive deficit was detected in 79 patients from the Republic of Bashkortostan (14.5 %), which is also significantly lower than the results of other researchers (40 %) [3]. Brain

damage was detected in some patients from the RB causing epilepsy in 20 (3.7 %) NF-1 patients, hydrocephalus in 23 (4.23 %), brain tumors in 21 (3.86 %) and brain cysts in 28 (5.15 %), which is statistically insignificantly different from the data of other researchers [8, 9, 26]. Optic nerve gliomas (34; 6.25 %), plexiform neurofibromas (38; 7 %) and Lisch nodules (5; 1 %) were not common for NF-1 patients from the RB compared to global studies [6, 8].

Plexiform neurofibromas can be detected both by visual examination and with MRI and CT [27]. They are characterized by unclear borders and invasion into surrounding tissues with location along nerve trunks, growth around deformed nerve bundles, along adjacent nerve branches, muscles and skin [28]. Based on these criteria, clinicians can establish plexiform neurofibromas in patients. Plexiform neurofibromas have a high rate of malignant transformation into MPNST tumors. Scintigraphy (with gallium-67) is recommended as a screening method for NF-1 patients with large plexiform neurofibromas. Plexiform neurofibromas have a high incidence of developing into malignant peripheral nerve sheath tumors (MPNSTs) with a 5-year survival rate of only 30 %. Fluorine-18 labeled tryptophan positron emission tomography is recommended for the differential diagnosis. Therefore, the accurate diagnosis and differentiation of MPNSTs from benign plexiform neurofibromas are critical to patient management [29].

The presence of plexiform neurofibromas is an indication for the administration of selumetinib. Cutaneous neurofibromas can be treated surgically [30] but excision of plexiform neurofibromas is difficult due to the infiltrative growth and invasion of the surrounding tissues. The use of selumetinib in different countries has shown efficacy in reducing the size of plexiform neurofibromas in children (objective response rate of 64 % [31], 68 % [32, 33]) and in adults (objective response rate of 63.6 % [34]). The efficacy of selumetinib in relation to the growth of spinal neurofibromas has also been determined [35].

MSS pathologies were detected in 206 (38 %) NF-1 patients from the RB including scoliosis detected in 95 individuals (17.4 %), short stature in 75 (13.8 %), facial dysmorphism in 49 (9 %), chest deformity in 29 (5.3 %), pseudoarthrosis of the tibia in 15 (3 %), flat feet in 10 (1.8 %), macrocephaly in 5 (1 %). Facial asymmetry, dysplasia of the sphenoid bone wing and osteoporosis were not described in any of the NF-1 patients from the RB.

A comparative analysis of impaired MSS in NF-1 patients from the RB (Table 1) indicates skeletal anomalies in general, facial dysmorphism and macrocephaly as a statistically rare condition [14–16]. There are no data on the presence of osteoporosis, facial asymmetry and dysplasia of the sphenoid bone wing, which significantly differs from the data worldwide [15, 19]. The incidence of chest wall deformities is relatively higher, and scoliosis, short stature and pseudoarthrosis are lower than the findings of other researchers, but statistically insignificant. In addition to MSS impairment NF-1 patients from the RB have a significantly lower incidence of cutaneous and subcutaneous neurofibromas, Lisch nodules, plexiform neurofibromas, and optic nerve gliomas compared to data from around the world [3, 6, 8, 10, 12] suggesting an insufficient examination of patients. Comparison of the frequency of these symptoms in individuals with impaired MSS in NF-1 patients from the RB and with data from around the world and with all NF-1 patients from the RB can be interesting.

A comparative analysis of the prevalence of clinical manifestations characteristic of NF-1 (Table 2) in NF-1 patients with orthopedic pathology from the RB, compared with global data, indicates a statistically significantly rarer registration of cutaneous and subcutaneous neurofibromas, MPNST, plexiform neurofibromas, optic nerve gliomas and learning difficulties. Compared with the general group of NF-1 patients in the RB, patients with orthopedic pathology showed a statistically insignificantly higher incidence of cognitive deficit (Table 3), but the prevalence of other manifestations was similar.

Table 1

Comparative characteristics of orthopedic pathology in NF-1

Clinical manifestations	Prevalence of the condition in the RB		Prevalence worldwide		χ^2 test; *p*-value with 1 degree of freedom
	abs.	%	%	[publication]	
skeletal anomalies in general	206	38.0	60	[14]	$\chi^2 = 9.684$; $p = 0.002$
chest deformity	29	5.3	3.7	[17]	$\chi^2 = 0.116$; $p = 0.734$
scoliosis	95	17.4	26.6	[11]	$\chi^2 = 2.914$; $p = 0.088$
low stature	75	13.8	24.0	[12]	$\chi^2 = 3.25$; $p = 0.072$
pseudarthrosis	15	3.0	5.0	[6]	$\chi^2 = 0.521$; $p = 0.471$
osteoporosis	0	0	50.0	[19]	$\chi^2 = 66.667$; $p < 0.001$
facial dysmorphism	49	9.0	53.0	[16]	$\chi^2 = 39.841$; $p < 0.001$
macrocephaly	5	1.0	25.0	[15]	$\chi^2 = 15.686$; $p < 0.001$
facial asymmetry	0	0	1.0	[15]	$\chi^2 = 10.526$; $p = 0.002$
sphenoid wing dysplasia	0	0	9.0	[15]	$\chi^2 = 9.424$; $p = 0.003$

Table 2

Comparative analysis of clinical manifestations of NF-1 in patients with orthopedic pathology

Clinical manifestations	Prevalence of the condition in NF-1 patients from the RB, *n* = 206		Prevalence of the condition in NF-1 patients worldwide		χ^2 test; *p*-value with 1 degree of freedom
	abs.	%	%	[publication]	
neurofibromas	123	59.7	99	[6]	$\chi^2 = 46.664$; $p < 0.001$
MPNST	0	0	13	[10]	$\chi^2 = 13.904$; $p < 0.001$
Lisch nodules	3	1.5	70	[6]	$\chi^2 = 100.347$; $p < 0.001$
plexiform neurofibromas	15	7.3	50	[6]	$\chi^2 = 45.369$; $p < 0.001$
optic nerve gliomas	17	8.3	27	[8]	$\chi^2 = 12.502$; $p < 0.001$
brain tumor	9	4.4	10	[8]	$\chi^2 = 2.765$; $p = 0.097$
brain cysts	13	6.3	2	[26]	$\chi^2 = 2.083$; $p = 0.149$
hydrocephalus	13	6.3	7.7	[8]	$\chi^2 = 0.307$; $p = 0.58$
epilepsy	8	3.9	8.1	[9]	$\chi^2 = 1.418$; $p = 0.234$
learning difficulties	45	22.0	40	[3]	$\chi^2 = 7.574$; $p = 0.006$

Table 3

Comparative analysis of clinical manifestations of NF-1 in patients with orthopedic pathology with a general group of patients with NF-1 from the RB

Clinical manifestations	Prevalence of the condition in NF-1 patients from the RB, *n* = 206		Prevalence of the condition in all NF-1 patients, *n* = 544		χ^2 test; *p*-value with 1 degree of freedom
	abs.	%	abs.	%	
neurofibromas	123	59.7	314	58	$\chi^2 = 0.243$; $p = 0.623$
MPNST	0	0	0	0	n/a
Lisch nodules	3	1.5	5	1	$\chi^2 = 0.409$; $p = 0.523$
plexiform neurofibromas	15	7.3	38	7	$\chi^2 = 0.02$; $p = 0.888$
optic nerve gliomas	17	8.3	34	6.25	$\chi^2 = 0.945$; $p = 0.331$
brain tumor	9	4.4	21	3.86	$\chi^2 = 0.101$; $p = 0.752$
brain cysts	13	6.3	28	5.15	$\chi^2 = 0.391$; $p = 0.532$
hydrocephalus	13	6.3	23	4.23	$\chi^2 = 1.418$; $p = 0.234$
epilepsy	8	3.9	20	3.7	$\chi^2 = 0.018$; $p = 0.894$
learning difficulties	45	22.0	79	14.5	$\chi^2 = 6.559$; $p = 0.011$

The absence of data on osteoporosis, facial asymmetry and sphenoid wing dysplasia, characteristic of NF-1 patients, among the group analyzed indicates the need for a more thorough examination of patients with mandatory consultations with an orthopedic surgeon and instrumentation researches to be performed.

CONCLUSION

Clinical manifestations of orthopedic pathology reviewed in NF-1 patients from the Republic of Bashkortostan showed a prevelance of chest deformity, scoliosis, short stature and pseudoarthrosis comparable with world data. However, skeletal anomalies in general, facial dysmorphism, and macrocephaly were not common for NF-1 patients from the RB. No data on osteoporosis, facial asymmetry and sphenoid wing dysplasia, characteristic of NF-1 patients, were found among the group examined. NF-1 patients with orthopedic pathology were found to have more frequent learning difficulties compared to the entire group of NF-1 patients from the Republic of Bashkortostan.

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Audiogram of ceramic friction noises in total hip arthroplasty and their relationship with acetabular component position

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Abstract

Introduction Noise from a total hip replacement's ceramic friction pair is known as hip squeaking. Acoustic arthrometry in total hip replacement (THR) involves using acoustic emission technology to visualize sound characteristics.

The **objective** was to identify the possibility of identifying noises of a THR ceramic friction pair using the acoustic arthrometry and to determine the relationship of noises with the position of the acetabular component.

Material and methods The retrospective study included 36 patients who underwent THR with a ceramic bearing pair. Seven patients (19.44 %) reported noise at the site of the THR joint. The patients were divided into two groups based on the noise (n = 7) and no noise reported (n = 29). Clinical and radiological parameters were reviewed through online survey considering age, follow-up period, BMI, inclination and anteversion of the acetabular component. Acoustic arthrometry was performed for 10 patients with the pulse height, PEAK, ASYMMETRY and WIDTH measured and compared.

Results Comparative analysis of individual clinical and radiological parameters showed no statistically significant differences in the two groups. However, deviations by any of the two criteria in the acetabular component position was 20.7 % in the no-noise group and 57.1 % in the noise reported group (p = 0.048). Acoustic emission of THR with noise had visual differences in acoustic signature with the mean PEAK measuring 0.492 in the no-noise group and 0.488 in the noise reported group; ASYMMETRY being 0.012 versus 0.015 and WIDTH measuring 479.2 versus 486.5, respectively.

Discussion The findings correlated with the results of previous studies and confirmed the relationship between the angles of the implanted acetabular component and the noise. In contrast to previous studies of acoustic arthrometry, the method offered facilitated objective statistical noise assessment in addition to visualization and analysis of acoustic signatures.

Conclusion The study demonstrated possibilities of acoustic arthrometry in identification of different states of the ceramic friction pair, characterization of the noise detected and its quantification.

Keywords: total hip replacement, ceramic bearings, hip squeaking, acoustic arthrometry

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INTRODUCTION

In the 21st century, total hip arthroplasty (THA) is a successful surgical procedure for treating end-stage degenerative hip diseases an optimal treatment for end-stage hip osteoarthritis. Friction-related wear and its consequences are one of the most devastating complications of THA [1]. The history of friction pair materials began with metal-metal progressing to ceramic-polyethylene friction pair [1, 2]. A ceramic-on-ceramic (CoC) total joint replacement was first developed in 1972 by Boutin and presented as wear-resistant and bio-inert with the mass production implemented by the German company Ceramtec [3]. The first generation of the material was characterized by high wear resistance and greater fragility [4]. The shortcomings were addressed with the next generations of ceramics. Fourth-generation ceramic friction material includes an alloy of aluminum oxide and zirconium (Al_2O_3, ZrO_2). Postoperative squeaking can occur in patients who applied the fourth-generation ceramic bearing in total joint replacement [5].

Stanat et al. reported creaking as the most common noise with crunching being the second most common among audible noises [6]. Data extracted from the National Joint Registry for UK, South Korea suggested more stable results with Delta bearings, the rate of ceramic fracture for the liner remained at the same level [7, 8]. More than 88 thousand primary and revision THRs were performed in 2019 in the Russian Federation. CoC friction pair is not commonly used ranging between 0.5 % and 8.2 % of the total THAs performed between 2008 and 2020. Ceramic friction pair is common for patients aged under 30 accounting for 30 % of the total THAs [9]. We can suggest that among these patients there will be those being dissatisfied with THA because of the audible noise.

Total hip replacements (THRs) may occasionally produce vibration and noise [10, 11]. There are studies aimed at exploring audible noises (knocking, creaking, crunching) and inaudible noises (vibrations) that are in ranges beyond the physiological characteristics of the human hearing system, infra- and ultrasound.

The acoustic arthrometry method, based on the acoustic signatures obtained with an accelerometer demonstrated the possibility of detecting loosening of THR implant and destruction of friction pairs, such as Ce–Ce [12]. The method does not rule out a hypothetical possibility of analyzing the acoustic phenomena of solid friction pairs in the infra- and ultrasound ranges, with the subsequent interpretation. In addition to that, the study of noise arising from friction of ceramic pairs of THR provides the prospect of predicting the service life of implants, which is a significant addition to the orthopedic arsenal for assessing the survival of implants at a long term.

The **objective** was to identify the possibility of identifying noises of a THR ceramic friction pair using the acoustic arthrometry and to determine the relationship of noises with the position of the acetabular component.

MATERIAL AND METHODS

Characteristics of patients and THR implants

A retrospective single-center study included 36 patients who underwent THR with a CoC friction pair between 2008 and 2020. The average age of patients was 46 years (18–69) at the time of surgery. There were 23 (64 %) female and 13 (36 %) male patients. The contralateral joint had been previously replaced in 16 (44 %) patients using implants with a metal-polyethylene friction pair and unilateral THR was performed in 20 (56 %) patients.

The participants were informed and signed consent to participate in the study prior to surgery.

The patients were divided into two groups. The first group consisted of patients who had no noise at the THR site ($n = 29$) and the second group included patients who reported audible noise at the THR site ($n = 7$).

The THR surgeries were primary and performed through the anterolateral approach.

The criteria analyzed included age, follow-up period, body mass index (BMI), inclination angle of the acetabular component and anteversion angle of the acetabular component, and reference of the angles with safe zones proposed by Lewinnek (acetabular inclination 45° ± 15° and anteversion 15° ± 10°).

Acoustic arthrometry

The acoustic arthrometry was performed for 10 patients with ceramic THR bearing pair including seven (70 %) patients with complaints of audible noise at the THR site and three patients reporting audible noise which was considered as a normal variant. An acoustic emission recording device equipped with a three-axis accelerometer (IP application, reg. No. 2024134340) was fixed in the projection of the greater trochanter according to the method developed (IP application, reg. No. 2025105401). The subjects were requested to walk a distance of 200 m on a flat surface at a normal individual pace.

The criteria that were used for decoding were developed, substantiated, defined and automated by the staff of the Department of Theoretical Foundations of Radio Engineering of the Federal State Budgetary Educational Institution Novosibirsk State Technical University (Head of Department, MA Raifeld; Professor of Department, VN Vasyukov) [13].

The following criteria were employed for decoding the acoustic signature (Fig. 1):

— pulse heights, designated by conventional units 0, 1, 2, 3…;

— PEAK, pulse distortion with threshold value < 0.49;

— ASYMMETRY, pulse asymmetry reflecting component wear with threshold value > 0.02;

— WIDTH, pulse width representing the looseness or destruction of components with a threshold > 500.

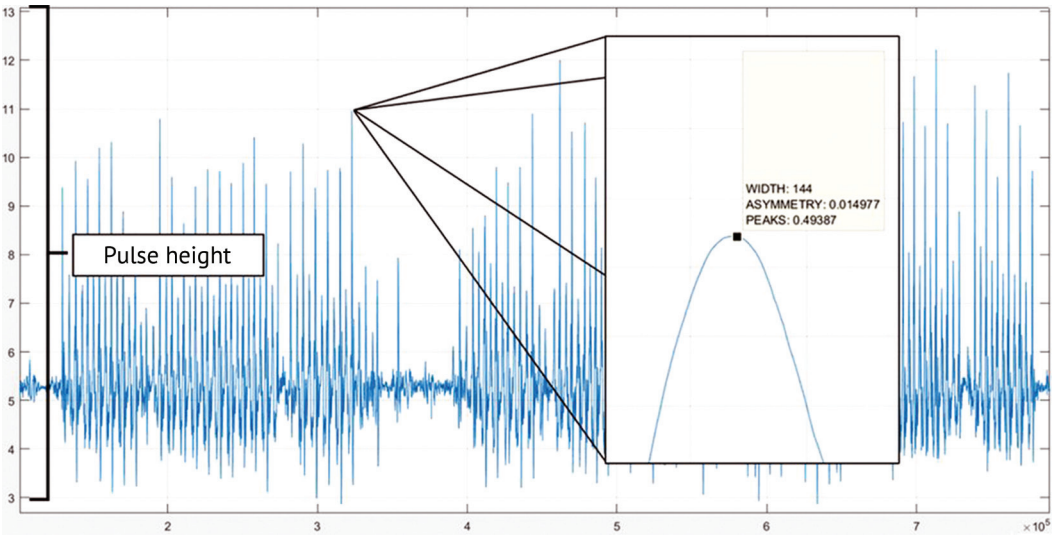

Fig. 1 Acoustic signature evaluation criteria. The rectangle shows a selectively taken normal pulse of the acoustic signature of ceramic pair friction (marked with converging black lines), which can be analyzed using the criteria offered: height, 11 units; PEAK, 0.49387; ASYMMETRY, 0.014977; WIDTH, 144

The acoustic signature analysis was performed using MATLAB software. The device mechanism was described in details in our previous work [13].

Statistical analysis

Python programming language (version 3.11) was used for data analysis. The mean and the range were estimated for quantitative variables of the two groups (age, follow-up time, BMI, inclination and anteversion of the acetabular component). The Student's t-test was used for independent samples and the Mann–Whitney U-test employed for the data violating the assumption of normal distribution. The Fisher exact test was used for categorical variables. The level of statistical significance was set at $p < 0.05$.

RESULTS

The survey and analysis of the findings indicated the noise in seven patients at the THR joint replaced with a ceramic friction pair, which corresponded to 19.44 % of the sample (7 out of 36). Three of the seven patients reported the noise being heard by themselves and by people nearby, the remaining four patients heard the noise by themselves only. 29 (80.56 %) patients in the group reported no noise at the THR site.

A comparative analysis of clinical and radiological parameters of the two groups revealed no statistically significant differences (Table 1).

Table 1

Parameters of patients in two groups divided by the presence or absence of audible noise

Description	Group I (no noise)	Group II (noise reported)	*p*-value
	n = 29; 80.56 %	*n* = 7; 19.44 %	
Age, years	51.17 ± 14.98	52.57 ± 10.89	0.779
BMI, kg/m^2	26.75 ± 4.32	26.32 ± 4.39	0.794
Follow-up period, years	6.20 ± 1.63	5.29 ± 1.30	0.089
Χυπ ινχλινατιον, °	42.00 ± 7.02	38.00 ± 9.59	0.181
Χυπ αντεωερσιον, °	12.63 ± 8.35	11.80 ± 4.30	0.758

The reference of the inclination angle of the acetabular component with the reference values (45 ± 15)° was reviewed. Deviation from the reference was detected in 17.2 % of cases of the first group of patients (no noise at the THR site) and in 42.9 % of the second group (noise reported). Deviations from the reference anteversion values proposed by Lewinnek (15 ± 10)° were detected in 13.8 % of cases in the noise-free group and in 28.6 % of cases in the noise-reported group. No statistically significant difference was found in any of the individual indicators. A significant difference was found in the percentage ratio of the total number of deviations in both angles of implantation of the acetabular component in the no-noise group: 20.7 % versus 57.1 % in the reported noise group (Table 2). The results of the study showed that deviation from the reference angles of implantation of the acetabular component can be associated with the occurrence of the noise.

Table 2

Comparative analysis of the deviation rates from the conventional norm of inclination and anteversion of the acetabular component in two groups divided by the "presence or absence" of audible noise

Description	Group I (no noise)		Group II (noise reported)		*p*-value
	n = 29; 80.56 %		*n* = 7; 19.44 %		
	abs.	%	abs.	%	
Deviation in inclination	5	17.2	3	42.9	0.145
Deviation in anteversion	4	13.8	2	28.6	0.290
Deviation in any criterion	6	20.7	4	57.1	0.048*

Acoustic arthrometry analysis

Acoustic emission of implants with audible noise had significant visual differences in the distorted acoustic signature (Fig. 2). The pulse height did not exceed 10 c.u. in average values in the second group with noise (n = 7) and the pulse height exceeded 10 c.u. in average values in the no-noise group (n = 3) with the audiogram taken as a conditional norm (red line, Fig. 2a). The average value of the PEAK was 0.492 in the no-noise group and 0.488 in the group with audible noise, ASYMMETRY was 0.012 versus 0.015, WIDTH measured 479.2 versus 486.5.

