

## ORIGINAL INVESTIGATIONS

# Factors associated with knee pain at early stages of osteoarthritis

Khalmetova A.R.<sup>1</sup>, Lila A.M.<sup>1,2</sup>, Taskina E.A.<sup>1</sup>, Alekseeva L.I.<sup>1,2</sup>, Savushkina N.M.<sup>1</sup>, Kashevarova N.G.<sup>1</sup>, Strebkova E.A.<sup>1</sup>, Alekseeva O.G.<sup>1</sup>

<sup>1</sup>V.A. Nasonova Research Institute of Rheumatology, Moscow; <sup>2</sup>Russian Medical Academy of Continuing Professional Education, Ministry of Health of Russia, Moscow

<sup>1</sup>34A, Kashirskoye Shosse, Moscow, 115522, Russia; <sup>2</sup>2/1, Barrikadnaya Street, Build. 1, 125993 Moscow, Russia

**Objective:** To investigate key risk factors associated with knee pain in early-stage osteoarthritis (OA).

**Material and methods.** The study included 109 women aged 35–75 years with knee pain lasting no more than one year and minimal radiographic changes (Kellgren–Lawrence grades 0–II). For each patient we filled in a personalized case form including anthropometric data, medical history, physical examination findings, pain and health status assessments using visual analog scale (VAS), and questionnaires (WOMAC, KOOS, DN4), along with information on comorbidities. All participants underwent standard knee radiography, ultrasound examination, and laboratory testing.

**Results and discussion.** One in six patients (15%) reported moderate or severe knee pain ( $\geq 40$  mm on VAS). Patients with more intense pain were older than those with VAS  $< 40$  mm (median age 52.5 [42; 62.5] vs. 44 [38; 52] years;  $p=0.02$ ) and had a higher body mass index (28 [25; 31.6] vs. 24 [21; 28] kg/m<sup>2</sup>;  $p=0.04$ ). Statistically significant differences were also observed in OA severity: the high-pain group had higher WOMAC and all its components' scores (median 1245 [872; 1510] vs. 248 [90; 410] mm;  $p<0.001$ ), lower self-rated health status (60 [47; 80] vs. 29.5 [10; 50] mm;  $p<0.001$ ), lower KOOS total scores and its components' scores (44 [37; 67] vs. 79 [63; 88] %;  $p<0.001$ ), and more frequent detection of synovitis on examination (50% vs. 19.3%;  $p<0.001$ ) and in the past history (75% vs. 31.1%;  $p=0.008$ ). Flexion restriction (50% vs. 19.3%;  $p=0.01$ ), presence of osteophytes on ultrasound (50% vs. 10.75%;  $p<0.001$ ), metabolic syndrome (56.25% vs. 25.8%;  $p=0.03$ ), and postmenopausal status (68.75% vs. 35.48%;  $p=0.01$ ) were also more frequent.

A discriminant model was developed to predict the risk of pain  $\geq 40$  mm on VAS, incorporating WOMAC functional limitations, presence of metabolic syndrome, ultrasound-detected osteophytes, and clinically significant synovitis. The model achieved an accuracy of 90.8%. Predictive performance was confirmed by ROC analysis (AUC=0.898, 95% CI 0.794–1.002), indicating high prognostic accuracy.

**Conclusion.** Severe knee pain at early stages of OA is associated with functional impairment according to WOMAC, clinical synovitis, ultrasound-detected osteophytes, and metabolic syndrome. These risk factors and the developed predictive model may be useful for planning individualized preventive and therapeutic strategies in OA patients.

**Keywords:** early-stage osteoarthritis; risk factors; pain.

**Contact:** Alsu Ravilievna Khalmetova; [halmetova2017@yandex.ru](mailto:halmetova2017@yandex.ru)

**For reference:** Khalmetova AR, Lila AM, Taskina EA, Alekseeva LI, Savushkina NM, Kashevarova NG, Strebkova EA, Alekseeva OG. Factors associated with knee pain at early stages of osteoarthritis. *Sovremennaya Revmatologiya=Modern Rheumatology Journal*. 2025;19(3):56–63. DOI: 10.14412/1996-7012-2025-3-56-63

Knee Osteoarthritis (OA) is one of the leading causes of disability and a significant decline in quality of life among working-age individuals worldwide, with a substantial increase in the number of cases reported over the past decade. According to forecasts, by 2050, one billion people globally will be diagnosed with OA [1].

