

MORPHOLOGICAL SUBCHONDRAL BONE TISSUE CHARACTERISTICS IN KNEE OSTEOARTHRITIS

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Morphological subchondral bone tissue alterations associated with knee osteoarthritis represent a key pathogenesis link and can precede articular cartilage destruction. The study aimed to identify typical morphological and morphometric signs of osteosclerosis and osteoporosis in the subchondral zone of the femur and tibia. Analysis of 40 bone tissue fragments collected when performing knee replacement surgery in 20 patients (12 females and 8 males) aged 58–75 years with stage III–IV osteoarthritis was performed. Histological and morphometric assessment involving the use of light microscopy and microfracture index (MFI) calculation revealed significant differences in trabecular thickness, intertrabecular distance, and the degree of microdamage between the sites of sclerosis and osteoporosis. High MFI values in the zones of osteoporosis can reflect reduced subchondral bone strength. The findings confirm the diagnostic value of the subchondral zone morphometry and the prospects of using MFI as a quantitative risk criterion when planning orthopedic treatment.

Keywords: osteoarthritis, subchondral bone, osteosclerosis, osteoporosis, morphometry, microcracks, microfracture index

Author contribution: Minasov BSh — study concept and design, data analysis and interpretation, manuscript editing; Yakupov RR — material collection, morphological assessment, primary data processing; Akbashev VN — statistical processing, visualization of results, manuscript writing; Shchekin VS — literature review, morphology data interpretation; Vlasova AO — preparing illustrations, morphometry analysis, manuscript proofreading; Minasov TB — preparing illustrations, discussion; Karimov KK — material collection, clinical follow-up of patients; Akhmeldinova AA — drawing up inclusion/exclusion criteria, coordination of ethical approval.

Compliance with ethical standards: the study was approved by the Ethics Committee of the Bashkir State Medical University (protocol No. 3 dated 12 March 2025) and conducted in accordance with the World Medical Association Declaration of Helsinki (2013 revision). All patients submitted the informed consent to participation in the study.

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МОРФОЛОГИЧЕСКАЯ ХАРАКТЕРИСТИКА СУБХОНДРАЛЬНОЙ КОСТНОЙ ТКАНИ ПРИ ОСТЕОАРТРОЗЕ КОЛЕННОГО СУСТАВА

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Морфологические изменения субхондральной костной ткани при остеоартрозе коленного сустава являются ключевым звеном патогенеза и могут предшествовать разрушению суставного хряща. Целью исследования было выявить характерные морфологические и морфометрические признаки остеосклероза и остеопороза в субхондральной зоне бедренной и большеберцовой костей. Выполняли анализ 40 участков костной ткани, полученных при эндопротезировании коленного сустава у 20 пациентов (12 женщин и 8 мужчин) в возрасте 58–75 лет с остеоартрозом III–IV стадий. При гистологической и морфометрической оценке с использованием световой микроскопии и расчетом индекса микрофрактуринга (MFI) установлены достоверные различия в толщине трабекул, интертрабекулярном расстоянии и степени микроповреждений между участками склероза и остеопороза. Повышенные значения MFI в зонах остеопороза могут отражать снижение прочности субхондральной кости. Полученные данные подтверждают диагностическую значимость морфометрической оценки субхондральной зоны и перспективность применения MFI как количественного критерия риска при планировании ортопедического лечения.