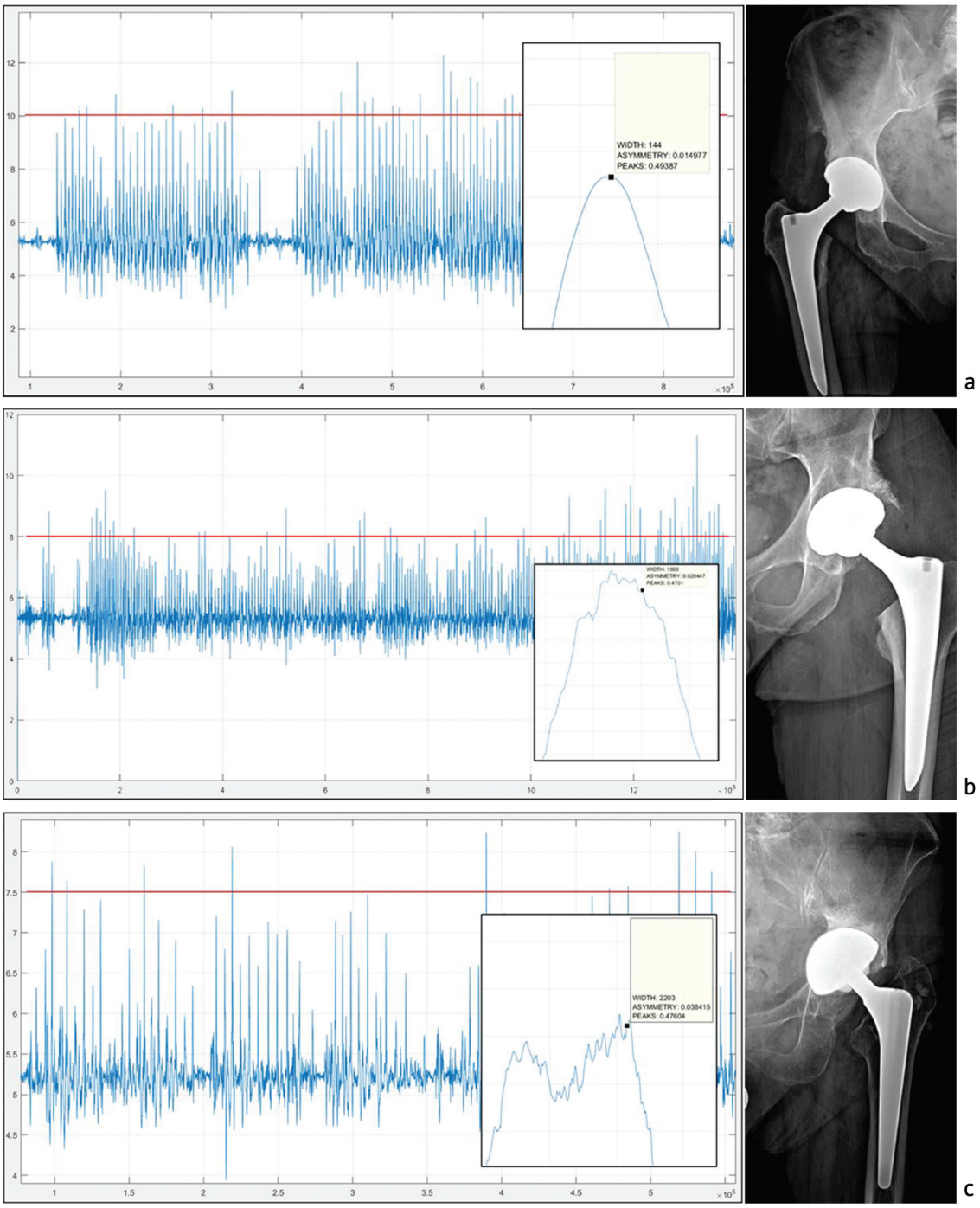

Fig. 2 General view of acoustic signatures showing individual pulse peaks and AP radiographs of the hip joint: (a) no noise, no loosening of the THA; inclination and anteversion of the acetabular component measuring 40° and 12°, correspondingly; (b) noise being reported (creaking), no THA loosening with inclination and anteversion of the acetabular component measuring 30° and 7°; (c) — with noise (crunch) and loosening (prolapse) of the acetabular component

Examination of the acoustic signature suggested requires an analysis of the overall graph picture and the pulse height (normally ⩾ 10.0 units) at the first stage regardless of the thickness of the soft tissues. The second stage involves an analysis of the Peak criterion (normally ⩾ 0.49 units). A value below the specified threshold indicated a violated congruence of the friction surface. The third stage involved the analysis of the ASYMMETRY criterion (⩽ 0.0200 units). A value obtained above the specified one indicated the destruction of the friction pair components. WIDTH was the fourth criterion to be analyzed with the normal values corresponding to ⩽ 500 units. One of the components was considered to be loose with the value being greater.

DISCUSSION

Our pilot study had limitations related to the fact that the sample of patients who underwent acoustic arthrometry was limited to 10 patients out of 36 with seven patients reporting audible noise of the ceramic friction pair, and the audiograms of three patients out of 29 patients reporting no noise were accepted as the norm. In terms of time, the use of ceramics in THA is relatively new compared to other bearing pairs. Considering the longevity of the THA, the bearing pair can be recommended for implantation in younger patients [14]. This is due to their active lifestyle and its duration relative to other age groups. Orthopaedic surgeons are to be more selective in the candidates for the friction pair or refuse it in favor of a polyethylene-ceramic friction pair.

No statistically significant differences in age, BMI, follow-up periods or acetabular component implantation angles were found in the series between the groups. However, a difference was recorded in the percentage of the total number of deviations in the comparison groups confirming the effect of adequate placement of the acetabular component on the occurrence of noise [5, 15, 16]. The number of patients who developed noise at the THA site varied from 3 % to 30 % [5, 15, 17]. The results of our study correlate with the data obtained by other authors.

The fact of the technical possibility of recording vibrations arising from friction of a ceramic pair in THA during movement contributes to the detailing of the sound signature depending on the type of ceramic, head size, inclination angle and anteversion of the acetabular component in the infrasound and ultrasound ranges. We were the first in the world who described vibrations occurring in the ceramic friction pair in the group of patients using our patented device. The findings would open up great opportunities for exploring audible noise, inaudible noise (vibrations), which theoretically should not exist in a solid and congruent ceramic friction pair since there is no dry friction, and the peaks of the pulses must be symmetrical and uniform. Noise alone can be perceived as an insignificant undesirable phenomenon, since it is not accompanied by pain and patients might neglect it. The noise can be associated with significant destruction (dry friction) of the ceramic friction pair [18]. The patient can resolve the problem of an “acceptable” noise (impact or load on the rear edge of the liner during excessive flexion) by limiting the volume of certain causal movements (favorable prognosis) [19]. If the noise results from the edge loading (ceramic head on the edge of the ceramic liner in a standing position), it is “unacceptable” and cannot be eliminated by preventive measures on the part of the patient. The consequences of “unacceptable” noise can be significant (unfavorable prognosis), including ceramic fracture and migration of ceramic debris into soft tissues, which is difficult to address during revision surgeries [20].

Lucchini et al. suggested that noise may be a sign of failed ceramic materials of the components and can lead to multi-stage destruction of the friction pair [21]. The event can lead to a complicated revision surgery requiring careful removal of the debris from the surrounding soft tissues.

The debris can spread chaotically with destroyed ceramic friction pair despite careful removal of ceramics from soft tissues with a risk of a repeated injury to revision ceramic friction pairs (liner/head) with remaining ceramic fragments (third body), and implantation of a polyethylene liner can be associated with early wear and tear and osteolysis of the bone tissue. Acoustic arthrometry, as a non-invasive and safe method, enables continuous monitoring of the implant with a ceramic friction pair.

Wakayama [22] and Yamada [23] were the first to suggest acoustic emission for diagnosis of microcracks in a rubbing ceramic surface, and experimentally proved that the increase in emission pulses (hits/impacts) corresponds to the moment of ceramic splitting. Analysis of the acoustic emission of friction pairs, including ceramic pairs, accompanied by video fluoroscopy was performed by Glaser et al. who reported a direct correspondence between the vibrations recorded with arthrometry and the movements in the prosthetic joint, including a correlation of changes in the presence of creaking, crunching and other noises [24]. Roffe et al. suggested that in CoC THA the recordable noise of a hip squeak in 82 joints did not originate nor had contribution from the trunnion morse taper connection [25]. In addition to that, the authors found that magnitude of emission may decrease depending on the thickness of the subcutaneous fat tissue with no changes in the number and frequency of oscillations.

Kummer et al. performed a study on 98 patients and found that the graph (acoustic signature) was subject to distortion depending on implant stability and integrity of the friction pair surface [26], which is consistent with our results. As shown in Figure 2, the acoustic signature depends on the stability of the components and is characterized by the absence of sharp and chaotic fluctuations. Rodgers et al. discovered and experimentally confirmed the difference in the pitch of acoustic emissions of various noises. Creaking differed from crunching and knocking by a high and prolonged oscillation, while crunching was characterized by a low frequency, and knocking by intermittency [27, 28]. New statistical units of measurement we offered for our research method include PEAK, ASYMMETRY and WIDTH to represent the nature of oscillation distortion, which will be practical for a physician to perceive information in an acoustic signature.

CONCLUSION

Проведенное The pilot study opens up prospects and possibilities for the application of the acoustic arthrometry to allow identification of the ceramic friction pair status standardizing noise measurement, characterizing the detected noise and measuring it in quantities. Description of noise by numerical values (quantities) will allow for a comparative analysis of noise with retrieving statistical data and correlation links and identifying the initial signs of destruction of the friction pair to facilitate early measures and prevent adverse events and complications.

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Informed consent *The patients gave informed consent for publication of the findings without identification.*

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Clinical case
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Treatment outcome in a patient with knee joint infection developed after arthroscopic plasty of the anterior cruciate ligament

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Abstract

Introduction Knee joint infection (septic arthritis) is a rare but severe postoperative complication. With the increasing number of primary and revision arthroscopic surgeries on large joints performed annually, the incidence of infectious complications has also grown.

The **aim** of this study is to present the outcome of a successful two-stage treatment of a female patient with knee joint infection caused by methicillin-resistant Staphylococcus epidermidis after arthroscopic anterior cruciate ligament reconstruction.

Materials and Methods A 22-year-old female patient diagnosed with chronic posttraumatic osteomyelitis of the right femur and tibia, arthritis of the right knee following reconstruction of the anterior cruciate ligament (ACL) of the right knee. Her medical records stated several failures of debridement surgeries. The first stage involved joint debridement, removal of the infected ACL graft, and filling of the bone defects with bone cement containing antibacterial agents. In the second stage, the bone cement was removed, the bone defects were filled with allograft bone chips, and ACL reconstruction was performed using the peroneus longus tendon. Clinical, instrumental, and functional evaluations of treatment effectiveness were performed.

Results The treatment managed to control the infection. Remission of the infection was achieved, and function of the affected limb was restored. The follow-up period was two years.

Discussion There are few publications in the Russian medical literature on the treatment of infection after arthroscopic surgery on large joints. This clinical case demonstrates a positive outcome in infection resolution after ACL reconstruction with forced ligament removal following failures of debridement procedures.

Conclusion The choice of treatment strategy was based on the patient's medical history and desired needs. The management of knee infection that developed after ACL reconstruction included appropriately selected and administered antibiotic therapy and the necessary number of timely surgical interventions. This optimally chosen approach ultimately resulted in good outcome.

Keywords: clinical case, revision arthroscopy, ACL reconstruction, bone grafting, infection, two-stage revision, osteomyelitis, MRSE

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INTRODUCTION

Knee joint infection (septic arthritis) is a rare but a severe postoperative complication. In the general population, infectious complications after surgical arthroscopic interventions occur with a frequency of 0.14–1.8 % [1]. The causative agents of infection are commonly coagulase-negative staphylococci and *Staphylococcus aureus* [2, 3, 4]. Young patients, those receiving corticosteroid injections, those with a history of diabetes mellitus, and patients with concomitant surgical interventions are at a higher risk of knee joint infection [5, 6, 7]. Some researchers claim that the incidence of infectious complications is higher if harmstring muscle tendons are chosen for grafting [8]. Late presentation of patients or delayed initiation of treatment threatens to results in such outcomes of infectious arthritis as cartilage detachment, its thinning, osteoarthritis, and osteomyelitis [9].

Diagnosis of infection after anterior cruciate ligament (ACL) reconstruction is based on the patient's history, physical examination, laboratory parameters, and synovial fluid study after joint aspiration. Clinically, septic arthritis is characterized by soft tissue swelling, hyperemia, localized fever, pain, and dysfunction of the affected joint along with non-healing postoperative wounds. Laboratory diagnosis includes tests for serum markers and intra-articular material (synovial fluid and tissue samples obtained intraoperatively) [5].

Many orthopedic surgeons initially prefer procedures that preserve the ligament graft: staged arthroscopies, debridement, and antibiotic therapy [1, 2, 10, 11]. However, if such treatment is ineffective or a therapy-resistant pathogen is identified, joint debridement includes removal of the graft and its fixing implants, due to the ability of microorganisms to adhere to the surface of elements implanted into the joint [6, 12].

Our study presents a clinical case of a patient with infectious complications following ACL reconstruction. A distinctive feature of this case is the filling of the bone canals with a cement spacer containing an antibiotic and the subsequent bone grafting of those canals after spacer removal. The authors of a similar clinical case report used cement spacers in the form of beads placed into the joint cavity [9].

Purpose of this study is to present the outcome of a successful two-stage treatment of a female patient with knee joint infection caused by methicillin-resistant Staphylococcus epidermidis after arthroscopic anterior cruciate ligament reconstruction.

MATERIAL AND METHODS

A 22-year-old female patient was admitted to the Bone and Joint Infection Clinic of the Ilizarov National Medical Research Center of Traumatology and Orthopedics with complaints of pulsating pain in the right knee joint at night and instability of the right knee joint.

Diagnosis: Chronic post-traumatic osteomyelitis of the right femur and tibia; arthritis of the right knee joint; condition after ACL reconstruction of the right knee joint (Fig. 1).

Medical history 2010: right knee injury, ACL injury, arthroscopic ACL replacement; June 2016: re-injury, therapeutic and diagnostic arthroscopy with medial

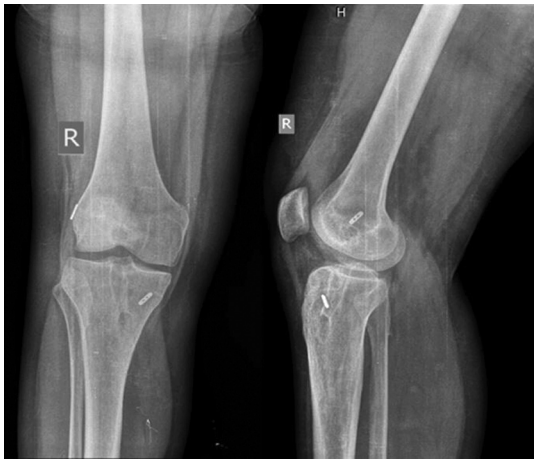

Fig. 1 AP and lateral radiographs of the right knee joint

meniscus resection; June 2021: right knee injury with ACL graft damage; July 2021: repeated arthroscopic medial meniscus resection and revision ACL replacement, postoperative purulent arthritis. August 2021: knee drainage.

Local status Skin condition: no wounds or fistulas; moderate swelling of the right knee joint; local hyperemia and hyperthermia of the skin. The anterior drawer symptom was positive. Lachman test was positive. Gait characteristics: walks with support on crutches. Orthopedic status: no shortening. Peripheral vascular pulse: pulsation on the dorsalis pedis artery was palpable on both lower extremities. Joint movements of the affected limb: flexion-extension contracture of the right knee joint (flexion/extension — 110/170°). Functional state of the right knee joint: 19.5 points (according to KSS), 40 points (according to Lysholm).

Results of laboratory tests Mild anemia (Hb 98 g/L), elevated ESR (61 mm/h) and CRP (6.7 mg/L). A puncture of the right hip joint revealed growth of Staphylococcus epidermidis, MRSE 10^3 CFU/ml.

The intervention at our clinic was performed in December 2021.

Fist treatment stage Right knee joint revision; ACL graft removal; debridement; ultrasound wound cavitation; defect reconstruction with vancomycin-impregnated bone cement (Fig. 2). Intraoperative microbiological tests revealed MRSE 103 CFU/ml. Intraoperative blood loss was 100 ml; no blood transfusion was performed. The wound healed by primary intention. The drain was removed on the third postoperative day.

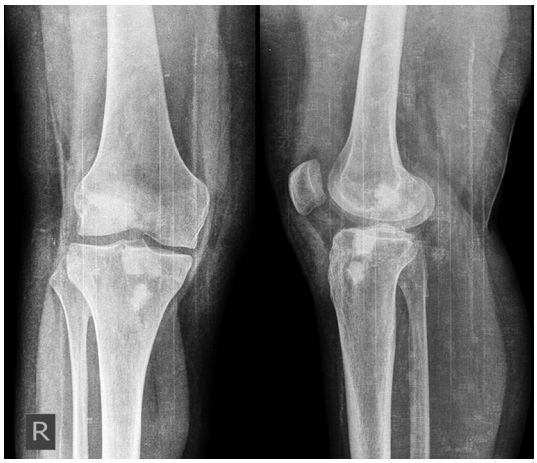

Fig. 2 AP and lateral radiographs of the right knee joint after the first treatment stage

After each stage of the surgical treatment, a two-week course of etiotropic antibacterial therapy with vancomycin 1.0 g twice daily and meropenem 1.0 g three times daily was administered in the hospital; a four-week course of moxifloxacin 400 mg once daily and co-trimoxazole 480 mg three times daily was administered during the outpatient period. The patient was advised to use crutches while walking, with limited weight-bearing on the operated limb.

Three months after the first stage of treatment, a diagnostic puncture of the right knee joint was performed; no growth of the pathogen was detected. Hematological parameters were: mild anemia (Hb 107 g/L), acute-phase reactants of inflammation within normal limits (ESR 2.0 mm/hour and CRP 1.6 mg/L).

In March 2022 the ***second treatment stage*** was performed: revision of the right knee joint; spacer removal; debridement of the right femur and tibia; ultrasound cavitation of the wound; plastic surgery of the femur and tibia defects with allograft material with the addition of vancomycin; open reconstruction of the ACL of the right knee joint using an autograft (Fig. 3).

Intraoperative blood loss was 150 ml; no blood transfusion was performed. Intraoperative microbiological tests revealed no pathogen growth. The patient received restorative treatment; mobilization was initiated on the second postoperative day with the assistance of a physical therapist. The drain was removed on the third postoperative day. The wound healed by primary intention.

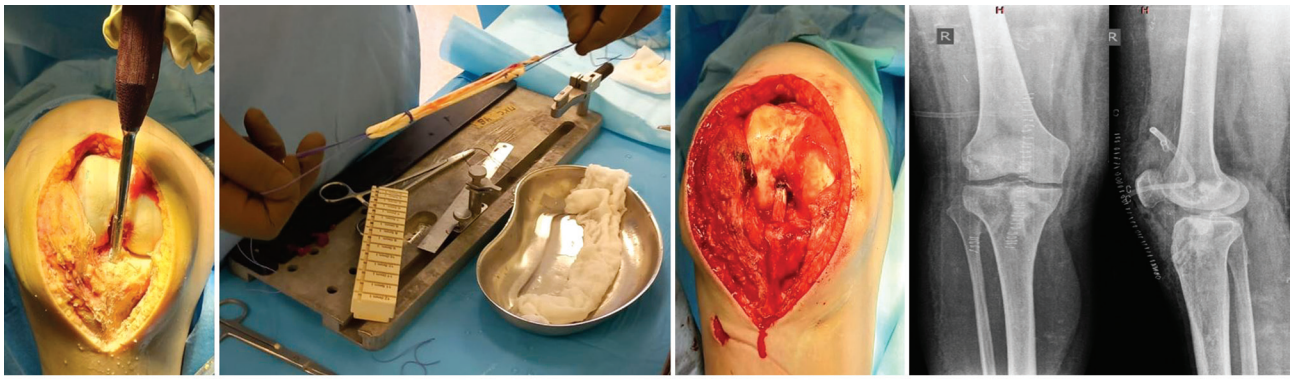

Fig. 3 The second stage of treatment: (a) plastic surgery of bone defects of the femur and tibia with allobone chips; (b) preparation of the ACL autograft from the tendon of m. peroneus longus dexter (length, 10 cm; diameter, 8 mm); (c) fixation of the ACL autograft in the femoral and tibial canals with fixation implants; (d) radiographs of the right knee joint in the frontal and lateral projections after the second stage of treatment

FOLLOW-PUS AND THE OUTCOME

At a two-year follow-up, no evidence of exacerbation of the purulent inflammatory process was detected. No instability in the knee joint was observed (anterior drawer sign, posterior drawer sign, and the Lachman test were negative), and inflammatory markers were within normal limits (ESR — 21 mm/hour; CRP — 3 mg/L). The functional status of the right knee joint was 77 points according to the KSS, 69 points according to the Lysholm (Fig. 4).