In recent years, there has been a marked increase in interest in studying OA at early stages, as it is assumed that early detection and treatment of the disease will help slow the progression of OA and reduce the frequency of joint replacement surgeries [2]. Despite this, early-stage OA remains an underexplored area. Currently, the diagnosis of OA is established using the classification criteria of R. Altman et al. [3]; however, these, like the Kellgren–Lawrence (K–L) radiographic classification, do not allow for the identification of patients with early-stage OA. Only a few proposed criteria for early OA exist, but they still require further refinement and validation [4–6].

Among patients with knee OA, pain and its intensity have a significant impact on daily activities and quality of life. It has

been shown that the presence and severity of knee pain are associated with an increased risk of disability, radiographic progression of OA [7, 8], and mortality [9]. Pain is the most common reason patients with OA seek medical care, determining the widespread use of nonsteroidal anti-inflammatory drugs (NSAIDs) [10] and remaining the main indication for surgical treatment, including joint replacement [11].

Typically, in the early stages of OA, pain is variable, intensifies with physical activity, and subsides at rest, thereby creating the impression of temporary or incidental discomfort. Subsequently, these episodes may become more prolonged. King L. et al. [12], in their study, described the clinical symptoms in patients at an early stage of OA. Within their work, patients with confirmed knee OA retrospectively recalled the initial manifestations of the disease. The study included 91 participants from different countries. Data from focus groups and individual interviews were used, in which participants were asked to describe in detail their first symptoms in the knee before receiving an OA diagnosis. The results showed that the early symptoms of the disease often

## ORIGINAL INVESTIGATIONS

developed gradually and episodically, accompanied by short-term pain, stiffness, and crepitus in the knee. Many patients noted that they could not precisely recall the onset of symptoms due to their gradual intensification and low severity in the initial stages. In addition, the symptoms were perceived as temporary and insignificant. Patients also frequently attributed their symptoms to factors such as minor knee trauma, age-related changes, or physical overexertion. An important observation was that many participants modified their lifestyle to avoid activities that could cause knee problems: they reduced the intensity of physical activity or changed the way they performed usual tasks. By the time patients eventually sought medical care, the disease was already at an advanced stage.

Previous scientific studies on early-stage OA have focused primarily on developing diagnostic methods, including imaging techniques and biochemical markers. However, the characteristics of pain and the factors determining its severity remain poorly studied, despite the fact that this symptom affects physical activity, emotional well-being, social functioning, and overall quality of life. Identifying such predictors and providing timely intervention may potentially reduce the frequency of temporary and permanent disability, which in turn could decrease the economic burden on the healthcare system and society as a whole.

**Objective:** To investigate the main risk factors associated with pain in early-stage knee osteoarthritis (OA).

**Materials and Methods:** This cross-sectional study included 109 women aged 35-75 years presenting with knee pain lasting no more than one year and radiographic stage K-L 0-II.

**Exclusion criteria:** Presence of another rheumatic disease; trauma of the studied knee joint requiring surgical treatment during the study period; radiographic stage K-L III-IV; pregnancy and/or breastfeeding during the study period.

A standardized individual case report form was completed for each patient, including anthropometric data (height, body weight, waist circumference, hip circumference, BMI), disease history, clinical examination data, including pain assessment in the knees using a visual analogue scale (VAS); the WOMAC (Western Ontario and McMaster Universities Osteoarthritis Index, comprising 24 items assessing pain, stiffness, and functional limitations), KOOS (Knee Injury & Osteoarthritis Outcome Score, comprising 42 items covering symptoms, pain, daily and sports activity function, and quality of life), DN4 (Douleur Neuropathique en 4 Questions, a diagnostic screening tool for neuropathic pain), the patient's global health assessment (PGHA), and information on comorbidities.

All patients underwent biochemical blood testing to determine levels of C-reactive protein (CRP), glucose, glycated hemoglobin (HbA1c), total cholesterol (TC), low-density lipoproteins (LDL), high-density lipoproteins (HDL), triglycerides (TG), alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatinine, alkaline phosphatase (ALP), uric acid (UA), phosphorus, and calcium.

Radiography of the knee joints was performed in a standing position with fixed flexion (posteroanterior view) using a po-

sitioning frame, with assessment of the radiographic stage according to Kellgren & Lawrence (K-L), as well as knee ultrasound, which evaluated the presence of joint effusion and osteophytes at the margins of articular surfaces, the thickness of the synovial membrane, and the articular cartilage on the femoral condyles in anterior and posterior compartments.