Ключевые слова: остеоартроз, субхондральная, кость, остеосклероз, остеопороз, морфометрия, микротрещины, индекс микрофрактуринга

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Osteoarthritis (OA) is one of the most common and socially significant musculoskeletal disorders representing a progressive multifactorial connective tissue lesion resulting in disturbed kinematic balance of the skeleton. It is accompanied by acute and chronic pain, limited mobility and high disability likelihood, especially in elderly people. According to the WHO data, more than 240 million people suffer from symptomatic OA, and their number continues to grow steadily with increasing longevity [1, 2]. The current understanding of the OA pathogenesis is beyond the limits of local articular cartilage damage. Today, this disorder is considered as a systemic connective tissue biomechanics and metabolism impairment, due to which all joint components are affected: cartilage, subchondral bone, synovial membrane, tendons, capsule, and periarticular muscles [3, 4]. Imbalance between adaptive and destructive processes occurring under exposure to overload, inflammation, and disturbed tissue homeostasis becomes a central element [5]. In recent years, special attention is paid to the subchondral bone as a key link of the OA pathogenesis. It has been found that alterations of its structure, including osteosclerosis, osteoporosis, subchondral microcracks, and trabecular remodeling, can precede cartilage degeneration and significantly affect the disease progression [6–8]. Such alterations are considered as effects of chronic overload and impaired mechanotransduction in the context of unstable biomechanical equilibrium.

Structural failure of the subchondral bone playing a role of both biomechanical cartilage support and metabolic process regulator is among the key links of OA pathogenesis [9]. Clinically, stepwise disease development is manifested by a complex of sclerotic, osteoporotic, and osteolytic processes. A simultaneous presence of those generates heterogeneous morphological features reflecting a conflict between compensatory and destructive alterations. Such transformations are not limited to anatomy: these are associated with impaired kinematic links, changes of the stress load vector and, as a result, clinical manifestations of pain and dysfunction [10].

The OA biomechanical aspect becomes a key issue due to galloping development of excessive lateral pressure syndrome. The joint functions as a single system maintaining the kinematic balance owing to liquid crystal connective tissue organization [11]. Disruption of this balance leads to overload of distinct components and triggers the cascade of destructive and dystrophic responses. The changing landscape of intra-tissue tension oppresses the role of mechanostat cells. The liquid crystal organization imbalance leads to mechanocyte death.

Visualization and quantification of these processes have become possible due to advanced histological and morphometric methods. Assessment of the subchondral bone thin sections involving the use of digital technologies allows one to identify alterations at the micro level, including trabecular architecture rearrangement, subchondral sclerosis, osteophytosis, and osteolysis. These data make it possible to not only clarify the diagnosis, but also evaluate the disease stage, predict the disease course and adaptation resources of the macroorganism [12].

In this regard, an integrative multifactorial approach combining biomechanics, morphology and clinical assessment is becoming increasingly important. True nature of OA, not as a local disorder of the joint, but as the systemic connective tissue dysfunction under conditions of unstable dynamic equilibrium, can be understood only within the limits of this model.

The study aimed to identify morphological and morphometric features of subchondral bone tissue in patients with stage III–IV knee OA, identify the differences between the areas of osteosclerosis and osteoporosis, and substantiate the microfracture index (MFI) as a quantitative criterion of the subchondral zone structural integrity.

METHODS

The study was conducted at the Laboratory of Morphology of the Institute of Fundamental Medicine, Bashkir State Medical University.

Inclusion criteria: patients aged over 55 year; clinically and radiologically verified stage III–IV primary (idiopathic) osteoarthritis according to the Kellgren–Lawrence classification, disease duration of at least 5 years; total knee replacement surgery; availability of the informed consent.

Exclusion criteria: rheumatic disease; systemic metabolic disorder (including osteoporosis verified by densitometry); malignant neoplasms; previous surgical management of the same joint; decompensated chronic disorder; infection in the area of the operated joint; long-term use of steroid hormones; refusal to participate in the study.

Research material

A total of 20 patients (12 females and 8 males) aged 58–75 years (average age 66.4 ± 5.2 years), who underwent elective total knee replacement due to stage III–IV osteoarthritis (according to the Kellgren–Lawrence classification), were included in the study. During surgery specimens were collected by standard method from similar sites determined by the priority force-stress vector and outside this (internal and external condyles of the femur and tibia). The specimen size was 10×15 mm. The subchondral bone tissue fragments showing signs of bone compaction (osteosclerosis) or loss (osteoporosis) were identified in all patients. In a number of cases, alterations of both types were found in the same sample, which enabled intra-object comparison.