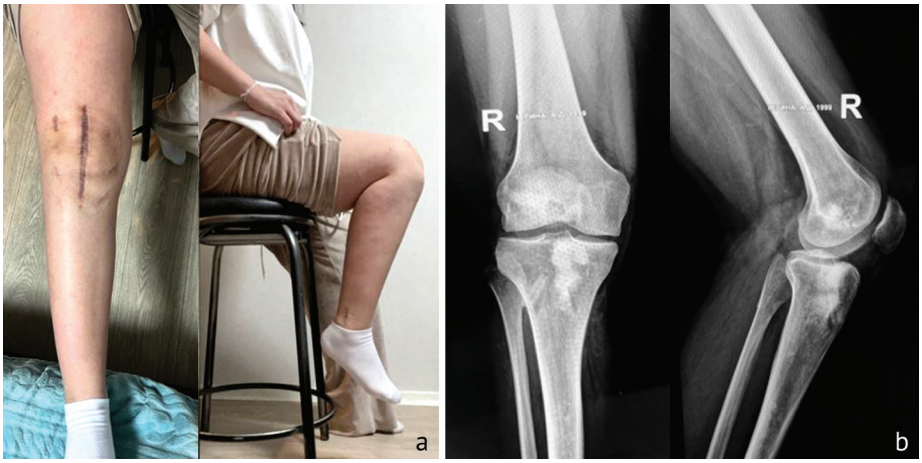

Fig. 4 The outcome two years after the treatment: (a) photo demonstrating the function of the limb; (b) radiographs of the right knee joint in the frontal and lateral projections

The outcome of the treatment was arrest of infection in the right knee joint and recovery of limb function. The patient is satisfied with the treatment results, no longer uses additional support devices, and returned to her daily work activities.

DISCUSSION

Septic arthritis after ACL reconstruction increases the risk of rapid knee joint destruction. Infectious complications after this surgical procedure occur with a frequency of 0.1 % to 1.7 % in the general population [2]. Timely diagnosis and appropriate patient management are key components of successful treatment and the prevention of early and significant deterioration of the joint. Despite the increasing incidence of this problem, there is no consensus on treatment strategies.

Arthroscopy provides easy access to the joint, adequate debridement, shorter postoperative recovery time and physiological lavage under pressure [13], and also enables to determine the stage of joint

destruction. According to the classification proposed by the German scientist A. Gaechter [14], four stages of joint damage are distinguished: stage I is joint effusion, redness of the synovial membrane and possible petechial bleeding; stage II is severe inflammation, fibrinous deposits and pus in the knee; stage III is thickening of the synovial membrane and multiple pockets due to adhesions; stage IV is aggressive pannus with infiltration into the cartilage, possibly undermining the cartilage, radiographic signs of subchondral osteolysis and possible bone erosions and cysts [5, 15].

During the initial arthroscopic evaluation and debridement, it is necessary to assess the integrity and viability of the graft, evaluate its tension, and perform an anterior drawer test. If the test is positive the viability of the graft poses doubts, and debridement arthroscopy with extensive lavage and complete synovectomy should be performed [2, 3, 4]. Upon completion of the procedure, a closed drainage system is installed and the knee joint is immobilized for a short period.

Most authors do not limit themselves to a single operation; the average number of arthroscopies is 2.8 (minimum one, maximum five operations) [10, 12, 13, 16]. During staged salvage arthroscopies, surgeons decide to remove the ligament and fixators. Preservation or removal of the graft is still a controversial issue and depends on preference, experience and expert opinion [17]. In some cases, the cause of recurrent infection is probably the formation of biofilm, and removal of the graft and all materials may lead to successful results in terms of infection control [17]. In addition, one of the factors that is crucial for graft viability is early diagnosis, since the patients diagnosed more than seven days after the onset of symptoms frequently undergo graft removal [18]. In this case, all fixators should be removed, and canal debridement is performed within healthy tissues. This operation can be performed either arthroscopically or by arthrotomy [2].

In cases of widened canals, bone grafting is actively used in aseptic revisions. According to an analysis of 460 repeated ACL reconstructions, bone plasty simultaneously with graft placement was performed in 3 % of cases, while 9 % of cases required staged treatment with defect compensation at the first stage and revision grafting at the second [19]. After graft removal, bone canals must be treated, since the risk of further spread of infection is extremely high [2, 16]. In our opinion, filling of femoral and tibial canals with a spacer containing an antibacterial agent provides better infection control in patients before subsequent reimplantation. In our case, the canals were filled with a spacer containing an antibiotic, while antibiotic beads are usually used which are placed into the joint cavity arthroscopically or openly during the debridement stage and removed during ligament reconstruction [20]. In the presented clinical case, due to a long history of septic arthritis, the presence of severe multidrug-resistant microflora, and the need to place a spacer containing an antibiotic in the bone canals, a decision was made to opt for open surgery. A study by Osti et al. confirms that in such cases, arthroscopic techniques should be avoided and arthrotomy should be the preferred [21].

Along with surgical intervention, a long course of etiotropic therapy (antibiotic therapy) is mandatory [7]. Parenteral administration of an antibiotic active against the most common microorganisms (Staphylococcus aureus and coagulase-negative staphylococcus) should be started immediately after receiving the results of microorganism culture from the knee joint puncture. To achieve clinical efficacy, a combination of antibiotics is recommended, the choice of which should be based on the microorganism and following consultation with a clinical pharmacologist [5]. A generally accepted combination is third-generation cephalosporins and vancomycin/gentamicin. However, the latter are used with caution due to their nephro- and ototoxicity. The course of antibiotics starts with intravenous administration for three to four weeks, followed by a switch to oral drugs [2, 16].

The second surgical intervention for ligament reimplantation is recommended to be delayed and performed six to eight months after the initial surgery [5]. However, a properly and timely first stage, absence of pathogen growth in the knee joint puncture specimen, and normal inflammatory parameters, as in the presented clinical case, allow for an earlier second stage to reduce the patient's recovery time [22].

In the early postoperative period, the limb is fixed in a brace at 175° extension. Rehabilitation measures start from the following day after surgery, aimed at relieving pain and swelling, increasing the range of passive and active motion, and strengthening the quadriceps femoris. The primary goal is to increase the load on the limb and enable walking without additional support [23].

Functionally, patients can return to work and daily life, as evidenced by the increased scores on the IKSSS and Lysholm scales in the clinical case presented. We compared our functional results with those of international surgeons. Gille's study recorded scores of 63.9 on the Lysholm scale and 63 on the IKSSS scale [15]. It should be noted that the final results in our clinical case are in no way inferior to the average values in the available international literature. Arrest of infection and joint stabilization improved the patient's quality of life, and in the long term, this should reduce the rate of gonarthrosis progression.

The strengths of this study include the originality of the technique, which nevertheless adheres to the general paradigm for treating patients with infectious complications, and a long-term treatment outcome. The use of this technique in the treatment of a single patient is undoubtedly a limitation of the study level of evidence.

CONCLUSION

This clinical case demonstrates a successful personalized approach to treating patients with infection following ACL reconstruction. The choice of treatment strategy was based on the patient's medical history and desired needs. Optimal management, including appropriately selected and administered antibiotic therapy and timely surgical interventions, ultimately resulted in a good outcome.

Conflict of interests *The authors declare neither obvious nor potential conflicts of interest related to the publication of this article.*

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Ethical statement *The study was approved by the ethics committee of the Federal State Budgetary Institution Ilizarov National Medical Research Center of Traumatology and Orthopedics of the Ministry of Health of the Russian Federation (protocol No. 1 (76) dated November 29, 2024) and was conducted in accordance with the ethical standards of the Helsinki Declaration developed by the World Medical Association "Ethical Principles for Medical Research Involving Human Subjects" with the amendments of 2000.*

Informed consent *The patient gave voluntary written consent to participation in the study and publication of its results.*

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Clinical case
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A rare case of severe deformity in a patient with ankylosing spondylitis

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Abstract

Introduction Ankylosing spondylitis (AS) is a chronic inflammatory disease with associated rigid spinal deformities and sagittal imbalance. The identity of the clinical case reported was characterized by AS combined with Andersson lesion, pronounced three-plane deformity and the need for multi-stage combined surgical treatment involving an original technique of external reduction.

The **objective** was to demonstrate surgical treatment of a patient with severe spinal deformities due to ankylosing spondylitis complicated by Andersson lesion and severe sagittal imbalance.

Material and methods The clinical case of a 53-year-old patient with severe kyphoscoliosis, chronic pain and horizontal gaze disorder is reported. Multicomponent surgical management included a Schwab type 6 osteotomy at the Th_{12}–L_1 level, spondylodesis via posterior and transpleural approaches, osteoplasty of post-screw defects, placement of laminar hooks and reconstruction of the metal construct. Preoperative 3D planning and original methods of fixation and reduction of the spine were employed.

Results With the implant instability developed after the primary operation, successive staged surgical interventions facilitated restoration of the axis and support of the spinal column. Reliable interbody spondylodesis with no signs of hardware instability and improvement in the patient's quality of life were observed at one-year follow-up.

Conclusion The clinical case demonstrated the need for a comprehensive multi-stage approach to the treatment of an AS patient with severe spinal deformities complicated by Andersen lesion and severe sagittal imbalance. The staged treatment resulted in sustainable clinical and functional improvement with the emphasis on individualized planning and adapted surgical strategy if complications arise.

Keywords: ankylosing spondylitis, spinal deformity, correction, complications, hardware instability

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INTRODUCTION

Ankylosing spondylitis (AS) is a rare seronegative spondyloarthropathy occurring in approximately 1.4 % of the population with a prevalence ranging from 0.03 to 1.80 % [1]. This chronic inflammatory disease primarily affects the sacroiliac joints and the spine and is characterized by the formation of spinal bridging syndesmophytes, enthesitis, sacroiliitis and uveitis. Progression of AS leads to the formation of kyphotic deformity and an increase in the chin-brow vertical angle (CBVA) causing functional impairment in 30 % of patients [2]. The main goal of surgery for AS is to correct sagittal imbalance, restore horizontal gaze, reduce pain and improve functional status.

The identity of the clinical case reported was characterized by AS combined with Andersson lesion, pronounced three-plane deformity and the need for multi-stage combined surgical treatment involving an original technique of external reduction.

The **objective** was to demonstrate surgical treatment of a patient with severe spinal deformities due to ankylosing spondylitis complicated by Andersson lesion and severe sagittal imbalance.

MATERIAL AND METHODS

A 53-year-old patient was admitted to the neurosurgery department in 2022 and presented with a constant pain score of 6–7 on the VAS in the thoracic and lumbar spine, major joints, spinal deformity, morning stiffness and impaired horizontal gaze.

Anamnesis morbi: The patient first developed back pain in 2000. The patient was not examined and treated, he was engaged in swimming and gymnastics. With the diagnosis of Bechterew's disease established in 2011, he received NSAIDs, pulse therapy with glucocorticosteroids, physiotherapy, exercise therapy. The pain improved due to the therapy with increasing spinal deformity and gradually impaired horizontal gaze. He sustained a fracture in 2021 with signs of instability at the level of C_6–C_7 type B3 AO Spine classification and was treated with dorsal fixation of $C_{5–6}$–$Th_{1–2}$. Transpedicular screws were used for fixation and stabilization of the broken spine. He received basic therapy between 2022 and 2023 with no improvement in the pain syndrome, deformity increased sharply decreasing quality of life.

Objectively: The patient has a hypersthenic build.

The patient was found to have:

— pronounced kyphoscoliosis (“beggar’s pose”) (Fig. 1a);

— severe pain at the spinous process of L_5, at the attachment of the Achilles tendon to the calcaneus, at the iliac crest on both sides, at the first and the seventh sternocostal joints, Maastricht Ankylosing Spondylitis Enthesitis Score (MASES) of 9;

— severely limited spinal mobility, Bath Ankylosing Spondylitis Metrology Index (BASMI) of 10;

— pronounced functional impairments, Bath Ankylosing Spondilitis Functional Index (BASFI) of 9.1).

Quantitative assessment of overall AS activity:

— Bath Ankylosing Spondilitis Disease Activity Index (BASDAI) of 9.2;

— Ankylosing Spondilitis Disease Activity Score with ESR (ASDAS-ESR) of 3.5.

Neurological status was unremarkable.

Instrumented examination showed:

— bilateral sacroiliitis grade 3;

— wedge-shaped deformity of the Th_{12}, L_1 vertebrae and Andersson lesion at this level and kyphoscoliosis (Fig. 1b);

— impaired sagittal balance (SVA 280 mm);

— gross violation of horizontal gaze (tragus-wall distance of 25 cm, CBVA of 75°.

Bone mineral density (BMD) was measured preoperatively using CT scanning and showed 98 HU at Th_9, 100 HU at Th_{10}, 102 HU at Th_{11}, 98 HU at L_2, 94 HU at L_3, 96 HU at L_4. The measurements indicated reduced BMD and corresponded to osteopenic range.

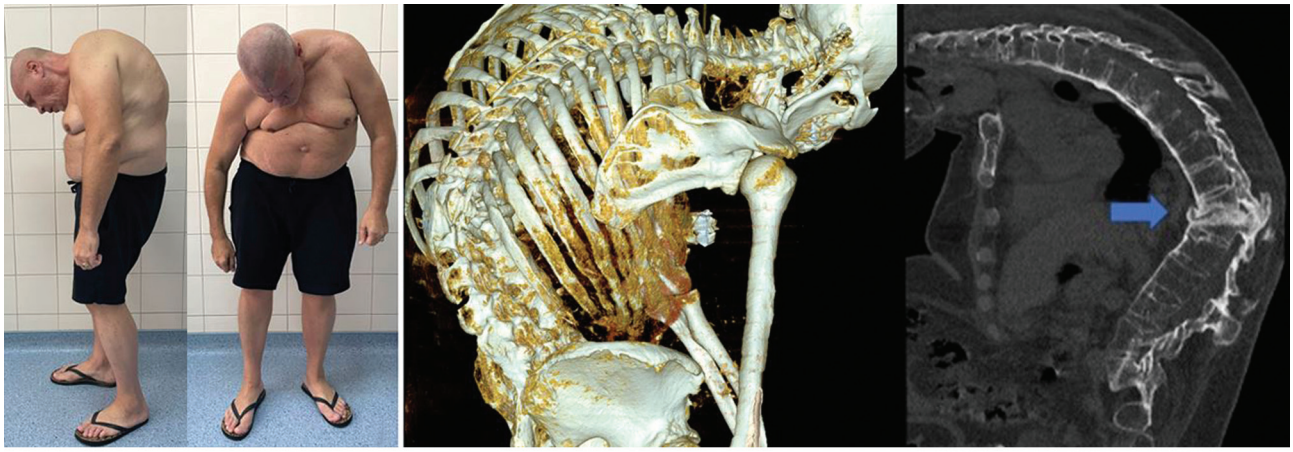

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Fig. 1 Preoperative photograph and CT scan of the thoracic and lumbar spine showing (a) patient's posture, pronounced kyphoscoliosis; (b) CT scan 3D VRT and MPR, sagittal view, signs of Andersson lesion, wedge-shaped deformity of Th_{12} and L_1, ventral spontaneous fusion and ossification of the anterior longitudinal ligament

Surgimap software was used for preoperative planning. The volume of surgical intervention was determined by the presence of rigid kyphoscoliotic deformity with the apex at the level of $Th_{12} – L_1$ due to a fracture and the formation of a ventral fusion. Transpedicular fixation of $Th_{9–10–11} – L_{2–3–4}$, Schwab type 6 osteotomy at the $Th_{12}–L_1$ level, spondylodesis from the dorsal approach using a titanium mesh implant and autogenous bone were produced. Correction of 52° was achieved. Duration of the operation was 260 min, blood loss was 1,100 ml (Fig. 2).

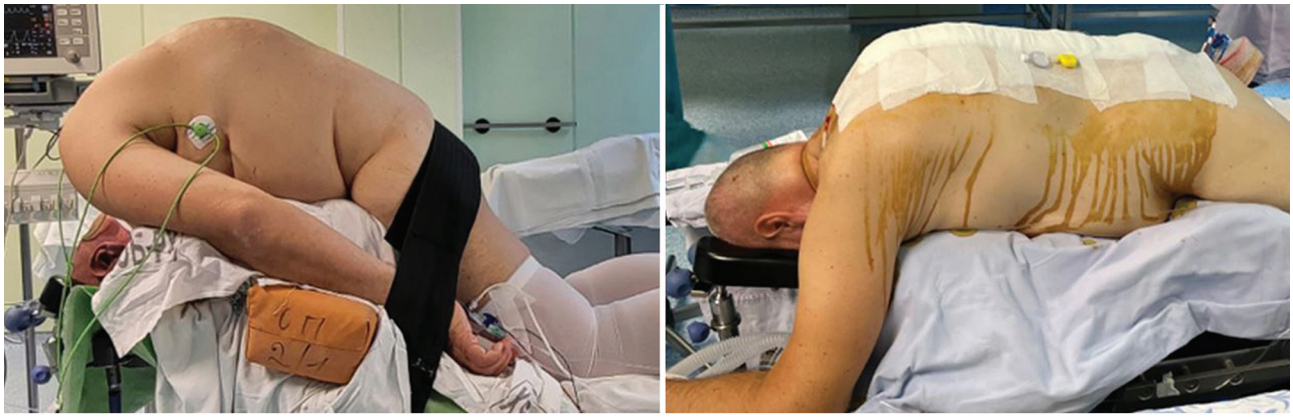

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Fig. 2 Intraoperative photographs of the patient, intraoperative radiographs and postoperative CT scan demonstrating surgical stages of spinal deformity correction showing (a) the patient positioned on the operating table before and after surgery, visual regression of kyphosis noted

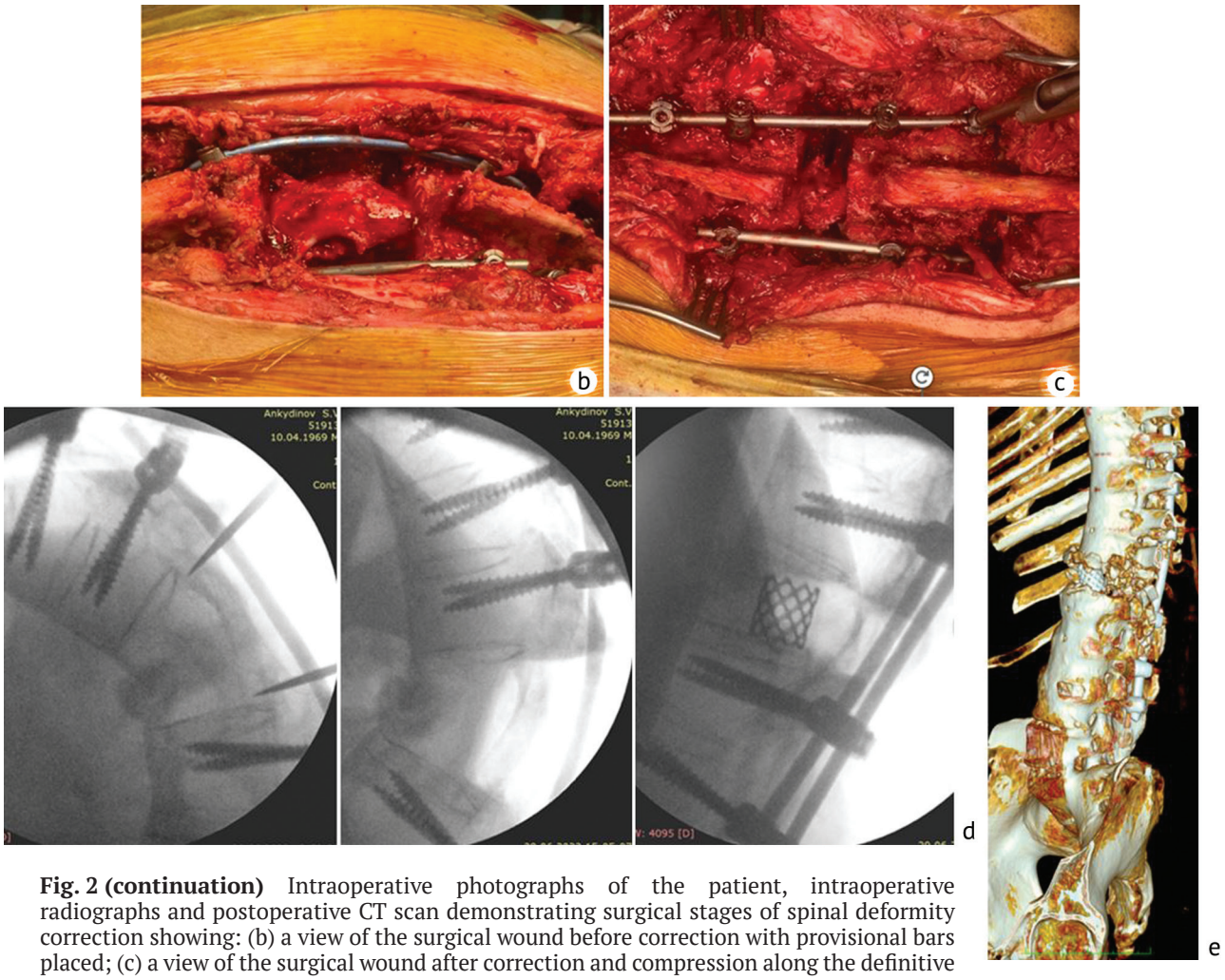


Fig. 2 (continuation) Intraoperative photographs of the patient, intraoperative radiographs and postoperative CT scan demonstrating surgical stages of spinal deformity correction showing: (b) a view of the surgical wound before correction with provisional bars placed; (c) a view of the surgical wound after correction and compression along the definitive bars (d) intraoperative radiographs showing stages of osteotomy and placement of a titanium implant filled with autogenous bone; (e) postoperative 3D-VRT-reconstruction of CT showing metal construct and interbody mesh implant in place

Passive rehabilitation started on the first day after operation, and active rehabilitation and verticalization of the patient was initiated with use of a thoracolumbar corset after four postoperative days. Regression of the pain and improvement of horizontal gaze were noted. Manifestation of the pain (VAS = 7) being resistant to NSAIDs and opioids occurred after 11 postoperative days. CT scan of the spine showed unstable metal construct with loosening and the inferior six screws being torn out, migration of the interbody implant, translation of the thoracic spine (Fig. 3a) treated with a complex and atypical revision procedure due to the changes in the anatomy.