Statistical analysis was performed using Statistica 10.0 software (StatSoft Inc., USA). Standard descriptive statistics methods were applied to calculate minimum and maximum values and, where appropriate, frequency analysis. Normality of distribution was assessed using the Kolmogorov-Smirnov and Shapiro-Wilk tests. For normally distributed variables, the mean and standard deviation were presented; Student's t-test was used. For non-normally distributed data, the median and interquartile range (Me [25th; 75th percentiles]) were used, and the Mann-Whitney U test was applied. Correlation analysis was performed to identify associations between variables, with Spearman's rank correlation method used to assess relationships between indicators. Differences were considered statistically significant at  $p < 0.05$ .

To analyze the effect of independent factors on the variable under study with the possibility of predicting its values, discriminant analysis was employed (backward stepwise method). Differences were considered statistically significant at  $p < 0.05$ .

To assess the significance of the association between knee pain and the factors identified in the multivariate analysis, an ROC curve was constructed to reflect the relationship between the true positive rate (sensitivity) and the false positive rate (specificity).

Written informed consent was obtained from all participants prior to inclusion in the study. The study was approved by the local ethics committee of V.A. Nasonova Research Institute of Rheumatology (Protocol No. 11 dated September 26, 2023).

## Results

The study included 109 female patients with knee pain lasting

**Table 1. General characteristics of patients**

Parameter	Value
Age, years, Me [25th; 75th percentiles]	45 [39; 53]
Symptom duration, years, Me [25th; 75th percentiles]	0.75 [0.5; 1]
BMI, kg/mI, $M \pm SD$	$26.7 \pm 5.7$
Waist circumference, cm, Me [25th; 75th percentiles]	80 [71; 93]
Hip circumference, cm, Me [25th; 75th percentiles]	100 [94; 108]
OA stage, %:	
0	0,9
I	80,7
II	18,4
Pain (VAS), mm, Me [25th; 75th percentiles]	30 [10; 50]
WOMAC pain subscale, mm, Me [25th; 75th percentiles]	70 [25; 150]
WOMAC function subscale, mm, Me [25th; 75th percentiles]	165 [70; 390]
Total WOMAC Index, mm, Me [25th; 75th percentiles]	265 [110; 640]
Patient's global health assessment, mm, Me [25th; 75th percentiles]	35 [10; 50]
OA at another site, %	41

## ORIGINAL INVESTIGATIONS

**Table 2. Correlation between pain and factors associated with OA and metabolic disturbances**

Parameter	r	p
Age, years	0.31	<0.001
BMI, kg/m <sup>2</sup>	0.337	<0.001
Waist circumference, cm	0.3	0.002
Hip circumference, cm	0.3	0.002
Knee stiffness	0.35	<0.001
Limited knee flexion	0.25	0.008
Synovitis : clinically significant	0.304	0.001
history of synovitis	0.254	0.008
Radiographic stage	0.229	0.016
WOMAC: stiffness subscale, mm	0.57	<0.001
function subscale, mm	0.666	<0.001
total Index, mm	0.712	<0.001
KOOS: symptoms, %	-0.37	<0.001
Daily Living Function, %	-0.57	<0.001
KOOS Sport/Recreation Function, %	-0.55	<0.001
Quality of Life, %	-0.42	<0.001
Total, %	-0.58	<0.001
Patient's global health assessment, mm	0.43	<0.001
DN4 score, points	0.42	<0.001
Osteophytes (ultrasound)	0.351	<0.001
Posterior lateral cartilage (ultrasound)	-0.24	0.01
Anterior lateral cartilage (ultrasound)	-0.26	0.007
Arterial hypertension	0.251	0.008
Metabolic syndrome	0.354	<0.001
Number of MS components	0.308	0.001
Obesity	0.225	0.01
Hypertriglyceridemia	0.311	<0.001
SCORE scale	0.28	0.002
Menopause	0.365	<0.001
HbA1c, %	0.24	0.01
Fasting glucose, mmol/L	0.24	0.01
Triglycerides, mmol/L	0.21	0.02
Alkaline phosphatase, U/L	0.2	0.04
Cartilage oligomeric matrix protein, ng/mL	0.5	0.004

no more than one year. The general characteristics of the patients are presented in Table 1.