A total of 40 bone tissue fragments were assessed: 20 showing signs of osteosclerosis and 20 showing signs of osteoporosis. Despite the possibility of obtaining up to 80 fragments (4 zones per patient), 40 most informative ones were selected for morphometric assessment — two zones per patient: one showing signs of osteosclerosis, another showing signs of osteoporosis. This enabled intra-object comparison of different types of alterations, increasing the comparative analysis accuracy.

Histological processing methods

Specimens were immediately fixed in the 10% buffered neutral formalin (Histosafe; Biovitrum, Russia) for 24–48 h at a temperature of $+4$ °C. Decalcification was performed using the Trilon B solution (AGAT-MED, Russia) until the mineral component was completely removed. Histological processing was performed using the automated carousel-type processor (AGOT-1, Russia) and increasing concentrations of isopropyl alcohols. Paraffin embedding was accomplished using the reagents manufactured by Biovitrum (Russia). The $4 \mu\text{m}$ slices were cut using the HM340E rotary microtome (Thermo Fisher Scientific, USA). Histological slides were stained with hematoxylin and eosin (Biovitrum, Russia) using the Gemini AS automated slide stainer (Thermo Fisher Scientific, USA).

Microscopy and digital processing

The stained slides were scanned with the Panoramic 250 digital scanning microscope (3DHISTECH Ltd., Hungary) with the Plan-APOCHROMAT $20\times$ lens (Zeiss, Germany). Histological slides were assessed using the CaseViewer (3DHISTECH Ltd., Hungary) and QuPath v.0.5.1 (Bankhead P. et al., Sci Rep 7, 16878, 2017) software tools.