The only fixation option involved removal of unstable screws, placement of laminar hooks at the level of loose screws and replacement of the interbody implant. Reduction of the dissociated spinal column to eliminate severe translation and prevent injury to the spinal cord was a technical intraoperative challenge. An original external fixator was designed (Fig. 3b) to allow gradual reduction of the lumbar spine and provisional fixation to prevent sagittal displacement during hook placement and definitive fixation.

The surgical intervention including reduction, fixation, replacement of the interbody cage lasted for 90 minutes, blood loss was 600 ml. Stable fixation was achieved (Fig. 3c).

Instability was diagnosed again at ten days and another revision performed. A two-stage surgical treatment offered for the repeated instability of the metal construct and mesh implant included.

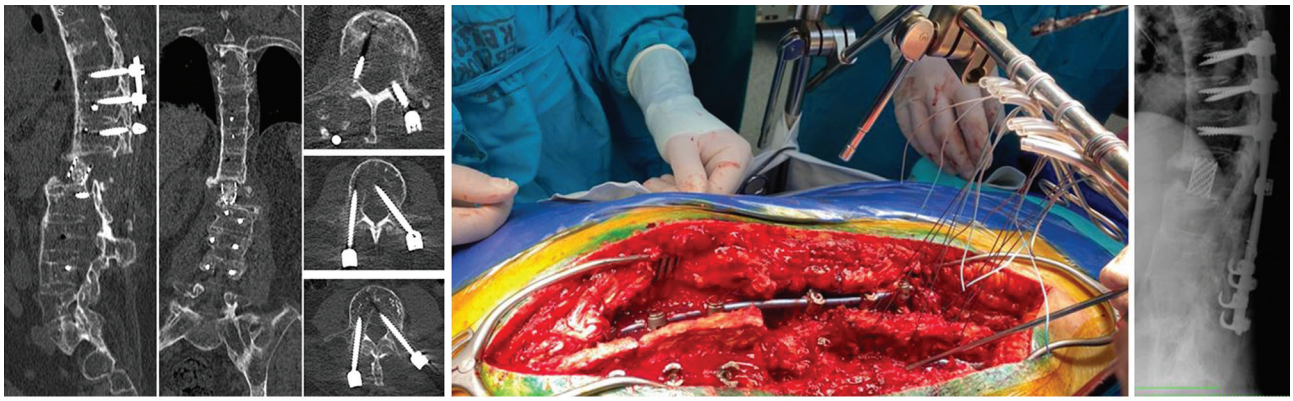


Fig. 3 Radiological and intraoperative signs of unstable metal construct and stages of the primary revision intervention seen on: (a) sagittal, frontal and axial CT scans on the 12th day after the primary operation showing translation of the thoracic spine, migration of the interbody implant, loosening of the screws in the lumbar spine with large (> 3 mm) zones of osteolysis in the L_2, L_3, L_4 vertebrae; (b) external fixator assembled of a Thompson retractor sleeve and lavsan threads passed through the spinous processes and fixed to the frame; (c) postoperative radiograph in the sagittal plane

First stage. Wound revision, laminar hooks to be placed in L_2, L_3, L_4 (n = 8), reassembly of the hybrid metal construct using screws and hooks, removal of the migrated mesh implant, osteoplasty of post-screw defects in the L_2, L_3, L_4 vertebrae. The revision surgery (Fig. 4) lasted for 140 min. with blood loss of 800 ml. No changes were seen postoperatively in the neurological status, muscle strength in the limbs scored five with no conduction disorders observed in the patient. Five-day bed rest was recommended to start the second stage. Forced restorative vascular therapy, blood transfusion, antibiotic therapy and prevention of venous thrombosis were performed during the period.

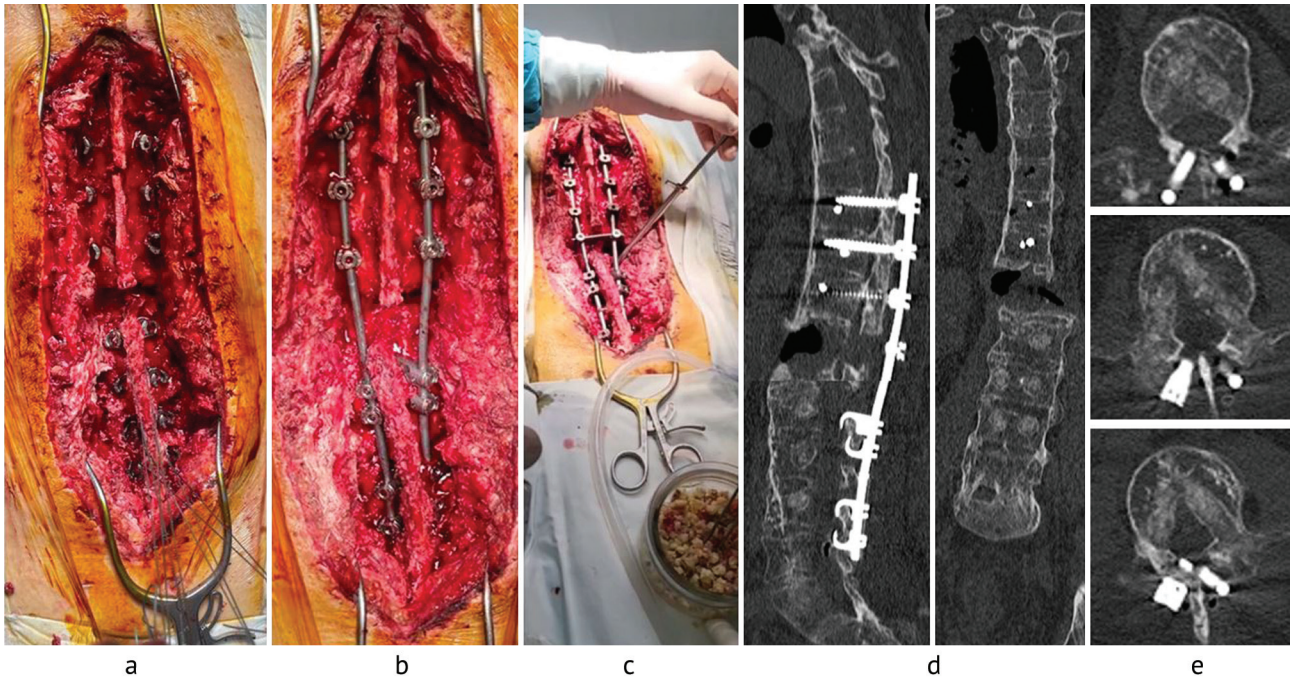


Fig. 4 Intraoperative photoes and CT scans demonstrating stages of the second revision intervention including osteoplasty of post-screw defects: (a) a view of the surgical wound with hooks in place, the dorsal part of the vertebra is "suspended" by the original fixator; (b) a view of the surgical wound after rod placement and definitive fixation; (c) osteoplasty of post-screw defects using allogenic bone chips and orthobiological product thrombogel; (d) sagittal and frontal scans of the thoracic and lumbar spine; (e) L_2, L_3, L_4 vertebrae with zones of osteoplasty of post-screw defects

Second stage. Transpleural corporodesis using a titanium mesh implant and a modeled allograft bone (Fig. 5). The operating time of the second stage of surgical intervention was 90 minutes, blood loss was 100 ml. The patient was verticalized on the tenth postoperative day due to pronounced orthostatic disorders. Passive and active rehabilitation, breathing exercises, physiotherapy, and HBO sessions were performed. The patient developed positive dynamics with improved pain scored 2–3 on the VAS scale, improved quality of life due to a change in the angle of gaze.

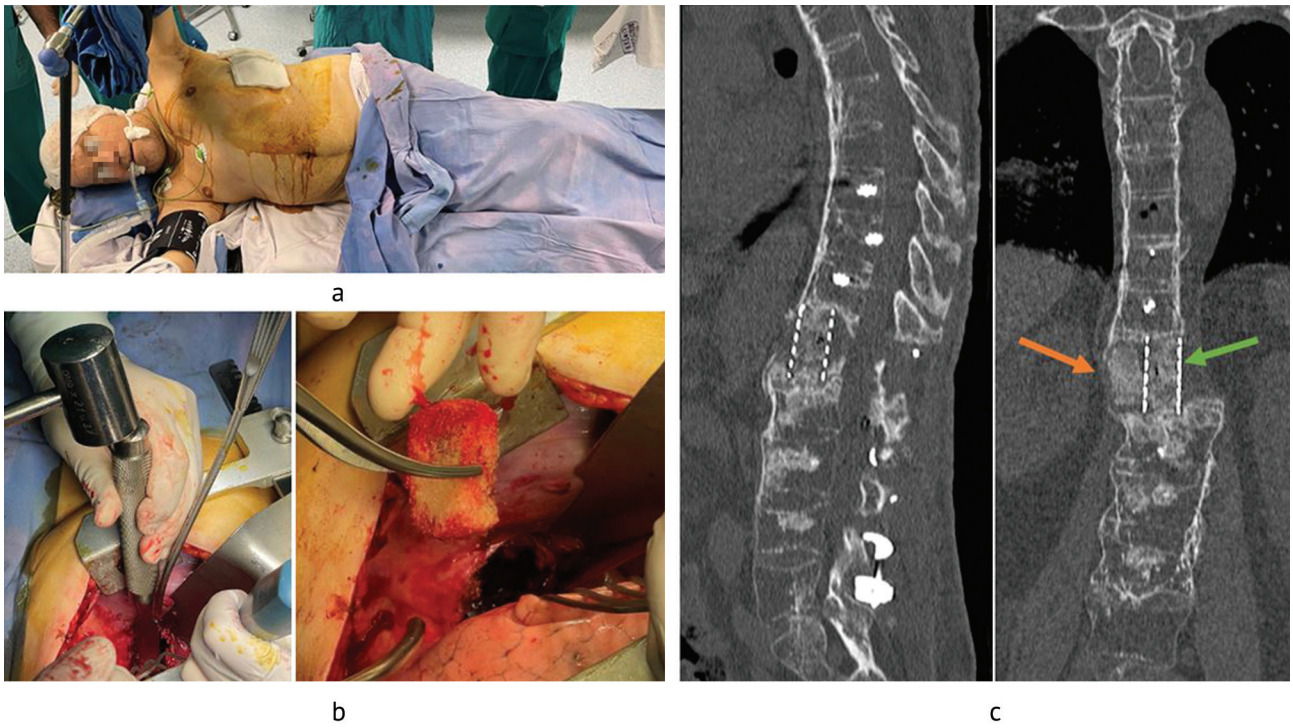


Fig. 5 Intraoperative photographs of the patient and CT scans showing stages of transpleural corporodesis aimed at restoring the support capacity of the anterior and middle spinal columns: (a) the patient positioned on the operating table on the left side; (b) a titanium implant and a modeled allograft bone implanted; (c) postoperative sagittal and frontal CT scans showing the interbody mesh implant (green arrow) and the modeled allograft bone fragment (orange arrow)

The patient was discharged from the hospital in a satisfactory condition after 41 days (Fig. 6a). CT control scans of all parts of the spine were produced at 6 and 12 months after discharge. CT scans demonstrated interbody spondylodesis (at the level of the mesh implant and supporting allograft), allograft bone chips completely integrated at the site of post-screw defects, and no signs of instability of the metal structure seen at one-year follow-up (Fig. 6b, c).

Postoperative CT scans revealed important adverse findings:

— the presence of two separate metal constructs at C_{5-6}–Th_{1-2} и $Th_{9-10-11}$–L_{2-3-4} levels;

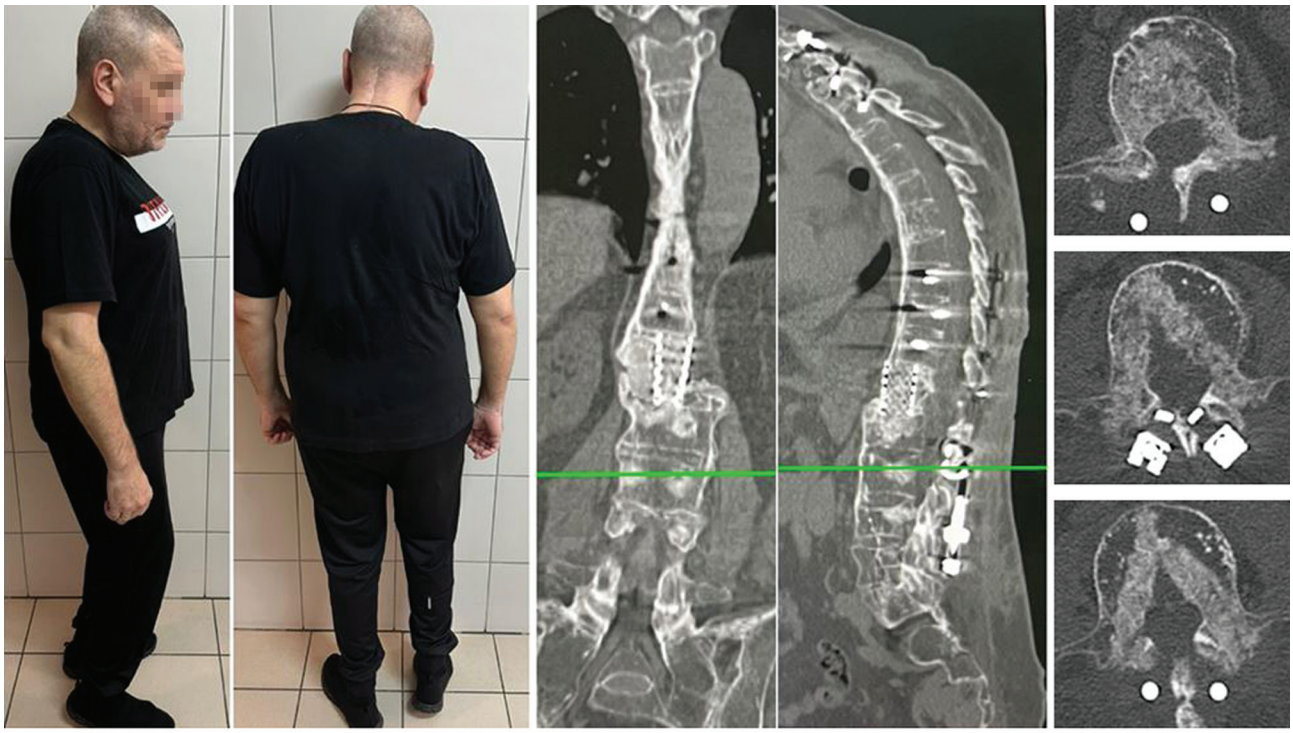
— free non-fixed zone Th_3–Th_8 and kyphosis of 22°;

— BMD of 78 HU in the vertebra Th8 directly above the metal construct.

With the clinical and radiological manifestations there was a high risk of proximal transitional kyphosis. The situation was discussed with the patient who underwent a surgical intervention including:

— transpedicular fixation of Th_3–Th_8, and L_2–L_4 (at the site of osteoplasty performed earlier);

— assembly of a single metal construct C_5–L_4 without replacement of previous constructs using connectors and additional rods (Fig. 7).



a b c

Fig. 6 The patient's appearance and CT scans of the cervical, thoracic and lumbar spine at one year of surgery: (a) photo of the patient after staged surgical interventions; (b) frontal and sagittal scans of the thoracic and lumbar spine showing signs of spondylodesis; (c) L_2, L_3, L_4 following vertebrae osteoplasty of post-screw defects, with signs of complete integration of implanted allograft bone chips

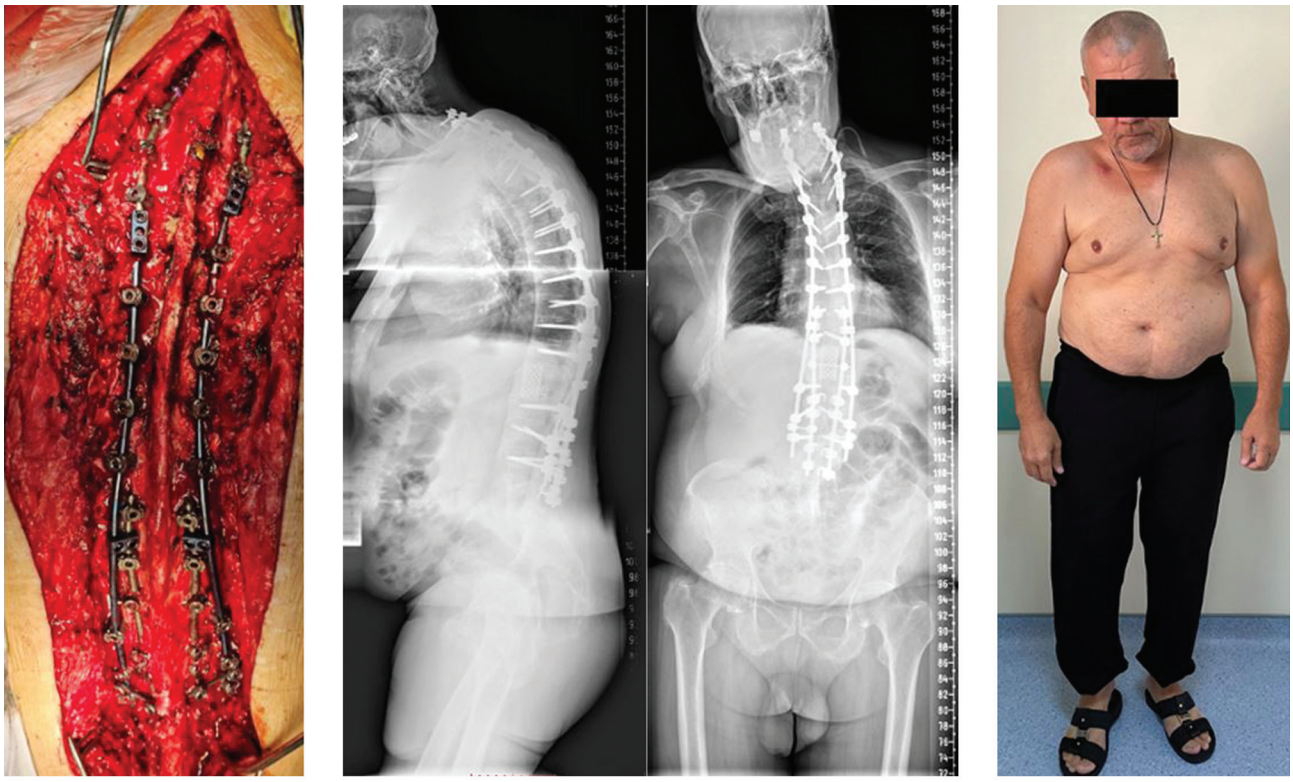


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Fig. 7 Intraoperative photo of the wound, postoperative survey radiograph and the patient's appearance: (a) definitive appearance of a single metal construct C_5–L_4 without replacement of previous constructs with the connection to new elements using connectors and additional rods; (b) X-ray topogram after surgery showing a single hybrid metal construct C_5–Th_2–Th_8–L_2–L_4 with a four-rod zone at the lumbar level; (c) photo of the patient after the final stage of spinal column reconstruction

Asymmetric PSO C_7 was planned to eliminate right-sided neck deviation, but the idea was abandoned due to the drop in motor potentials. The operating time was 120 min., blood loss was 500 ml.

RESULTS

The patient continued active and passive rehabilitation, physiotherapy, breathing exercises and HBO sessions, and drug therapy postoperatively. Neurological examination showed the functions restored to the initial level. He was discharged in a satisfactory condition at 14 days of operation.

The follow-up from the last operation at the time of writing is more than 12 months. Cervical, thoracic and lumbar CT scans showed no signs of instability of the metal construct, the patient was well, could ambulate unassisted without additional support with the quality of life improved significantly. Pain scored according 1–2 on the VAS scale.

DISCUSSION

AS belongs to a group of diseases called seronegative spondyloarthritis. The prevalence of AS in different countries ranges between 0.03 % and 2 %. Kyphosis developed in 30 % of patients during their lifetime [3]. Aseptic inflammation is one of the rare complications of AS aggravating the severity of the deformity and leading to a transdiscal or transvertebral “fatigue fracture”, segmental instability and severe pain. The complex of radiographic signs including erosion of the supporting surfaces of the vertebral bodies surrounded by reactive sclerosis wedge-shaped vertebral deformity is referred to as Andersen lesion in scientific literature. The incidence of Andersen lesion is 6.7–10 % [4]. The patient presented with a pronounced three-plane deformity due to Andersen lesion at the Th_{12}–L_1 level. Kyphosis in ankylosing spondylitis can be corrected according to the following indications:

— severely disturbed sleep due to difficulty in remaining in a supine position;

— decreased quality of life due to impaired horizontal gaze;

— compression of abdominal organs, the digestive system, in particular;

— restricted respiratory movements;

— pain that does not respond to conservative therapy.

A variety of osteotomies can be performed to correct clinically significant deformity. Schwab types 4, 5, 6 osteotomies can be produced to address rigid kyphotic deformity and/or ventral bone blocking of the vertebrae in the kyphosis position [5, 6, 7].