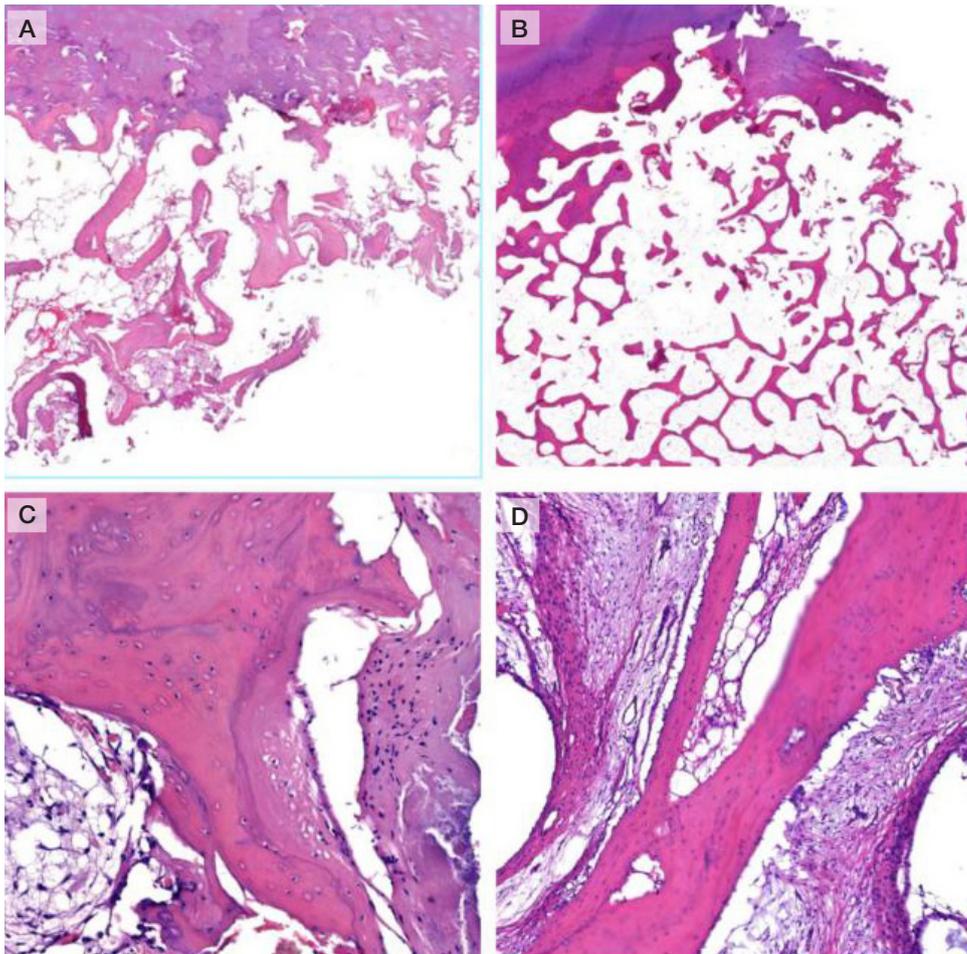


Fig. 1. Morphological alterations in the areas of subchondral bone sclerosis in osteoarthritis. Histological slides stained with hematoxylin and eosin; 20× (A, B), 200× (C, D) magnification. **A.** Fragment of the femoral subchondral zone: thickened trabeculae, anastomosing trabecular structure, narrowed intertrabecular spaces. **B.** Fragment of the tibia: huge osteosclerotic trabeculae, chaotic arrangement, reduced number of haversian canals, intratrabecular space partially replaced with fibrous tissue. **C.** Paratrabecular zone showing signs of sclerotic rearrangement: disorganized lamellar structure, foci of replacement with connective tissue. **D.** Bone marrow space: diffuse replacement with fibrous tissue with predominance of collagen fibers, trabeculae with reduced osteocytic lacunae

Morphometry analysis

The following parameters were measured in five independent fields of view with the 100× magnification:

- 1) trabecular thickness (μm);
- 2) intertrabecular distance (μm);
- 3) width of the basophil band (tidemark) at the boundary of the cartilage and subchondral zones (μm).

When performing morphometry, the calcified cartilage zone visualized as the intensely stained basophil layer in the hematoxylin and eosin stained slides was considered the basophil band. Measurements were performed in the most perpendicular areas between the cartilage border and the beginning of the trabecular bone. The stained band width was considered instead of cellular elements.

Morphometry was performed manually using the QuPath features. In addition, the amount of bone tissue microdamage (microcracks) per studied area (mm^2) was calculated.

Statistical analysis

Statistical data processing was performed using the Statistica 13.0 (StatSoft Inc., USA) and GraphPad Prism 9.0 (GraphPad Software, USA) software packages. The distribution of samples was tested for normality using the Shapiro–Wilk test. Since the distribution of most parameters was non-normal, quantitative data were presented as the median and interquartile range (Me (25–75%)).

The Mann–Whitney U test was used to compare independent groups, and the Kruskal–Wallis H test was used to compare more than two groups, with subsequent pairwise comparison. The differences were considered significant at $p < 0.05$.

RESULTS

Microscopic examination of subchondral bone tissue specimens from the femur and tibia of patients with osteoarthritis revealed typical histological alterations corresponding to two opposing disease processes: osteosclerosis and osteoporosis.

In the areas of bone sclerosis (BS), marked trabecular thickening with enhanced bone matrix production was observed. The trabeculae anastomosed tightly with each other formed coarse fibrous structures (Fig. 1A, B). Intertrabecular spaces were significantly narrowed and partially replaced by fibrous tissue (Fig. 1B). In specific cases, foci of endosteal fibrosis, degenerative changes in osteocytes, and focal osteoblast hyperplasia were reported (Fig. 1C, D).

In the areas of bone tissue loss (BTL), the opposite was observed: severe thinning and fragmentation of bone trabeculae, dilated intertrabecular spaces filled mostly with adipose tissue. Numerous microcracks were reported in atrophic trabeculae, along with sporadic osteoblasts against the background of increased osteoclast counts (Fig. 2).

Morphometric analysis revealed significant differences in trabecular width and intertrabecular distances between BS and

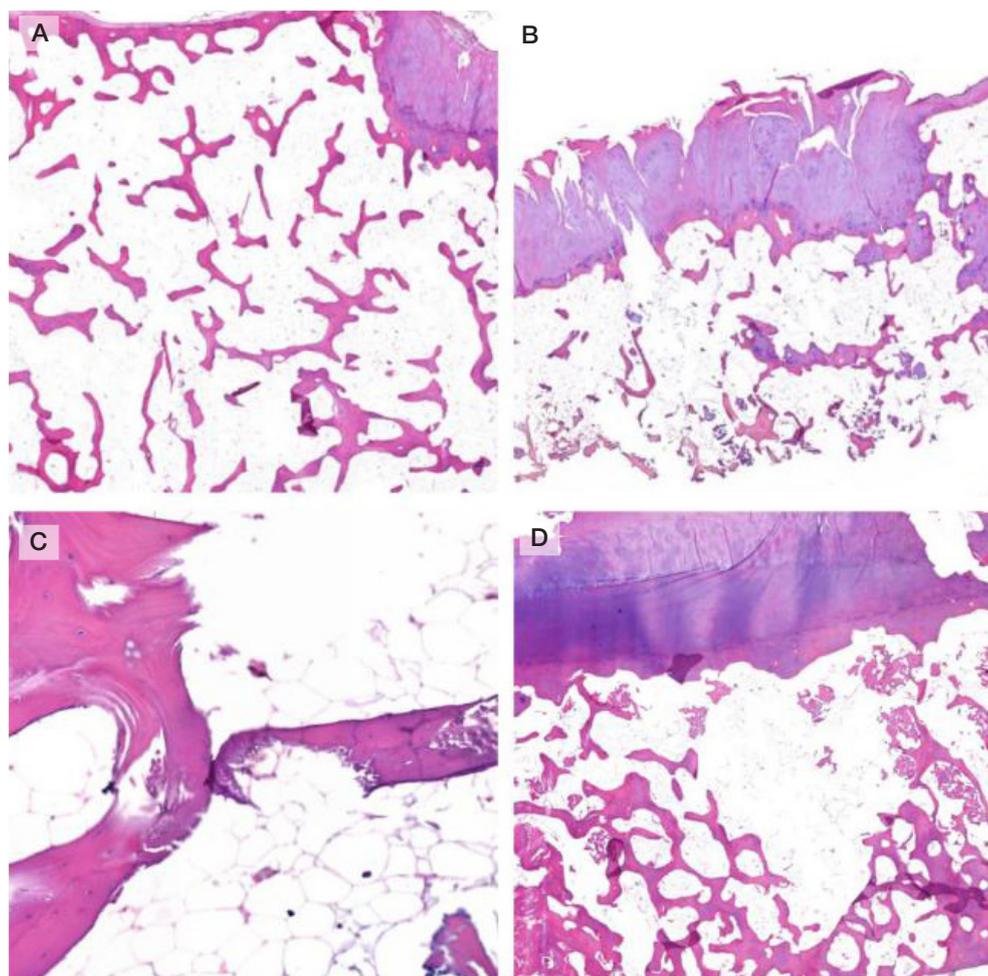


Fig. 2. Morphological characteristics of subchondral bone loss areas in osteoarthritis. Histological slides stained with hematoxylin and eosin; 20× (A, B), 200× (C, D) magnification. **A.** Subchondral zone of the femur: thinned trabeculae, dilated intertrabecular spaces, sporadic microcracks. **B.** Fragment of the tibia: disorganized trabecular structure, sparse architecture, disrupted trabeculae. **C.** Paratrabecular zone of the femur: clearly visible intertrabecular spaces filled with bone marrow fat, trabeculae showing signs of thinning. **D.** Bone marrow space of the tibia: areas of fibrous transformation, linear defects within the trabeculae

BTL areas. Trabecular width was significantly larger in the areas of osteosclerosis vs. osteoporosis ($p < 0.001$), while intertrabecular distances were larger in the areas of osteoporosis (Table 1).