BDBO (Bone – Disc – Bone Osteotomy) or SRS-Schwab type 4 osteotomy is designed to correct kyphosis by removing the disc and adjacent endplates. It can be divided into three types to ensure correction from 35° to 60° [8]. Kyphosis, sagittal imbalance requiring correction and cannot be eliminated with PSO (type 3) are indications for BDBO. BDBO has a correction potential close to Vertebral Column Resection (VCR), with fewer intraoperative and postoperative complications [9].

Lenke and Suk reported the first level VCR or the SRS-Schwab fifth type osteotomy being able of an average deformity correction from 30° to 60° with satisfactory radiographic and clinical results [10, 11]. Vertebrotomies of the fifth and sixth types have the maximum possibilities for deformity correction. These appear to be the most traumatic, "bloody" and risky surgeries in terms of neurological complications. Their choice should be strictly substantiated and justified during preoperative planning to be applied for cases where less invasive osteotomies do not allow achieving the necessary clinical result.

In our situation, a double fracture of adjacent vertebrae, formation of a three-plane deformity and the occurrence of a spontaneous block predetermined the use of the type six vertebrotomy for maximum correction and the possibility of restoring the support capacity of the anterior column with the cage resting on the bodies of the intact vertebrae.

The success of operations would depend on the precision of the intervention to prevent of neurological deficit, minimize blood loss and trauma, restore acceptable anatomical relationships in the operated segments ensuring stable fixation of the posterior and support capacity of the anterior columns of the spine.

In our case, the first task of performing vertebrotomy Th_{12}–L_1 of the Schwab type 6 allowed us to achieve the results scheduled, but the second component of the operation including reliable fixation of the anterior and posterior columns of the spine was not achieved at a short term. Despite the fact that the screws were implanted correctly, the interbody cage placed adequately, compression performed and a mechanical intraoperative test for the stability of the system with the construct waggling showed absolute stability of the system, the instability that led to translation of the spine was diagnosed after 11 days.

The instability in the case was probably caused by two components that were so close to each other and it was difficult to determine which of the components was the main one. Incomplete congruence between the interbody implant and the plane of the endplates could cause micromobility in the spondylodesis site, and reduced BMD contributed to the destabilization of the three inferior pairs of screws. Decreased BMD measuring less than 120 HU on CT scan is associated with a high risk of implant instability and screw loosening [12].

In our clinical case, BMD measured less than 100 HU in the L_2–L_4 vertebrae and was identified as an osteopenic density level. Both of the components potentiated each other and being combined with early ambulation of the patient led to destabilization of the system. In addition to that there was an extended lever between the heads of the Th_{11} and L_2 screws.

With instability and severe sagittal translation diagnosed the scope of the operation, the method of restoring the spinal axis and the fixation technique were essential for revision surgery. CT and MRI scans were thoroughly examined, and surgical treatment included treatment of the interbody space and replacement of the supporting implant with fixation of the distal spine using laminar hooks (transpedicular screws cannot be re-implanted due to extensive zones of osteolysis at the sites of the previous placement. Translation was addressed intraoperatively in an improvisational way. With the correction being impossible with positioning and acute reduction using instruments, a system for suspension and gradual traction of the distal spine was designed due to the Thompson retractor frame fixed to the table and lavsan threads No. 5 passing through additional perforations in the spinous processes of the L_2, L_3, L_4 and L_5 vertebrae. Thus, the spinal axis was restored, the risk of neurological complications minimized and four hooks implanted.

Another instability diagnosed at 10 days included dislocated hooks and migrated interbody cage suggesting the previous situation with insufficient reliability of fixation and lack of rigid support of the anterior spinal column. We concluded that both cases of instability were caused by unstable interbody implant placed in the formed bed that resulted in circular instability together with insufficient rigidity of the dorsal fixators. In case of another revision we decided to abandon one-stage interbody spondylodesis from the dorsal approach taking into account the assumption about the reasons for failures. The spine was realigned during the next surgery using the method

developed and described above with eight hooks placed according to the “crab claw” principle and the interbody implant removed. Osteoplasty of post-screw defects in the L_2, L_3, and L_4 bodies was performed in the same session to create fixation points to prevent destabilization of the metal construct [13].

Support ability of the anterior column was restored with delayed interbody transpleural spondylodesis. Visually wide, direct view of the support areas allowed to identify their unevenness which caused likely instability of the implant after previous operations. Combined corporodesis with a mesh implant, bone chips and a solid supporting allograft allowed us to fill the interbody space completely and form a transplant and an implant according to the existing dimensions. The surgical strategy facilitated stable long-term spondylodesis.

The final stage of the surgical treatment including re-implantation of screws and connection of the constructs) was aimed at prevention of the proximal transitional kyphosis and instability at a long term. The metal construct was strengthened with this approach preventing a formidable complication in the form of PJK/PJF.

CONCLUSION

The combination of ankylosing spondylitis, Andersen lesion and severe global sagittal imbalance is an extremely complex clinical scenario that requires a high degree of alertness and a comprehensive approach. The clinical case presented covers the staged treatment and observation of the patient during 2022–2023, with a follow-up period of more than 12 months.

A thorough preoperative assessment of the risk factors including bone mineral density, anatomical features of the deformation zone and the length of the lever between the supporting segments is essential for surgical planning to prevent metal construct instability. The factors are important for a tailored surgical strategy even before the primary intervention.

However, the patient developed implant instability early post-op with technically adequate primary fixation provided. The surgical treatment aimed at addressing the adverse events included removal of the loose screws, the use of laminar hooks, osteoplasty of post-screw defects, delayed transpleural corporodesis with a tailored supporting implant and the formation of a single extended metal construct.

This clinical case demonstrated the need for thoughtful and flexible preoperative planning considering possible complications. Pre-defined alternative solutions and adapted surgical strategy would be practical to address intra- and postoperative complications and achieve stable anatomical and functional results in the treatment of patients with severe spinal deformities associated with ankylosing spondylitis.

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Ethical Approval *The study was performed in accordance with ethical principles for medical research involving human subjects stated in the Declaration of Helsinki developed by the World Medical Association.*

Informed consent *The patients gave informed consent for publication of the findings without identification.*

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Review
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Management of Achilles tendon rupture: surgical versus conservative method

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Abstract

Introduction Current therapy for managing achilles tendon rupture are classified into surgical and conservative method. Randomized controlled trials were performed in multiple healthcare facilities in multiple centers across the world yet functional outcomes, re-rupture rate and complications are still indecisive.

The **aim** of this study is to compare surgical versus conservative methods for the treatment of acute Achilles tendon rupture; including functional outcome, re-rupture rate, and complications to provide better guidance in selecting therapeutic method.

Materials and Methods We conducted a comprehensive electronic database. Original articles until November 2023 were screened, focusing on randomized controlled trials with at least 12 months follow up. Our protocol has been registered at PROSPERO ID (CRD42023486152).

Results and Discussion The initial search yielded 354 studies. Twelve randomized controlled trials study with a total of 1525 participants were assessed. Surgical treatment has better outcomes for preventing: re-rupture ($p \leqslant 0.001$), abnormal ankle movement ($p \leqslant 0.001$), and calf muscle atrophy ($p = 0.005$). Functional outcomes at 6 months follow-up were better for hopping ($p \leqslant 0.001$), heel-rise height ($p \leqslant 0.001$), and heel-rise work ($p = 0.007$) in surgical treatment. Functional outcomes at 12 months of follow-up were better only for heel-rise work test ($p \leqslant 0.001$) in surgical treatment. However, incidence of sural nerve injury ($p = 0.006$) was found lower in the conservative group. Complications other than re-rupture ($p = 0.08$) had no significant difference between two groups. At 6-month follow-up, functional outcome tends to be better compared to conservative management of Achilles tendon rupture. At 12-month follow-up, functional outcomes was comparable between two groups. However, the risk of re- rupture rate is higher in the conservative management.

Conclusion Reduced rates of re-rupture and quicker functional recovery are benefits of surgical repair. Conservative treatment can yield good results in terms of functional outcomes and re-rupture rates in long-term follow up, particularly when combined with contemporary rehabilitation procedures. Conservative treatment eliminates the hazards associated with surgery, but it may have a slightly higher chance of re-rupture and a shorter initial recovery of some functional outcomes. Both of these treatment methods are good for treating Achilles tendon rupture.

Level of Evidence: I.

Keywords: Achilles Tendon Rupture, Surgical Management, Conservative Management, Functional Outcome, Re-rupture

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INTRODUCTION

Achilles tendon is the strongest and largest tendon in the human body. This tendon plays an important role of supporting heel movement. Its rupture often occurs during sport activities and excessive exercise [1]. The rupture of this tendon is associated with inability of lifting the heel and decreased range of movement of the knee. The rupture of this tendon also causes severe pain that decreases one's quality of life [2]. Hence, proper, and adequate management of Achilles tendon rupture is needed.

Rupture of the Achilles tendon is commonly found in the adult population. The rising incidence of Achilles tendon rupture can be linked to increased number of sport activities throughout the years. Annually, up to 40 out of 100.000 population reported incidence of Achilles tendon rupture. Seventy three percent of Achilles tendon rupture was reported in recreational sport and 18 % was reported in athletes [3].

Randomized controlled trials were performed in numerous healthcare facilities across the world, yet functional outcomes and complications rate are still indecisive. Although the surgical method of its management results in better outcomes such as lower risk of re-rupture as compared to the conservative method, complications that follow were also higher in surgical management [4, 5, 6]. Hence, we conducted a systematic review and meta-analysis to compare surgical versus conservative methods for the treatment of acute Achilles tendon rupture; including re-rupture rate, complications and functional outcomes to provide better guidance in selecting the therapeutic method.

MATERIALS AND METHODS

Inclusion and Exclusion Criteria

We conducted this systematic review following the PRISMA and Cochrane handbook guidelines for conducting a systematic review of interventions. Our protocol has been registered at PROSPERO ID (CRD42023486152). This research includes a direct comparative study between surgical and conservative method for managing Achilles tendon rupture in adult population. We included original clinical studies which were written in English and available in full text. Systematic reviews, meta-analyses, case reports, expert opinions, abstract conferences, book chapters, letters to editor, summaries of meetings, study protocols, technical reports, narrative reviews, studies with incomplete data, experimental studies on animals, and cadavers, laboratory (*in vitro*), duplication of publications, and computational studies are not included in this research. The population used in this study was adults diagnosed with Achilles tendon rupture who underwent either surgical or conservative treatment. Randomized Controlled Trials (RCTs) with at least 1 year follow-up comparing surgical intervention with conservative method were assessed. The exclusion criteria include patients with re-rupture, rupture caused by pathological aspect, research with insufficient primary outcome data, and research using combined approaches. Re-rupture rate, complications, functional outcome were assessed.

Search Strategy

We conducted a comprehensive electronic database search until November 2023 in PubMed, MEDLINE, and ScienceDirect using the keywords "Surgical versus Nonsurgical" OR "Operative versus Nonoperative" OR "Surgical versus Conservative" OR "Operative versus Conservative" AND "Achilles Tendon Rupture" OR "Rupture Tendon Achilles". Based on the PICO (Patient, Intervention, Comparison, Outcome) concept, our research strategy concept is as follows:

P = Adults aged above 16 years old diagnosed with Achilles tendon rupture who underwent surgical or conservative treatment;

I = Surgical and conservative methods;

C = Surgical versus conservative method;

O = Re-rupture rate, complications, functional outcome, pain score.

Study Selection

The literature selection was performed by 2 reviewers (NSNW and NLPSWP) independently using the standardized study selection forms. A third reviewer (IWS) would be consulted, and a decision would be made through discussion if there was any disagreement between the first two reviewers.

Our literature search identified a total of 354 studies, and after excluding irrelevant and duplicate reports, the remaining 125 articles were assessed using eligibility criteria after reading the full text. Finally, 12 eligible RCTs were included in our meta-analysis [6–17]. A PRISMA flow chart of the article selection steps is shown in Figure 1.

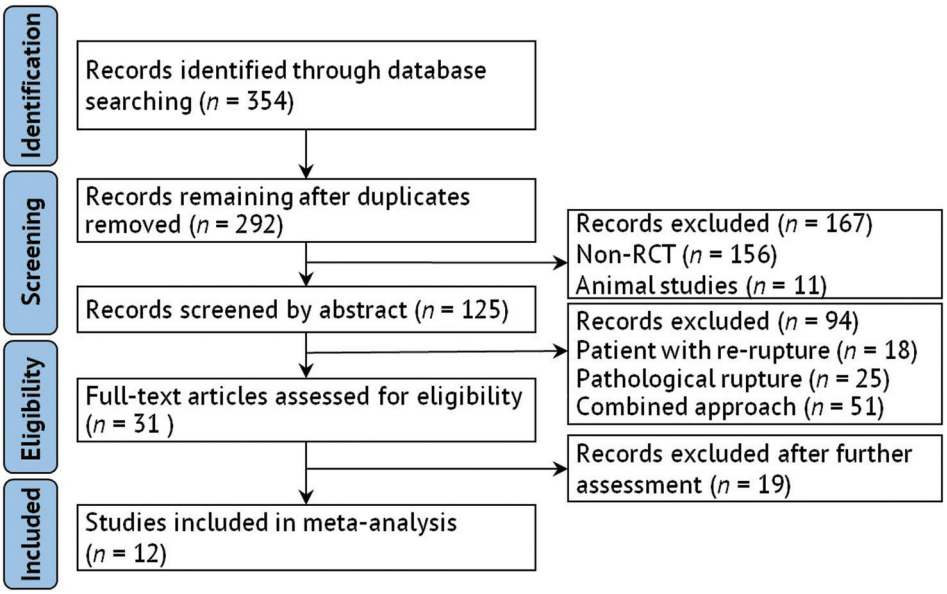

Fig. 1 PRISMA 2019 flowchart diagram

Data Extraction

Two authors (NSNW and SM) independently extracted data from eligible studies by completing a pre-designed data form, with discrepancies being arbitrated by a third reviewer (CGOD, IGNWA, IWSD, IWS). The primary outcomes extracted from each study included the re-rupture rate, complications, and functional outcome.

Methodological Assesment

Bias analysis was carried out by 2 reviewers (NSNW and NLPSWP) using the risk of bias tools formulated by the Cochrane group. For Randomized Controlled Trial (RCT) studies, we used the second version of the Cochrane tool, Risk of Bias (ROB). Potential causes of bias were assessed with signaling questions to detect biases caused by the randomization process, deviation from initial intervention intent, missing data, measurement of outcomes, and reporting of selective bias. Disagreements were resolved by consulting the third reviewer (IWS). The Cochrane risk of bias consists of 6 items (randomization generation, allocation concealment, blinding of participant and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting). Based on the analysis performed, it revealed that most studies showed a low risk of bias in the majority of domains (Fig. 2).

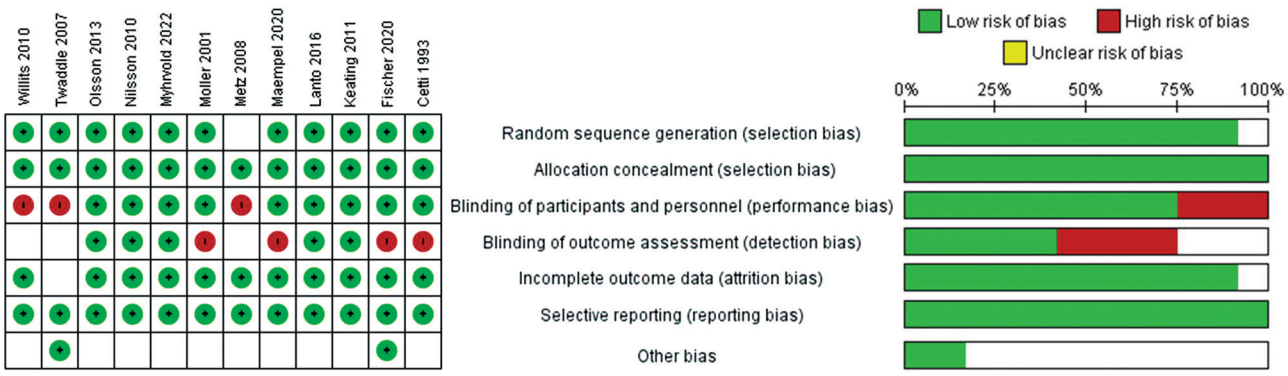

Fig. 2 Risk of bias summary and graph

Statistical Analysis

Odds ratios (ORs) were assessed with a 95 % confidence interval (CI) for the data. Heterogeneity (inconsistency) was analyzed using the Chi^2 and I^2 tests. A low *p*-value result ($p < 0.1$) of the Chi^2 test indicates significant heterogeneity. Because the Chi^2 test has a low detection ability in a small sample of data, we also used the I^2 test to assess heterogeneity. An I^2 test score of more than 50 % has significant heterogeneity. Statistical analyses were performed using the Review Manager (RevMan)® version 5.4.1. If the heterogeneity test results showed no significant heterogeneity, we planned to use the fixed-effect models. Otherwise, the researchers used random-effect models to process the data.

RESULTS

Study Characteristics

Twelve studies were qualified and are included to inclusion criteria. A total of six studies were multicenter and the other six were single-center studies. The total number of patients in those studies was 1.525 patients. Of the twelve studies included in this study, it was found that 1.215 patients (79.7 %) were male, and 310 patients (20.3 %) were female. Further details are elaborated in Table 1 and Table 2. Table 3 presents a summary of the findings from this study.

Table 1

Characteristics of selected studies

Name of study, Year	Center(s); Country	Follow-up Duration	Type of Surgery	Type of Conservative Method
Lantto et al., 2016 [6]	Single, Finland	18	Open repair	Plaster Cast and orthosis
Cetti et al., 1993 [7]	Multi, Denmark	30	Open repair	Plaster Cast
Fischer et al. 2020 [8]	Single, Germany	24	Open repair and Minimally Invasive Surgery	Plaster Cast and orthosis
Keating et al., 2011 [9]	Single, England	12	Open repair	Plaster Cast
Maempel et al., 2020 [10]	Single, United Kingdom	188	Open repair	Plaster Cast
Metz et al., 2008 [11]	Multi, Netherlands	12	Minimally Invasive Surgery	Plaster Cast and tape bandage
Moller et al., 2001 [12]	Multi, Sweden	24	Open repair	Plaster Cast and orthosis
Myhrvold et al., 2022 [13]	Multi, Norway	12	Open repair and Minimally Invasive Surgery	Plaster Cast and orthosis
Nilsson-Helander et al., 2010 [14]	Single, Sweden	12	Open repair	Plaster Cast and orthosis
Olsson et al., 2013 [15]	Single, Sweden	12	Open repair	Orthosis
Twaddle et al., 2007 [16]	Multi, New Zealand	12	Open repair	Plaster Cast and orthosis
Willits et al., 2010 [17]	Multi, Canada	12	Open repair	Plaster Cast and orthosis

Table 2

Characteristics of patients

Name of Study, Year	Total Patients	Male		Female		Age	
		Surgical	Conservative	Surgical	Conservative	Surgical	Conservative
Lantto et al., 2016 [6]	60	30	25	2	3	40 (27–57)	39 (28–60)
Cetti et al., 1993 [7]	111	47	45	9	10	37.2 (21–62)	37.8 (21–65)
Fischer et al. 2020 [8]	90	54	27	6	3	39.3 (7.9)	45.2 (9.5)
Keating et al., 2011 [9]	80	28	32	11	9	41.2 (27–59)	39.5 (21–58)
Maempel et al., 2020 [10]	80	28	32	11	9	41.2 (27–59)	39.5 (21–58)
Metz et al., 2008 [11]	83	31	35	11	6	40 (23–63)	41 (25–62)
Moller et al., 2001 [12]	112	51	48	8	5	39.6 (21–63)	38.5 (26–59)
Myhrvold et al., 2022 [13]	526	255	136	93	42	39.9 (8.9)	39.9 (8.1)
Nilsson-Helander et al., 2010 [14]	97	40	39	9	9	40.9 (24–59)	41.2 (23–63)
Olsson et al., 2013 [15]	100	39	47	10	4	39.8 (8.9)	39.5 (9.7)
Twaddle et al., 2007 [16]	42	14	14	6	8	41.8 (27–59)	40.3 (18–50)
Willits et al., 2010 [17]	144	59	59	13	13	39.7 (11.0)	41.1 (8.0)

Table 3

Forest plots summary

Parameters	Number of Studies	Odds Ratio / Mean Difference [95 % CI]	*p*
Functional outcome at 6 months follow-up			
Hopping test	3	SMD 0.36 [0.17, 0.56]	< 0.001*
Heel-rise height	3	SMD 0.65 [0.29, 1.01]	< 0.001*
Heel-rise work	3	SMD 0.33 [0.09, 0.57]	0.007*
Drop counter movement jump	3	SMD 0.13 [−0.14, 0.41]	0.33
Concentric power	3	SMD 0.29 [−0.05, 0.64]	0.1
Eccentric power	3	SMD −0.10 [−0.66, 0.46]	0.73
Functional outcome at 12 months follow-up			
Hopping test	3	SMD −0.06 [−0.88, 0.76]	0.88
Heel-rise height	3	SMD 0.38 [−0.00, 0.76]	0.05
Heel-rise work	3	SMD 0.40 [0.20, 0.60]	< 0.001*
Drop counter movement jump	3	SMD −0.02 [−0.96, 0.92]	0.97
Concentric power	3	SMD 0.03 [−0.35, 0.41]	0.88
Eccentric power	3	SMD −0.13 [−0.84, 0.58]	0.72
Calf muscle atrophy	3	OR 0.46 [0.27, 0.79]	**0.005***
Abnormal ankle movement	3	OR 0.34 [0.20, 0.60]	**< 0.001***
Chronic pain	**3**	**OR 0.85 [0.42, 1.72]**	**0.65**
Re-rupture rate	**10**	**OR 0.34 [0.20, 0.58]**	**< 0.001***
Complications			
Superficial infection	7	OR 0.88 [0.42, 1.83]	0.73
Deep infection	7	OR 2.52 [0.88, 7.24]	0.09
Deep vein thrombosis	6	OR 0.64 [0.22, 1.85]	0.41
Sural nerve injury	4	OR 5.07 [1.60, 16.07]	0.006*
Total	**10**	**OR 1.35 [0.96, 1.90]**	**0.08**

Our initial electronic search results yielded 354 studies that matched the search keyword algorithm in the three major databases. The duplication removal process resulted in a total of 292 studies. The remaining studies were then screened by title and abstracts that had conformity to the inclusion and exclusion criteria. Twelve studies qualified and are included in the meta-analysis (Fig. 1).

The assessment risk of bias was done according to Cochrane risk of bias tool by conducting data of each included study to the RevMan 5.4.1 computer program. Out of the 12 studies, seven were found to have a high risk of bias due to various reasons. Three studies were found with a high risk of performance bias where these studies were not double-blinded. Furthermore, four studies were found with a high risk of detection bias where blinding of outcome was failed to be performed or was not mentioned in the study. Unclear risk was found mostly on other bias (Fig. 2).

Figure 3 explains the publication bias depicted through the funnel plot.

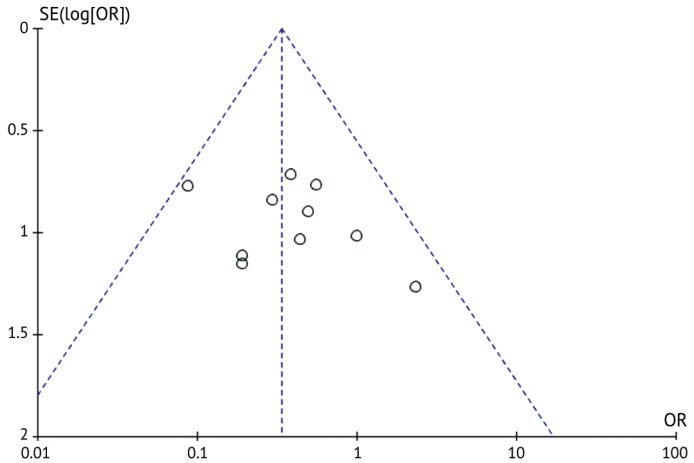

Fig. 3 Funnel plot re-rupture rate illustrating the publication bias

Functional outcome at 6 months follow-up

Hopping test at 6 months of follow-up (SMD 0.36; 95 % CI: 0.17 to 0.56; $p \leqslant 0.001$), heel-rise height test (SMD 0.65; 95 % CI: 0.29 to 1.01; $p \leqslant 0.001$), heel-rise work test (SMD 0.33; 95 % CI: 0.09 to 0.57; $p = 0.007$, were significantly higher in the surgical group compared to conservative group. Drop counter movement jump test (SMD 0.13; 95 % CI: –0.14 to 0.41; $p = 0.33$), concentric power test (SMD 0.29; 95 % CI: –0.55 to 0.64; $p = 0.1$) and eccentric power test (SMD –0.10; 95 % CI: –0.66 to 0.46; $p = 0.73$) at 6-month follow-up showed non-significant difference between the two groups (Fig. 4).

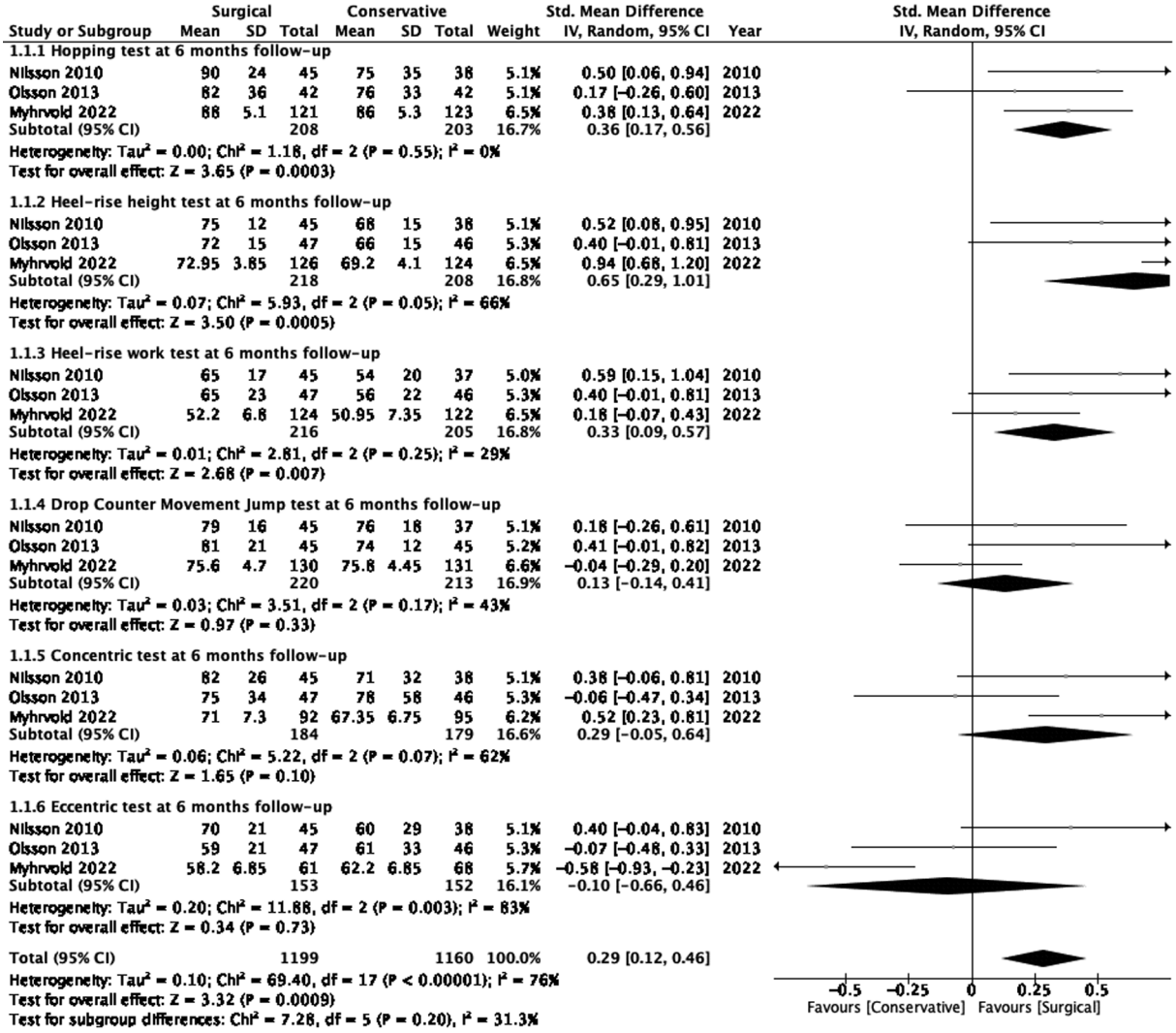

Fig. 4 Comparison of functional outcome after 6 months in surgical versus conservative group

Functional outcome at 12 months follow-up

Heel-rise work test (SMD 0.40; 95 % CI: 0.20 to 0.40; $p \leqslant 0.001$) was found significantly higher in the surgical group compared to the conservative group. Hopping (SMD 0.06; 95 % CI: –0.88 to 0.76; $p = 0.88$), heel-rise height (SMD 0.38; 95 % CI: –0.00 to 0.76; $p = 0.05$), drop counter movement jump (SMD –0.02; 95 % CI: –0.96 to 0.92; $p = 0.97$), concentric power (SMD 0.33; 95 % CI: –0.35 to 0.41; $p = 0.88$), and eccentric power (MD –0.13; 95 % CI: –0.84 to 0.58; $p = 0.72$) test on the other hand showed no significant difference between the two groups (Fig. 5).

Calf muscle atrophy

Results showed calf muscle atrophy (OR 0.46; 95 % CI: 0.27 to 0.79; $p = 0.005$) was significantly higher in the conservative group compared to the surgical group (Fig. 6).

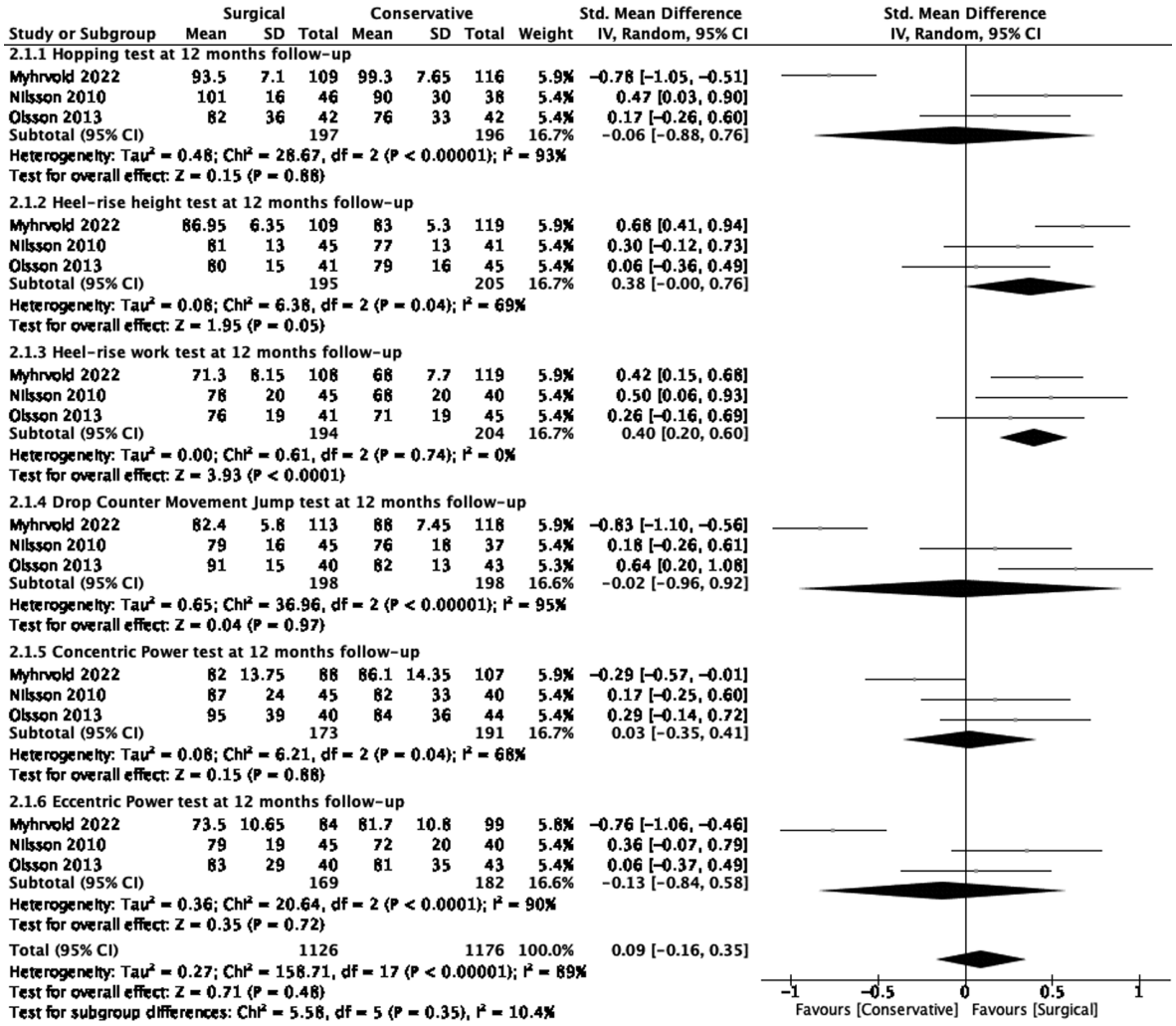

Fig. 5 Comparison of functional outcome after 12 month in surgical versus conservative group

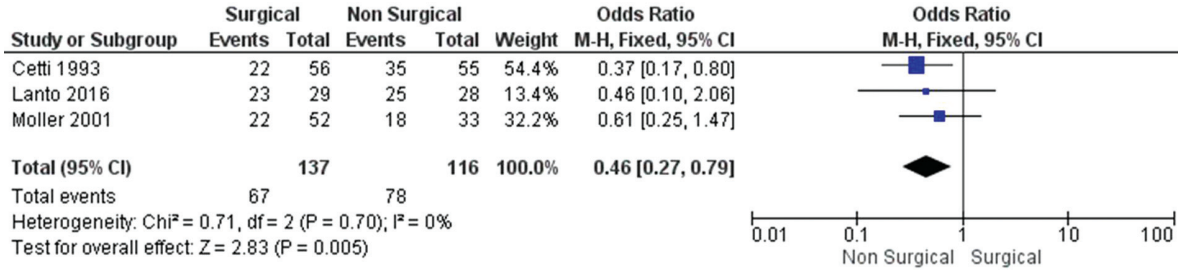

Fig. 6 Comparison of calf muscle atrophy in surgical versus conservative group

Re-rupture rate

Results showed re-rupture rate (OR 0.34; 95 % CI: 0.20 to 0.58; $p \leqslant 0.001$) was significantly higher in the conservative group compared to the surgical group (Fig. 7).

General complications

General complications (OR 1.35; 95 % CI: 0.96 to 1.90; $p = 0.08$) were not significantly different between the two groups (Fig. 8).

Complications other than general complications

Sural nerve injury rate (OR 5.07; 95 % CI: 1.60 to 16.07; $p = 0.006$) was found significantly higher in the surgical group compared to the conservative group. Neither superficial infection (OR 0.88; 95 % CI: 0.42 to 1.83; $p = 0.73$), deep infection (OR 2.52; 95 % CI: 0.88 to 7.24; $p = 0.09$), deep vein thrombosis rate (OR 0.64; 95 % CI: 0.22 to 1.85; $p = 0.41$) (Fig. 9).

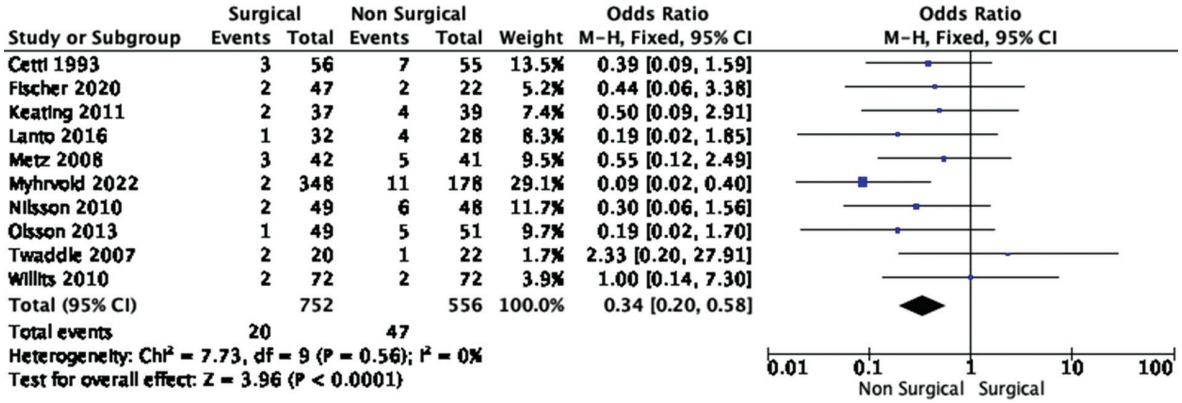

Fig. 7 Comparison of re-rupture rate in surgical versus conservative group

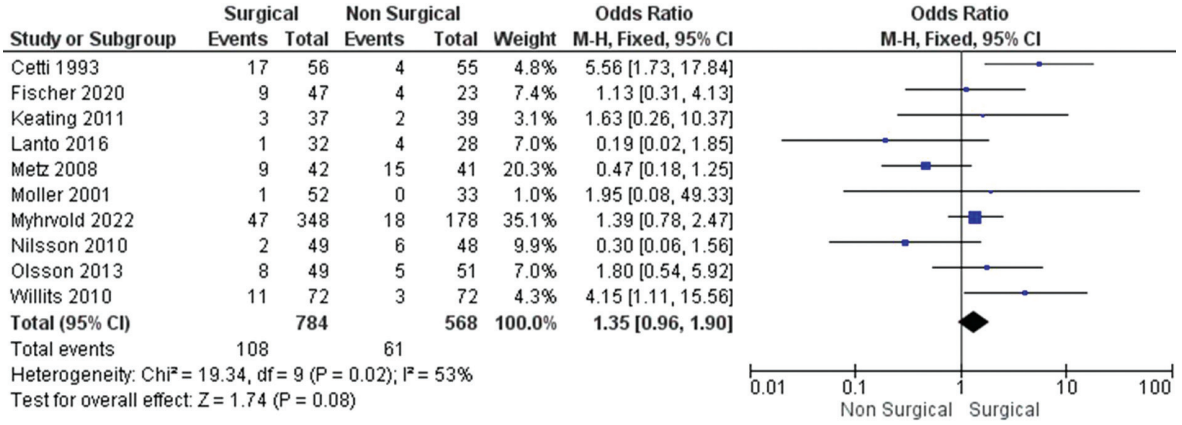

Fig. 8 Comparison of general complications other than re-rupture in surgical versus conservative group

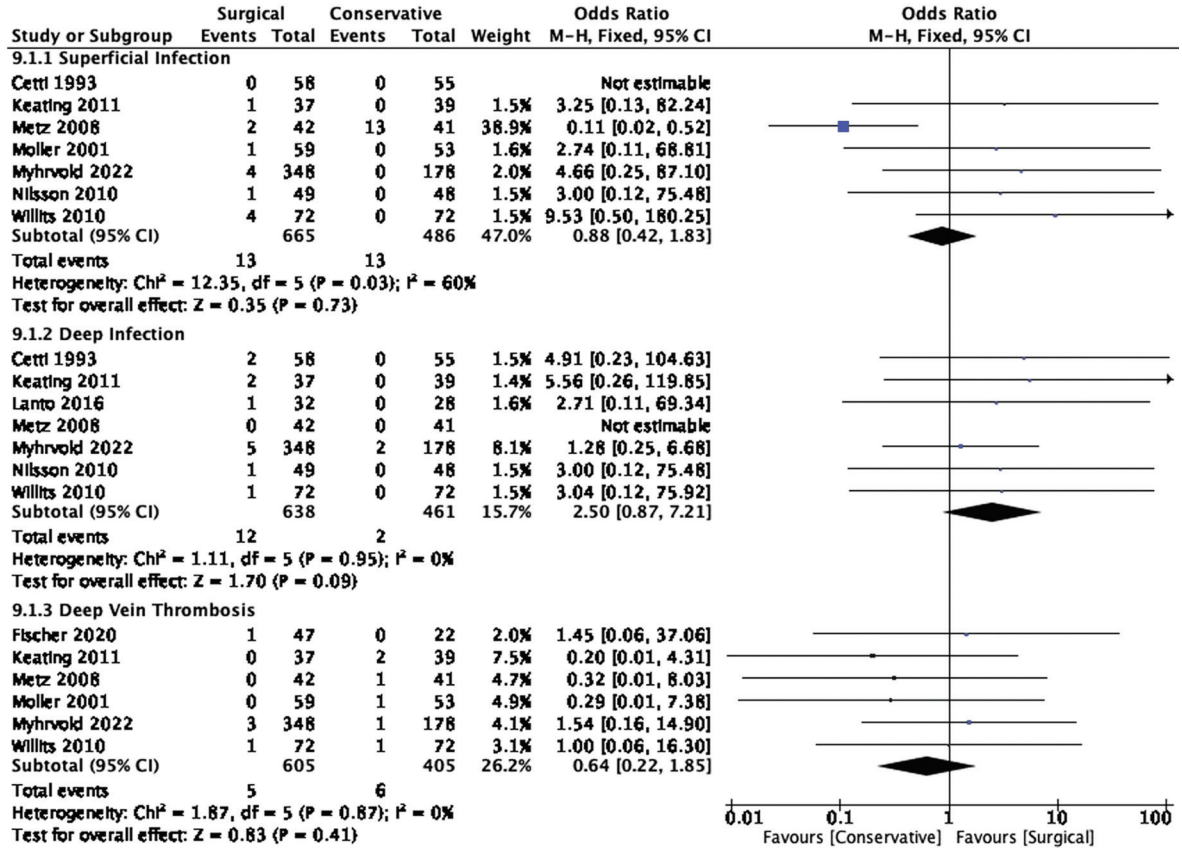

Fig. 9 Comparison of complications other than general complications in surgical versus conservative group

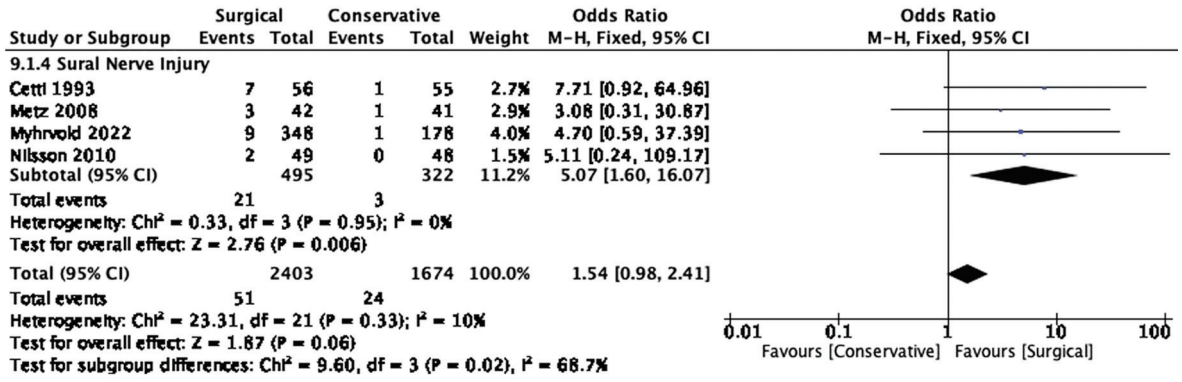

Fig. 9 (continuation) Comparison of complications other than general complications in surgical versus conservative group

DISCUSSION

Assessing functional outcomes such as hopping tests, heel rise height and work, drop counter movement jump, and power measurements (concentric and eccentric) are important for evaluating recovery and performance following Achilles tendon rupture treatment.