Morphometric analysis showed that in the areas of osteosclerosis trabecular width was significantly larger in the tibia, than in the femur ($p = 0.0007$), while intertrabecular distances, in contrast, were larger in the femur ($p = 0.0377$). In the areas of osteoporosis, trabeculae were significantly thinner in the femur relative to similar zones of the tibia ($p = 0.0001$). Such differences reflect the features of the subchondral bone tissue focal remodeling depending on the anatomical region and the type of load. Furthermore, tidemark width was significantly larger in the tibia, than in the femur ($p = 0.0035$), significant differences were revealed when comparing the femur (BS) and the tibia (BTL) ($p = 0.0113$).

Analysis of the number of microcracks (bone fragility index) in the studied specimens was of special interest. It was shown

that the median bone fragility index was higher in the areas of bone tissue loss (BTL), 0.25, compared to the areas of compaction (BS), where the index value was 0.20 (Fig. 3). These differences were significant (Mann–Whitney U test; $p < 0.05$). Comparison of the data obtained with the control values reported in the literature has shown that both studied conditions are characterized by the increase in the number of microcracks relative to control, but the most pronounced differences from the control group have been found specifically in the areas of osteoporosis [13] (Fig. 4).

Microfracture index as a prognostic criterion

In the specimens assessed, the median MFI for the areas of osteosclerosis was 0.20, while that for the areas of osteoporosis was 0.25. These differences were significant ($p < 0.05$). Preliminary risk scale is proposed based on the distribution of values (Table 2).

Table 1. Subchondral bone morphometric parameters in the studied groups (Me (25–75%))

Parameter	Sclerosis: femur ($n = 10$)	Sclerosis: tibia ($n = 10$)	Osteoporosis: femur ($n = 10$)	Osteoporosis: tibia ($n = 10$)	Kruskal–Wallis H test (p)
Trabecular width, μm	122.4 (89.1–178.6)	139.6 (99.2–193.6)	114.5 (87.8–155.9)	131.4 (95.1–180.8)	$H = 41.03$ ($p = 0.0001$)
Intertrabecular distance, μm	334.7 (232.6–442.3)	300.7 (219.4–413.9)	289.7 (197.3–402.4)	310.2 (211.4–431.9)	$H = 11.01$ ($p = 0.0001$)
Tidemark width, μm	62.5 (47.3–78.7)	66.4 (47.7–105.1)	64.3 (44.6–79.5)	81.6 (61.5–113.4)	$H = 9.55$ ($p = 0.0229$)

Note: the values are presented as the median (25th–75th percentiles). Significance of differences between groups is assessed using the Mann–Whitney U test. The differences are considered significant at $p < 0.05$.

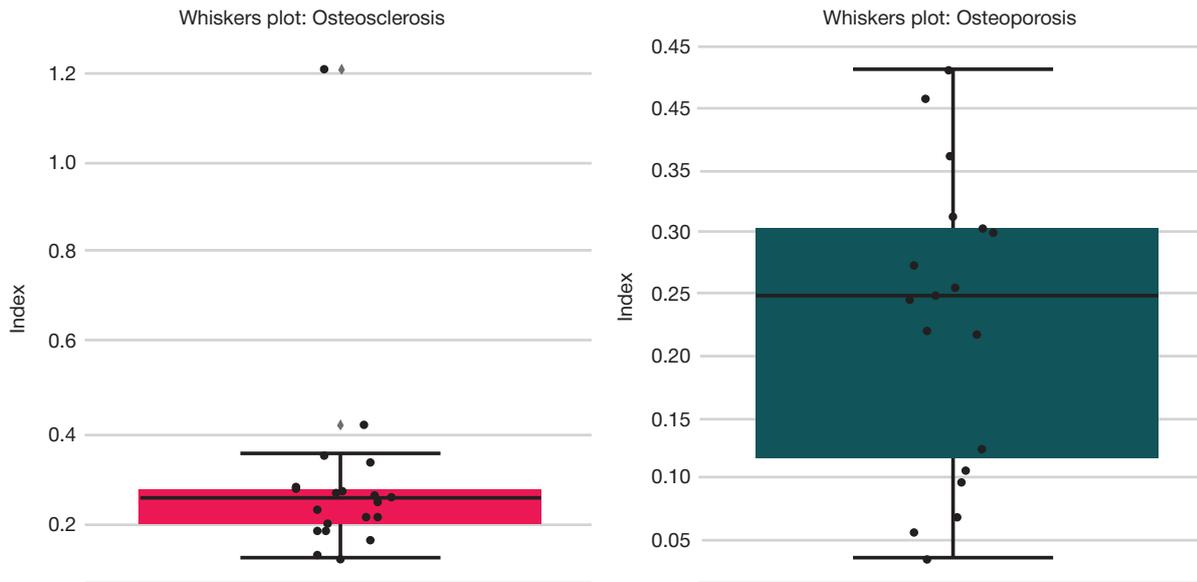


Fig. 3. Distribution of indices in the bone sclerosis and loss areas. The median values and interquartile range are provided. The analysis includes 40 fragments (2 per patient; $n = 20$) collected from the internal and external condyles of the femur and tibia. Areas of osteoporosis are characterized by significantly higher MFI values compared to the areas of sclerosis ($p \leq 0.05$)

DISCUSSION

The findings demonstrate that there are considerable morphological differences between the subchondral bone areas showing signs of osteosclerosis and osteoporosis in knee osteoarthritis. Trabecular width was significantly higher in the areas of sclerosis, while intertrabecular spaces were dilated in the zones of bone tissue loss. Such results confirm that osteoarthritis is accompanied by heterogeneous remodeling processes geared towards both bone sclerosis and structural disorganization in the subchondral zone.

Structural features of the alterations identified are consistent with the literature data emphasizing the key role of subchondral bone in the osteoarthritis pathogenesis. Initial changes of the subchondral bone trabecular architecture can precede chondral degeneration and can be associated with impaired mechanotransduction and microcirculation. The compacted structure with atypical trabecular orientation is formed in the areas of osteosclerosis, which can lead to the depreciation function impairment and increased load on the

articular cartilage. In turn, zones of osteoporosis demonstrate the decreased density and microfragmentation, which can contribute to the decreased subchondral zone strength and increased risk of microfractures.

The published data obtained using micro-CT in women aged 32–37 and 78–80 years were used to compare the morphometric characteristics obtained [13]. It should be noted that methodological differences (optical microscopy vs. micro-CT), as well as differences in age and gender make it impossible to use these data as a direct control. However, these were used as a tentative literature model for discussion of age-related bone structure alterations.

The analysis of microfracture index (MFI) has shown its sensitivity to bone morphology alterations. Higher MFI values in the zones of osteoporosis suggest the bone tissue strength decrease and the possibility of using this indicator as a quantitative prognostic criterion of fractures and endoprosthesis instability. In the study conducted, MFI was determined as microcrack density per unit of bone tissue area (mm^2), which allowed one to quantify the degree of microdamage to the subchondral zone.