Our study found that functional outcomes at 6-month follow-up were better in patients who underwent surgery compared with conservative treatment. However, there was no significant difference in functional outcomes after 12 months of follow-up between surgical and conservative groups. In line with previous study [18] which found strength, calf circumference, and functional result did not differ between surgical and conservative interventions.

Based on the results of our study, it can be seen that the functional outcome at 6-month follow-up was significantly better in the surgical group compared to the conservative group in several tests such as hopping test, heel rise height, heel rise work, and concentric power. However, the functional outcome at 12-month follow-up was only heel rise work with significantly better results for the surgical compared to the conservative method. This shows that conservative treatment is no less good than surgical treatment.

Compared to patients treated conservatively, surgical patients frequently restore hopping, heel rise height, heel rise work, drop counter movement jump, concentric and eccentric power more rapidly. Because surgery can more successfully repair tendon integrity, those who have it frequently perform better on early weight-bearing after recovering. Surgical treatment also allows for faster restoration of explosive power in the lower extremity. This benefit is frequently brought about by the tendon's direct mechanical healing, which might offer more rapid stability [19].

Research suggests that when early and adequate rehabilitation protocols are followed, both surgical and conservative treatments can produce comparable functional outcomes. In patients receiving conservative treatment, there was no statistically significant difference in re-rupture, return to employment, or return to sports between early and late weight-bearing [20].

When early functional rehabilitation was applied in both groups, a thorough meta-analysis revealed no discernible difference in hopping, heel rise height, heel rise work, drop counter movement jump, concentric and eccentric power test performance one year after injury between surgically and conservatively treated individuals [5, 19]. While surgical repair initially improved hopping, heel rise work, heel rise height, and concentric performance, a study by Nilsson-Helander et al. [14]. Olsson et al. [15] found that at long-term follow-up, there were no significant differences between the surgical and conservative groups; the heel rise work test was the only area where there was a significant difference, indicating that similar functional results can be obtained from both methods.

The re-rupture rate in this study was significantly higher in the conservative group compared to the surgical group. Comparatively speaking, conservative therapy for an Achilles tendon rupture is often linked to a higher risk of re-rupture. Through stronger healing and a lower chance of re-rupture, the surgical technique seeks to restore the tendon's anatomical continuity. Surgery considerably

decreased the re-rupture rate when compared to conservative treatment [18, 21–24]. Less re-rupture rates were also noted in the surgical group, according to a study conducted by Soroceanu et al. [25].

Choosing early or later rehabilitation following either conservative or surgical treatment had no effect on the outcome [24, 26]. Not in line with previous studies [23] that reduced risk of rupture during conservative treatment as opposed to surgical treatment if both types of treatment included a functional rehabilitation plan that included early range of motion. Re-rupture rates from the surgical method may range from 1 % to 5 %, according to the overall trend of various researchers.

While conservative treatment avoids the dangers associated with surgery, it may result in a higher rate of re-ruptures. In conservative treatment, functional bracing is becoming more popular since it can enhance results and possibly lower the rate of re-ruptures. When deciding between conservative and surgical method treatment patient's age, degree of activity, and coexisting conditions should all be taken into account.

In this study, general complications other than re-rupture were higher in the surgical group compared to the conservative group, but not significantly. General complications such as skin necrosis, deep infection, tendon lengthening, adhesion, superficial infection, disturbances of sensibility, suture granuloma, and delayed wound healing were encountered. In line with previous research, the results of complications were higher in the surgical group compared to the conservative group [18, 22, 23]. However, general complications other than re-rupture in this study were not significant as the previous studies discovered [26].

Superficial infection in this study was higher in the conservative group compared to the surgical group, but not significantly. Seow et al. [24], Soroceanu et al. [25] found that the complication that was more frequently linked to surgical repair of Achilles tendon ruptures was superficial infection. After surgical repair, superficial infections are a common consequence that usually arises at the site of the surgical incision. Because conservative treatment involves no surgical incision, the risk of surface infection is typically avoided.

Deep infections in this study were higher in the surgical group compared to the conservative group, but not significantly. Deep infections, which can happen in the tissue around the Achilles tendon after surgery, are more dangerous. Deep infection can occur during surgical repair and have a significant influence on overall recovery and function [27].

Deep vein thrombosis in this study was higher in the conservative group compared to the surgical group but not significantly, in line with previous meta-analysis [21]. During the early stages of recuperation following surgery, immobility may result, which raises the risk of DVT. Often, preventative actions are done to lessen this risk. Prolonged immobility following conservative therapy, especially with casting, may also raise the risk of DVT.

Sural nerve injury in this study was significantly higher in the surgical group compared to the conservative group. Deficits in senses may result from complications related to injury to the sural nerve sustained after surgery or immobilization. When compared to certain less invasive methods, open repair approaches often carry a lower risk of sural nerve injury. This is mainly because the surgical area is more exposed and directly visible, which makes it easier for surgeons to avoid the nerve [13, 28]. In conservative treatment, sural nerve injury can occur because the sural nerve is proximal to the Achilles tendon. When using functional bracing or casting in a non-anatomical position it can put pressure on the sural nerve. Inadequate bracing or misalignment can further raise the risk of nerve damage [28, 29].

The limitations of this study are that the demographics of participants in various studies can also cause bias. In addition, the surgical and conservative techniques used are diverse. Finally, the duration of follow-up in various studies can also cause bias.

CONCLUSION

Reduced rates of re-rupture, possibly quicker recovery for functional outcomes like hopping, heel rise tests are some benefits of surgical repair. Conversely, conservative treatment can yield good results in terms of functional outcomes and re-rupture rates in long-term follow-up, particularly

when combined with contemporary rehabilitation procedures that include functional bracing and early mobilization. Conservative treatment eliminates the hazards associated with surgery, such as nerve damage, but it may have a slightly higher chance of re-rupture and a shorter initial recovery of some functional outcomes. Both treatment methods are good for Achilles tendon rupture repair.

Conflicts of interest *The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.*

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Analysis of existing approaches to determine culture-negative periprosthetic infection of the hip and knee joints and assessment of its treatment outcomes

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Abstract

Introduction Periprosthetic infection is one of the most frequent and devastating complications after total hip replacement. The effectiveness of infection management depends on possibility of prescribing etiotropic antibiotics after the operation and the rational choice of a surgical technique. In 5–30 % of all patients the etiology of the infectious process remains unknown throughout the entire treatment period. Such cases are described by the term "culture-negative periprosthetic joint infection". Nowaday, there is no single definition for culture-negative PJI in the professional community.

The **aim** of this study is to evaluate the treatment results of patients with culture-negative periprosthetic infection, depending on the approach to its detection, as well as formulate possible ways to reduce its rates.

Methods Literature search was performed in electronic databases eLIBRARY, PubMed (MEDLINE), ScienceDirect, Google Scholar according to PRISMA recommendations. The study included articles in Russian and English, original articles and case series on the treatment of chronic culture-negative periprosthetic infection of the hip joint and/or knee joints in patients over 18 years of age using any surgical operations and in which there was at least one indicator of treatment effectiveness. The existing approaches to detection of culture-negative periprosthetic joint infection of the knee and hip and the outcomes of treatment of patients with this pathology were analyzed, as well as possible ways to reduce the number of patients with an unknown etiology of the infectious process were formulated.

Results and Discussion Our analysis of scientific publications revealed no clear difference in the effectiveness of infection control depending on the approach to detection of culture-negative PJI. For the first time, the effectiveness of treatment for patients with culture-negative PJI is examined depending on the approach to detection of this pathology. Significant heterogeneity was identified in both the interpretation of culture-negative PJI and the choice of surgical techniques. The high rate of successful outcomes indicates the importance of appropriate selection of drugs for empirical antibiotic therapy (ABT) and regular monitoring of the spectrum of nosocomial pathogens. Potential ways to reduce the incidence of negative microbiological test results are proposed.

Conclusion The efficacy of treatment of culture-negative PJI did not differ significantly depending on the interpretation of this term. Ways to reduce the incidence of this pathology are aimed at modifying the factors that cause negative results of MBI of biomaterial samples and removed structures.

Keywords: chronic periprosthetic infection, pre-operative examination, microbiological test, revision arthroplasty

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INTRODUCTION

Periprosthetic joint infection (PJI) is considered one of the most devastating complications of total hip arthroplasty (THA) that impairs quality of life and overall life expectancy of patients [1, 2]. Infectious complications in arthroplasty pose a heavy socioeconomic burden on the healthcare system [3, 4], while the risk of failure remains quite high, ranging from 10–29 % in two-stage revision arthroplasty, which is still considered the “gold standard” [5, 6].

One of the key factors that significantly affect the success of treatment is the etiology of the infectious process, or the type of microbial pathogen and its antibiotic sensitivity [7]. The proportion of patients in whom microbiological diagnosis was not made based on the results of preoperative studies, and in some cases, based on the results of intraoperative cultures, has been grown. This phenomenon is known as culture-negative PJI, the incidence of which reaches 5–30 % [8, 9]. The main causes of culture-negative PJI are the use of antimicrobial drugs within less than two weeks before microbiological tests, presence of low-virulent or difficult-to-cultivate PJI pathogens [10], as well as the peculiarities of the pathogenesis of the infectious process associated with orthopedic implants (a bacterial depot in patient's body which includes biofilms, intracellular bacteria and colonized osteocyte-lacunar tubules) [11]. All these factors make it practically impossible to routinely prescribe etiotropic antibiotic therapy (ABT) at the time of performing a sanitizing operation on a patient with PJI.

There is no consensus within the professional community regarding this phenomenon. Some authors define culture-negative PJI as the absence of pathogen growth based on preoperative microbiological studies (PMS), although the pathogen may be detected in intraoperative specimens [12–17]. Other authors define this term as a complete lack of pathogen data [18–22]. These differences explain the wide range of this pathology rates and, consequently, the impossibility of developing uniform treatment recommendations for these patients.

The **aim** of this study is to evaluate the treatment results of patients with culture-negative periprosthetic hip and knee joint infection, depending on the approach to its determination, as well as formulate possible ways to reduce its rates.

MATERIALS AND METHODS

This systemic analysis was conducted according to the international requirements PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [23].

The search for literature sources was performed in the electronic databases eLIBRARY, PubMed (MEDLINE), ScienceDirect, Google Scholar.

The search phrases in the PubMed (MEDLINE), ScienceDirect, Google Scholar, Ovid, as recommended by Aromataris and Riitano [24], included combinations of key words: "periprosthetic joint infection" or "prosthetic joint infection" or PJI) and ("single-stage" or "one-stage" or "two-stage" or "2-stage" or "revision" or "revisions") and ("culture negative" or "negative") and ("culture positive" or "positive").

The eLIBRARY database search query included the following combination of keywords: "culture-negative infection," "culture-negative periprosthetic joint infection," and "chronic hip periprosthetic joint infection OR chronic knee periprosthetic joint infection." The search was not retrospectively restricted; the last query date was February 4, 2025. Various combinations of search queries were used in the listed databases as a preliminary option.

At the first stage, the criteria for inclusion and exclusion of articles in the study were determined.

Inclusion criteria:

— articles in the Russian and English languages;

— original articles and case series including five or more observations devoted to the treatment of chronic culture-negative periprosthetic infection of the hip and/or knee joints, infectious complications after hip and/or knee arthroplasty;

— age of patients: older than 18 years;

— at least one indicator of treatment effectiveness (proportion of positive and negative outcomes, survival rate);

— any surgical intervention for PJI.

Exclusion criteria:

— articles in veterinary fileld;

— studies that depict coxitis consequences;

— literature reviews, meta-analyses, text books, book chapters, letters to editors, expert opinions;

— articles devoted to the treatment of acute PJI only;

— articles devoted to the diagnosis of PJI;

— case reports;

— absence of comparison groups in the study (culture-negative and culture-positive groups);

— lack of a clearly defined definition of culture-negative PJI in the publication.

A manual search for references in the identified articles was conducted to find additional publications that could be included in the study. Abstracts of the publications were then reviewed for inclusion and exclusion criteria, and duplicate studies were identified and eliminated. Finally, full-text articles were reviewed.

During the analysis of the included works the following indicators were assessed:

— general information about the study (authors, country and year of publication, type and duration of study, duration of follow-up, diagnostic criteria, number of clinical groups, joints involved, types of surgical interventions and antibiotic therapy);

— study results that included the rates of positive and negative treatment outcomes.

Recurrent infection was defined as the presence of general or systemic signs of PJI, repeated debridement surgeries on the same joint for the infectious process, and a fatal outcome resulting from PJI. International guidelines based on the Delphi-based international multidisciplinary consensus were used to determine a successful outcome for patients with PJI [25].

Study design

The initial search identified 850 publications, of which 640 (commentaries, book chapters, articles irrelevant to the topic, and duplicates) were excluded. After reviewing the titles and abstracts for relevance to the search topic, 50 publications were selected. After checking the availability of full-text articles in the public domain and their compliance with the inclusion and exclusion criteria, 26 studies were included in the final analysis (Fig. 1).

The selected studies were published between 2007 and 2024 and included 7,713 cases of PJI. The follow-up period ranged from 12 to 120 months. For the diagnosis of PJI, the MSIS (Musculoskeletal Infection Society) criteria [26] were used in 17 studies, the ICM (International Consensus Meeting) criteria [27] in five studies, the IDSA (Infectious Diseases Society of America) criteria [28] in one study, and the EBJIS (European Bone and Joint Infection Society) criteria [29] in one study. Four studies used criteria developed by authors, and three other publications did not provide data.

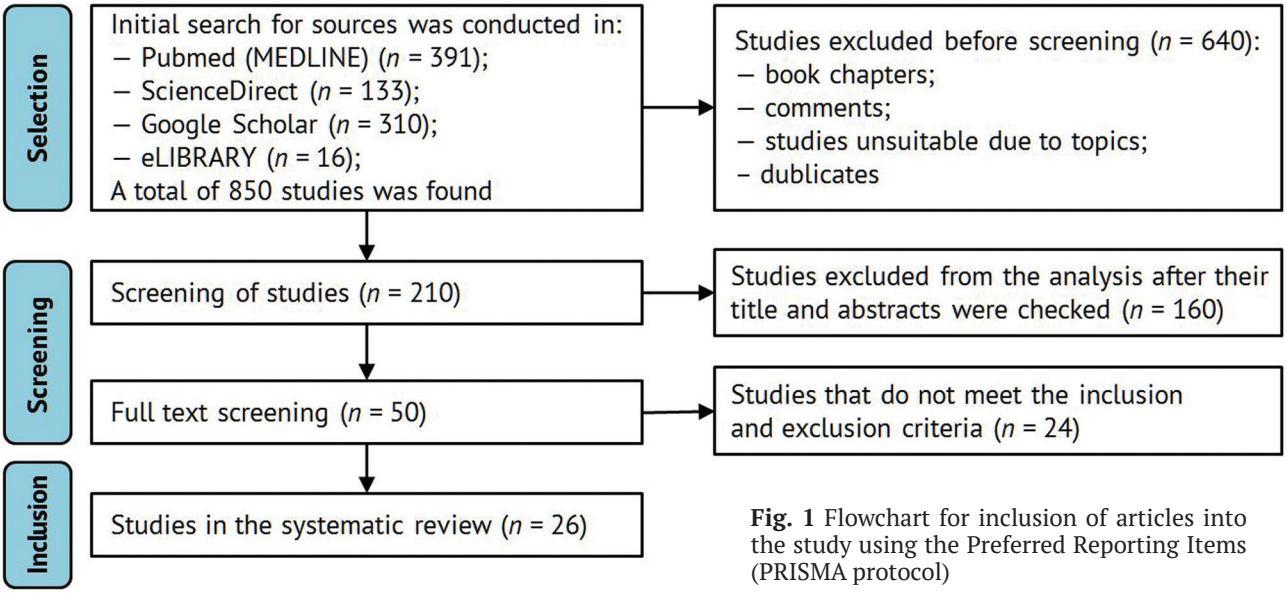

Fig. 1 Flowchart for inclusion of articles into the study using the Preferred Reporting Items (PRISMA protocol)

Risk of systemic error

Each study was methodologically assessed for quality according to the Oxford Center for Evidence-Based Medicine (CEBM) criteria to determine its level of evidence. For both case series and cohort studies, the Joanna Briggs Institute Critical Appraisal Tools (JBI) checklist, consisting of 11 questions, was applied (Fig. 2).

Statistical analysis

Data from all 26 articles were included in the statistical analysis. The analysis was performed using IBM SPSS Statistics v.26 (IBM Corporation). To describe quantitative indicators, we tested for normality of distribution using the Shapiro-Wilk and Kolmogorov-Smirnov tests. The median (Me) was used to describe quantitative variables, and the lower (Q1) and upper (Q3) quartiles (25–75 % IQR) were used as measures of dispersion. Comparisons within the study groups were performed using the Mann – Whitney test. Differences between the groups were considered statistically significant at $p < 0.05$.

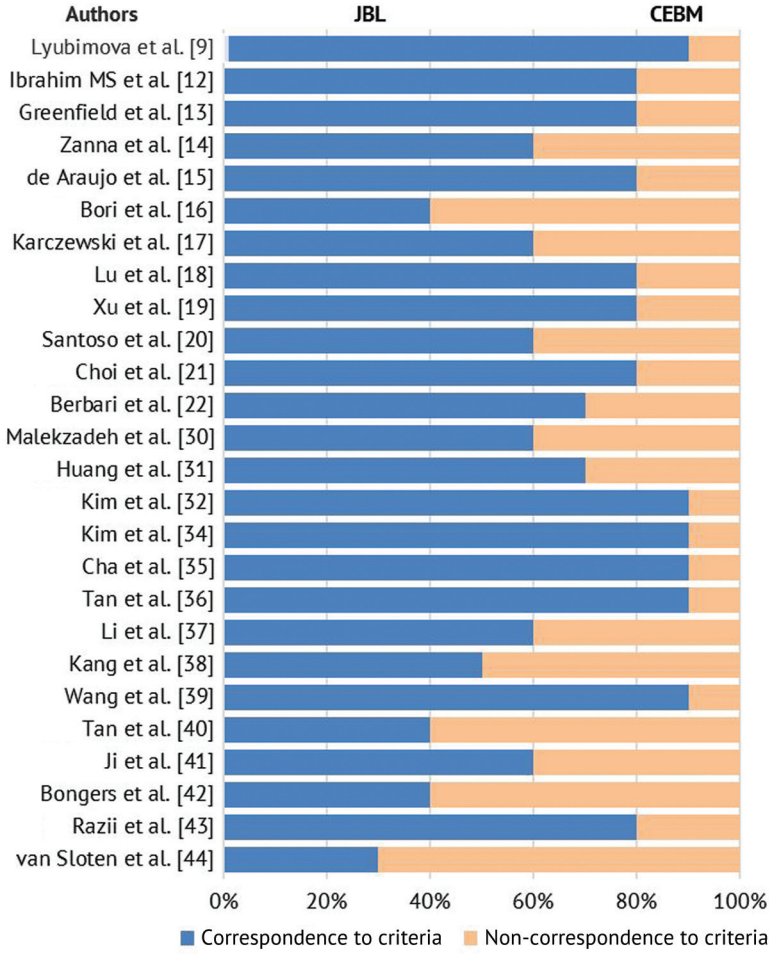

Fig. 2 Results of methodological evaluation of the quality of articles included in the study

All studies were divided into two groups based on their approach to detection CNI. The first group, in which the authors defined CNI as the absence of pathogen growth in all samples, included 20 publications. The second group, which considered the absence of microbial growth only in preoperative studies, included six publications. For each study, the proportion of successful CNI

treatment outcomes was calculated. The mean infection resolution rate (MIR) in each group was then calculated. The Mann-Whitney test was used to test for statistically significant differences between the groups.

RESULTS AND DISCUSSION

Investigation of treatment outcomes by different approaches to detection of culture-negative PJI does not reveal any significant differences in the effectiveness of infection control. In the first group (CNI, no pathogen growth in all samples), infection eradication was achieved in an average of 91.5 % of cases (IQR = 78.0–95.5 %); the data distribution was not normal ($p = 0.03$). In the second group (no microbial growth in preoperative tests only), the rate of successful CNI treatment outcomes averaged 92.0 % of cases (IQR = 86.0–97.0 %); the distribution of results did not differ from normal ($p = 0.326$).