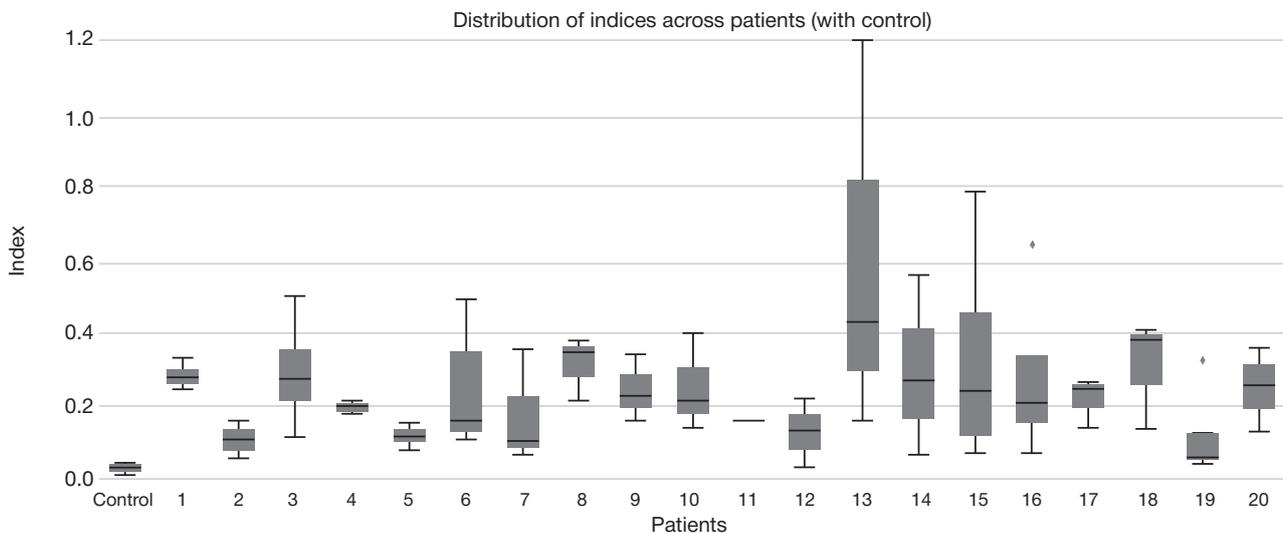


Fig. 4. Bone tissue microfracture index (MFI) in patients with osteoarthritis (based on the data on the areas of osteosclerosis and osteoporosis in the femur and tibia) compared to the literature data [13]. Aggregate MFI values are reported for each patient ($n = 20$), including two areas (of compaction and loss). The literature data are provided for tentative comparison, these have not been used as a control group

Table 2. Microfracture index (MFI)

№	Risk	MFI range	Status description
1	Low	< 0,20	Low number of microcracks, high structural stability
2	Medium	0,20–0,25	Moderate amount of microdamage, potential strength decrease
3	High	≥ 0,25	High density of microcracks, marked bone brittleness

This conclusion is consistent with the results of modern morphometric studies emphasizing the importance of assessing microdamage in the subchondral zone and the interplay between the subchondral zone and the articular cartilage in the context of osteoarthritis [14, 15].

Elevated MFI values can indicate the decreased mechanical bone strength and increased risk of fractures after surgery. In the future this index can be introduced as an additional morphometric criterion for planning of postoperative patient management; this can also be used to substantiate prescription of therapy aimed at remodeling. Further research including clinical follow-up and comparison with the data on actual fractures will make it possible to clarify prognostic value of this indicator and its threshold values with high sensitivity and specificity.

Thus, the structural features identified confirm the need to consider subchondral bone morphology when planning orthopedic treatment, including total knee replacement.

CONCLUSIONS

The study suggests that the subchondral bone tissue demonstrates high morphological heterogeneity in knee osteoarthritis: in distinct zones, signs of osteosclerosis prevail, while signs of osteoporosis prevail in other zones. Morphometric analysis has shown that trabeculae are thickened and intertrabecular spaces are narrowed in the areas of sclerosis, while trabecular thinning and fragmentation, along with dilated intertrabecular spaces are observed in osteoporosis. Microfracture index (MFI) turned out to be significantly higher in the areas of bone tissue loss, which suggests decreased strength and potential instability of the bone. These data indicate the possibility of using morphometric assessment of the subchondral zone, including MFI values, as a prognostic tool when planning orthopedic interventions and total knee replacement.

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