No statistically significant difference in the effectiveness of PJI treatment was found between the two study groups ($p = 0.582$). It is noteworthy that studies in which the authors described CNI as the absence of pathogen growth only before surgery included a small number of cases and did not always include a comparison group. A number of studies did not specify the criteria used to confirm the PJI diagnosis (Table 1). All studies analyzed were retrospective.

Table 1

Characteristics of studies on the treatment of patients with culture-negative PJI based on the approach to its detection

Authors [reference number]	Joint, %		Analysys (period)	PJI criteria	CNI detection	Total cases	КНИ		Surgery
	knee	hip					*n*	%	
Lubimova et al. [9]	100		2017–2021	ICM (2018)	preop + intra	103	30	29.1	2-stage revision
Ibrahim MS et al. [12]		100	2007–2012	Berbari EF et al. [22]	preop + intra	100	50	50	2-stage revision
Greenfield et al. [13]		100	2006–2015	MSIS (2011)	preop	105	28	26.7	1-stage revision
Zanna et al. [14]	45.5	54.5	2016–2018	НД	preop	640	22	3.4	1-stage revision
de Araujo et al. [15]	50.0	50.0	2003–2020	ICM (2018)	preop + intra	53	6	11.1	DAIR, 2-stage revision, 1-stage revision, RA, amputation, disarticulation, arthrodesis
Bori et al. [16]	100		1998–2007	НД	preop	24	6	15.8	1-stage revision
Karczewski et al. [17]		100	2011–2021	EBJIS (2021)	preop	30	10	33.3	1-stage revision
Lu et al. [18]	34.5	65.5	2008–2020	MSIS (2013)	preop + intra	87	24	27.6	2-stage revision
Xu et al. [19]	41.6	58.4	2012–2017	ICM (2018), MSIS (2011)	preop + intra	77	24	31.2	DAIR, 2-stage revision, 1-stage revision
Santoso et al. [20]		100	2010–2015	MSIS (2011)	preop + intra	84	27	32.1	2-stage revision
Choi et al. [21]	50.0	50.0	2000–2009	MSIS (2013)	preop + intra	175	40	23	2-stage revision
Berbari et al. [22]	55.0	45.0	1990–1999	НД	preop + intra	897	60	7	DAIR, 2-stage revision, PA
Malekzadeh et al. [30]	50.0	50.0	1985–2000	НД	preop + intra	270	135	50	DAIR, 2-stage revision, 1-stage revision, RA, amputation
Huang et al. [31]	44.0	56.0	2000–2007	MSIS (2011)	preop + intra	250	48	19.2	DAIR, 2-stage revision
Kim et al. [32]	100		1991–2008	McPherson et al. [33]	preop + intra	191	51	26.7	DAIR, 2-stage revision
Kim et al. [34]	100		2001–2008	MSIS (2011)	preop + intra	242	102	42.1	DAIR, 2-stage revision
Cha et al. [35]	100		1998–2011	MSIS (2011)	preop + intra	76	22	29.0	2-stage revision
Tan et al. [36]	62.9	37.1	2000–2014	MSIS (2013)	preop + intra	1045	159	15.2	2-stage revision
Li et al. [37]	100		2003–2014	MSIS (2011)	preop + intra	129	18	13.9	1-stage revision, 2-stage revision
Kang et al. [38]		100	1996–2015	MSIS (2011)	preop + intra	85	15	17.6	2-stage revision
Wang et al. [39]		100	2003–2006	MSIS (2011)	preop + intra	58	19	32.7	2-stage revision

Table 1 (continuation)

Characteristics of studies on the treatment of patients with culture-negative PJI based on the approach to its detection

Authors [reference number]	Joint, %		Analysys (period)	PJI criteria	CNI detection	Total cases	КНИ		Surgery
	knee	hip					*n*	%	
Tan et al. [40]	37.0	63.0	2000–2014	MSIS (2013)	preop + intra	996	219	22	DAIR, 2-stage revision, 1-stage revision
Ji et al. [41]		100	2009–2016	McPherson et al. [33], MSIS (2011)	preop + intra	243	51	21	1-stage revision
Bongers et al. [42]	100		2003–2013	MSIS (2013)	preop	113	53	46.9	2-stage revision
Razii et al. [43]	100		2006–2016	MSIS (2011), IDSA, ICM (2013, 2018)	preop	84	16	19	1-stage revision
van Sloten et al. [44]	74.3	25.7	2013–2018	EBJIS (2021), ICM (2018), MSIS (2013)	preop + intra	1556	70	4.5	DAIR, 2-stage revision, 1-stage revision

Notes: DAIR — wound debridement, antibiotics and implant retention; RA – resection arthroplasty

Existing approaches to defining culture-negative PJI

Currently, there is no consensus in the orthopaedic trauma community regarding the specific cases in which periprosthetic joint infection can be considered culture-negative. The term "culture-negative PJI" was first described by Berbari et al. as the absence of growth of aerobic or anaerobic pathogens in microbiological tests of tissue samples harvested around the endoprosthesis. The authors listed the following diagnostic criteria: pus in the area of the implants, elevated number of leukocytes (> 1.7×10^3/ml) and/or the percentage of polymorphonuclear neutrophils (> 65 %) in the synovial fluid, acute inflammation according to histological study, and a fistula tract communicating with the implant [22]. The rate of culture-negative PJI in that study was 7 % (60/897), with more than half (53 %) of patients having a history of preoperative intake of antibacterial drugs. Palan et al. point out the need to differentiate between a “true negative” preoperative MBI result (7–15 % of cases) when it is more likely to be aseptic loosening, and a “false negative” result, when for a number of reasons it is impossible to isolate the causative agent of the infectious process but its presence is beyond doubt [45]. Accordingly, all cases of presumed culture-negative PJI can be divided into two large groups. The first group includes patients with evident periprosthetic infection, the etiology of which cannot be determined at the moment. The authors propose to include patients with suspected periprosthetic joint infection in the second group if the results of MBI of tissue from the affected joint are negative but there are no clear signs of infection (visible suppuration or a functioning fistula). The described clinical picture may indicate the presence of low-virulence or atypical pathogens, such as fungi or bacteria of the genus *Mycobacterium spp*., *Propionibacterium spp*. and others. This division appears reasonable and appropriate, as patients in both groups differ significantly in the severity of symptoms and infection nature. It should be noted that not all publications on culture-negative PJI clearly define the CNI criteria for inclusion in the study.

The term "culture-negative PJI" is often understood as the absence of growth of aerobic and anaerobic pathogens in all samples taken both preoperatively and intraoperatively [9, 17–22]. In studies in which the authors used the described above approach, the incidence of culture-negative PJI was 7–30.8 % of cases. Thus, in the study by Lu et al. the incidence of infection of unknown etiology was 27.6 %, while in 25.0 % of cases a functioning fistula tract was described. However, in 91.7 % of cases the presence of inflammation was confirmed histopathologically and in 70.8 % of cases pus was detected in the area of the endoprosthesis during surgery [19]. In the work of Lyubimova et al., the proportion of patients without pathogen growth was 29.1 %, while only 76.6 % of patients had an infectious process confirmed according to the ICM criteria (2018), while in the culture-positive PJI group it was 98.6 % ($p = 0.0006$) [9]. Although the clinical picture was comparable in the groups, blood tests for ESR, CRP and the leukocyte level in the synovial fluid were

significantly higher in the preoperative period in the group where the causative agent of PJI was identified ($p < 0.05$). These data are consistent with the results of Choi et al., according to which the proportion of patients with CNI was 23 % in the analyzed sample, while their ESR levels were significantly lower than in the group of patients with positive cultures [19]. Prior hospitalization, treatment with antibacterial drugs was significantly more common in the group without pathogen growth ($p = 0.005$).

A different approach can be found in a number of scientific papers, where the term "culture-negative" is used in cases where the growth of the pathogen was not detected only in the preoperative tests. Thus, Ibrahim et al., based on the growth or absence of growth of pathogens before surgery, identified two equal groups of patients; periprosthetic infection was confirmed by the criteria of Berbari et al. [18]. At the same time, the authors indicate that the MBI of biomaterial samples from patients with culture-negative PJI were negative at all stages of treatment. According to the authors, the greatest influence on the probability of the absence of pathogen growth was exerted by the use of antibacterial drugs in the preoperative period ($p = 0.003$, OR 4.1) and if there was previous treatment of periprosthetic infection at other hospitals ($p = 0.001$, OR 3.1).

Greenfield et al. assessed the impact of preoperative pathogen identification on the effectiveness of single-stage revision arthroplasty. It should be noted that the authors did not introduce the concept of culture-negative infection per se, but divided patients into two groups based on whether the preoperative MBI tests were positive or negative [13]. Thus, the etiology of PJI was known at the time of surgery in only 27 % of cases.

A different approach to expanding the indications for a one-stage technique was demonstrated in the work of Zanna et al. The study sample included those patients whose MBI results were negative only in the preoperative period; their proportion amounted to 3.4 % [14]. The authors considered the absence of pathogen growth to be negative in two microbiological studies of synovial fluid and one open biopsy. It is noteworthy that in a half of the cases included in the study, microbial associations were detected in intraoperatively taken tissue biopsies. Bori et al. studied the effectiveness of one-stage revision arthroplasty using femoral components with cementless fixation and found that six (15.8 %) patients had no data on the pathogen at the time of surgery [16]. However, in subsequent five cases, growth of coagulase-negative staphylococci was found in from intraoperatively taken biopsies and growth of *Peptostreptococcus spp*. in one case.

A group of scientists from the Charité Clinic in Berlin put forward a more radical hypothesis in their study, suggesting that pathogen identification prior to single-stage revision arthroplasty is not mandatory [17]. According to the authors, the use of a single-stage technique may depend more on the condition of soft tissues and bone, patient's somatic status, and patient's medical history than on the specific pathogen. It should be emphasized that the authors do not introduce the concept of "culture-negative PJI,"but they repeatedly reference studies on this condition in the discussion.

Current approaches to treating patients with culture-negative PJI

Currently, the professional community of trauma- and orthopedic surgeons has accumulated a certain experience in treating patients with culture-negative PJI, which allows them to analyze the outcomes of various surgical treatment methods, including the comparison with the results of treating patients with culture-positive infection. According to the results of a meta-analysis by Lai et al. that included 11 studies, the etiology of the infectious process was not determined in an average of 32.5 % of patients (9.9–73.3 %) [46]. Moreover, treatment outcomes in culture-negative and culture-positive PJI did not differ significantly (OR = 1.20, 95 % CI: 0.84–1.70). The effectiveness of two-stage revision arthroplasty was 82.5 % in each group, the effectiveness of one-stage revision arthroplasty was 90.6 % and 94.5 %, respectively. It is noteworthy that the meta-analysis included studies on the treatment of patients with acute PJI [32; 47], which implies perioperative antibiotic prophylaxis which may affect the results of the MBI of the joint fluid. In particular, in the work of Kim et al. more than a half (51 %) of the cases in the culture-negative

group were classified as acute (early) infection [32]. In addition, the effect of antibiotic-containing bone cement, which was used to fix the implant components, cannot be excluded. In addition to the above factors, the limitations include the predominantly retrospective nature of the included studies, the use of various diagnostic criteria for both the periprosthetic infection itself and the concepts of relapse and reinfection, as well as the inclusion of patients with pathology of both the knee and hip joints in the studied samples.

The data presented are consistent with the results of another meta-analysis of 30 studies devoted to the comparison of the effectiveness of treatment of patients with PJI of known and unknown etiology [48]. The treatment outcomes of patients with chronic PJI after two-stage revision arthroplasty were significantly better in patients with an unknown infectious agent than in cases with an identified pathogen: infection control was achieved in 83.9 % and 79.6 %, respectively ($p = 0.002$). The effectiveness of one-stage revision arthroplasty did not differ significantly between the compared groups: 88.5 % and 92.4 %, respectively ($p = 0.23$). It is noteworthy that the authors do not provide an unambiguous definition of the term "culture-negative" and do not select publications based on this principle, what may affect the reliability of the results obtained. Despite a number of limitations, this meta-analysis represents one of the most extensive studies on this topic.

It should be noted that the lack of data on pathogens was long considered a contraindication for the use of a one-stage technique, since in this case the prescription of etiotropic antibiotic therapy immediately after surgery is impossible [49]. At the same time, this intervention is extremely attractive for both the physician and the patient, allowing for the avoidance of re-hospitalization, surgery, and, consequently, repeated courses of antibiotic therapy, and shortening the rehabilitation period so that the patient may return to the normal lifestyle faster. In this regard, an increasing number of studies have recently been published devoted to the successful expansion of indications for this intervention [19, 41, 50, 51]. Most authors report comparable results of using a one-stage technique in culture-negative and culture-positive PJI groups [17, 19, 41, 50, 51]. Extremely high efficacy was demonstrated by combining one-stage re-arthroplasty with intra-articular vancomycin administration in patients with unknown etiology of PJI: the infection was stopped in 90.2 % of cases [50]. According to the authors, intra-articular administration of antimicrobial drugs allows for high concentrations to be achieved at the site of infection in the absence of systemic toxic effects, which are characteristic of classical systemic high-dose therapy [52]. However, Xu et al. report lower efficacy of the one-stage technique in patients in the culture-negative group than in the culture-positive group, while the incidence of complications from systemic antibiotic therapy differs significantly: 58.3 % and 11.3 %, respectively ($p < 0.05$) [19]. Patients in the CNI group received a combination of vancomycin with a third-generation cephalosporin or carbapenem postoperatively, with intravenous antibiotic therapy lasting two to four weeks. Although the authors do not specify the antimicrobial dosing regimen, it can be assumed that such a high complication rate is related to the administration of significantly higher antibiotic doses than in patients in the culture-positive group.

Two-stage revision arthroplasty is considered the "gold standard" for treating patients with culture-negative PJI, since etiotropic antibiotic therapy is impossible in such cases, and detection of pathogens difficult to eradicate in intraoperative biopsies always remains possible. Furthermore, the advantages of staged treatment include the ability to prepare soft tissues and bone for subsequent reimplantation and reinsertion of a spacer with a long course of antibiotic therapy in the event of infection recurrence. Many publications devoted to this topic report good and even excellent results using a two-stage technique in patients with an unknown etiology of the infectious process, while the treatment efficacy is comparable, and in some cases even significantly higher, than that in patients with an identified pathogen [12, 18, 20, 21, 53]. Thus, in a study by Choi et al. failures were noted in 15 % of cases in patients without pathogen growth, while in the group with an identified pathogen it was 39 % ($p = 0.006$). However, in the first case, “desperation operations” (such as hip arthrodesis) were significantly more frequent during treatment ($p = 0.003$) [21].

We focused on existing approaches to defining culture-negative PJI. Treatment outcomes for patients with this condition were examined within the context of the term "culture-negative PJI." The rate of successful treatment outcomes in both the group that included only preoperative microbiological testing (MBT) and the group that included both preoperative and intraoperative cultures exceeded 90 % and showed no statistically significant differences ($p = 0.582$). It should be noted that such high infection control efficacy was achieved without the possibility of prescribing etiotropic antibiotics in the early postoperative period, highlighting the importance of timely and regular monitoring of the spectrum of nosocomial pathogens for the appropriate selection of drugs for empirical antibiotic therapy. Thus, a reduction in the rates of patients with CNI can be achieved by modifying the factors that predict negative MBT results.

Possible ways to reduce the number of patients with unknown etiology of periprosthetic joint infection

Management of patients with infectious complications after large lower limb joint replacement is a complex task requiring the participation of a multidisciplinary team of specialists. The treatment process can be roughly divided into two major phases: the first includes the preoperative period and the surgical procedure itself, and the second, the postoperative period.

The results of microbiological cultures of biospecimens taken preoperatively significantly influence the choice of intervention. In most cases, patients receive empirical antibiotic therapy in the early postoperative period, while microbiological cultures of intraoperative samples determine the type of etiotropic antibiotic therapy that will be continued after the patient's discharge for outpatient treatment. Accordingly, several factors can be identified whose modification could help reduce the incidence of negative culture results (Fig. 3).

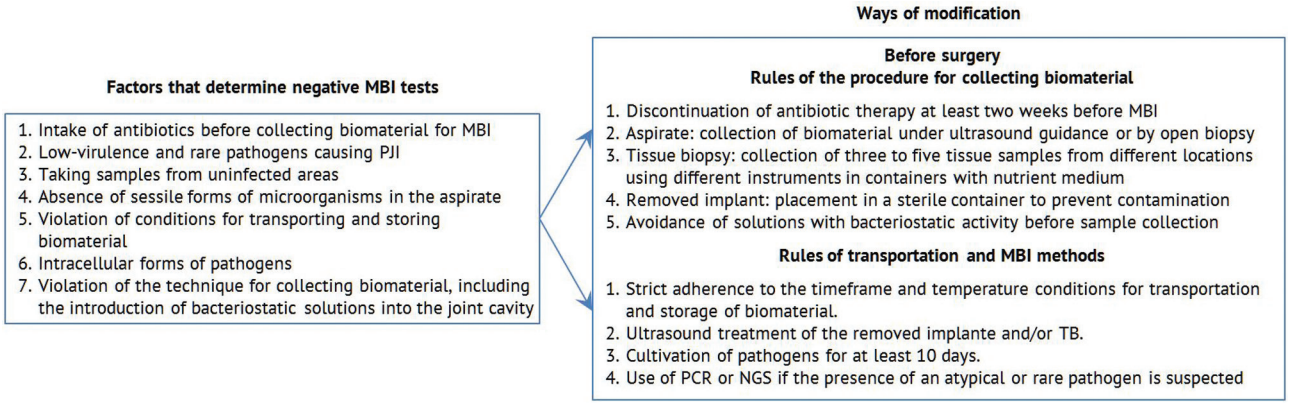

Fig. 3 Factors that have impact on identification of PJI agent and ways of their modification

Recommendations for microbiological diagnosis in the treatment of implant-associated infection are described in detail and summarized by Drago et al. [54]. Thus, in the preoperative period, a key role is given to the cancellation of antibiotic therapy before performing diagnostic tests, as well as an increase in the period of culture cultivation in cases of suspected low virulent pathogens or rare bacteria. For performing percutaneous biopsy, the use of ultrasound navigation is recommended since the probability of detecting a pathogen varies in different anatomical areas. According to Walker et al., the preferred locations for tissue sampling in the hip are the joint bursa (specificity, 100 %) and the joint capsule (sensitivity, 68 %), and the preferred tissue types are the synovial membrane (specificity, 93 %) and pus (sensitivity, 83 %) [55]. If a patient has a fistula tract leading into the joint cavity, fistula discharge collection for analysis is not recommended due to its contamination by skin microflora. A group of Russian scientists has developed and patented a technique for harvesting biopsies from deep within the fistula tract (RU 2 698 175 C1), which significantly improves the effectiveness of preoperative microbiological imaging. During surgery, it is recommended to collect tissue adjacent to the endoprosthesis or tissue with macroscopic signs of infection. Clean, sterile instruments should be used for sampling, avoiding contact with the skin. The biopsy volume

should be at least 1 cm^3. Also, for extracting endoprosthesis components, gentle surgical techniques are recommended, avoiding contact with the skin, and placing each component in a separate container. If delivery of materials to the laboratory is delayed, tissue biopsies and metal components should be stored at 4 °C. Synovial fluid can be stored in specialized vials at room temperature for no longer than 48 hours. The use of sonication significantly increases the effectiveness of microbiological studies [56, 57], and if this is not possible, the use of dithiothreitol (DTT) [58] is an alternative.

Molecular methods such as polymerase chain reaction and next-generation sequencing (NGS) are indicated in cases where identification of the pathogen by conventional methods is ineffective (e.g., in cases of infection caused by Abiotrophia defectiva, Granulicatella adiacens), the clinical picture is not obvious, and the diagnosis of periprosthetic joint infection is questionable. According to the literature, the use of molecular methods enables identification of the pathogen in 4–13 % of patients with aseptic loosening [59]. Many publications on NGS demonstrated an extremely high sensitivity of the method compared to standard cultural studies [60–63]. According to Tarabichi et al., the use of next-generation sequencing allows establishing the etiology of the infectious process in 82 % of culture-negative PJI cases [63].

Limitations of this systematic review include retrospective nature of its material, the design of the included articles (case-control or cohort studies), and the lack of randomized controlled trials. Various studies used different criteria for PJI, its recurrence, and infection resolution. A number of studies failed to include a number of clinical parameters, such as duration of surgery, intraoperative blood loss, duration of antibiotic therapy, and others. Furthermore, a significant limitation is the small number and significant heterogeneity of studies that considered preoperative culture results only. For these reasons, the authors of the present study decided against conducting a meta-analysis. Thus, the obtained results can have only limited practical application; however, an increase in the number of studies devoted to this topic could enable the development of universal treatment guidelines for patients.

CONCLUSION

Based on to the data obtained, no significant differences in the effectiveness of treatment in patients with CNI were found that depend on the approach to defining this term. The greatest challenge in treating patients with CNI is the inability to administer etiotropic antibiotics in the early postoperative period which can negatively impact the entire treatment process. The proposed approaches to reducing the incidence of CNI are aimed at modifying the factors that contribute to negative results in MBI tests of biomaterial samples and removed implants.

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