In the analysis of comorbid diseases and conditions, obesity was diagnosed most frequently — observed in 23.85% of patients

— followed by arterial hypertension (AH) in 22.9%, metabolic syndrome (MS) in 30.3%, type 2 diabetes mellitus (T2DM) in 4.6%, hypercholesterolemia (hyperchol) in 19.3%, hypertriglyceridemia (hyperTG) in 14.7%, and hyperglycemia in 8.3%.

In the course of the study, we conducted a correlation analysis between knee pain and factors related to OA, metabolic disorders, and laboratory and instrumental findings. Significant associations were identified with many of the studied factors (Table 2).

In the Spearman correlation analysis, significant associations ( $p < 0.05$  for all cases) were identified between pain intensity and the following variables: age, BMI, waist circumference, hip circumference, clinical findings (clinically significant synovitis, limited knee flexion), history of synovitis, knee stiffness, radiographic stage, WOMAC index, KOOS score, patient's global health assessment (PGHA), DN4 questionnaire, and ultrasound parameters (osteophytes, cartilage thickness). Additionally, knee pain was found to correlate with MS and the number of its components, arterial hypertension (AH), obesity, hypertriglyceridemia (hyperTG), menopause, as well as with laboratory parameters such as glycated hemoglobin, fasting glucose, triglycerides, alkaline phosphatase (ALP), and cartilage oligomeric matrix protein (COMP, a marker of cartilage degradation).

In particular, it was demonstrated that patients older than 45 years experienced significantly higher pain intensity compared to those younger than 45 years (20 [0; 40] mm vs 5 [0; 20] mm,  $p < 0.001$ ). In the presence of MS, pain intensity was also significantly higher than in individuals without MS (20 [0; 40] mm vs 5 [0; 20] mm,  $p = 0.017$ ). A similar pattern was observed for obesity (30 [10; 40] mm vs 10 [0; 30] mm,  $p = 0.022$ ), AH (30 [10; 40] mm vs 10 [0; 25] mm,  $p = 0.01$ ), and hyperTG (35 [15; 57] mm vs 10 [0; 30] mm,  $p = 0.001$ ). A statistically significant association was also found with menopause ( $r = 0.365$ ,  $p < 0.001$ ). Specifically, among postmenopausal women, the median pain intensity was 27 [5; 42.5] mm, while in patients with preserved reproductive function it was 4 [0; 20] mm ( $p < 0.001$ ).

Moreover, it was confirmed that patients with stage II disease according to the K-L classification experienced higher pain intensity compared to those without radiographic changes (22.5 [10; 45] mm vs 10 [0; 30] mm,  $p = 0.017$ ). Higher pain intensity was also observed in patients with a history of synovitis (25 [0; 50] mm vs 10 [0; 20] mm,  $p = 0.004$ ), with clinically significant synovitis at the time of examination (30 [20; 50] mm vs 10 [0; 30] mm,  $p = 0.002$ ), and in those with ultrasound-confirmed osteophytes (40 [20; 50] mm vs 10 [0; 30] mm,  $p = 0.001$ ).

We further aimed to identify factors determining the development of moderate or severe pain in patients at early stages of the disease. In our study, 15% of patients experienced moderate ( $n = 10$ ) or severe knee pain ( $n = 6$ ). Depending on pain severity, all patients were divided into two groups (Table 3).

Individuals with moderate or severe pain were older and had a higher BMI. Statistically significant differences were also found when assessing disease severity: patients with more intense pain showed higher total WOMAC index scores and its subscales, lower KOOS scores, lower PGHA values, and more frequent signs of neuropathic pain (DN4 questionnaire). Clinically significant synovitis at examination and in the patient's history, ultrasound-detected osteophytes, and restricted knee flexion were more common in this group. Patients with more severe pain more frequently had metabolic syndrome (MS) and two or more of its components. This group also included a higher proportion of postmenopausal women.

## ORIGINAL INVESTIGATIONS

Table 3. Comparative characteristics of patients based on pain intensity

Parameter	Patients with pain <40 mm (VAS) (n=93)	Patients with pain ≥40 mm (VAS) (n=16)	p-value
Age, years, Me [25th; 75th percentiles]	44 [38; 52]	52.5 [42; 62.5]	<b>0.02</b>
BMI, kg/m <sup>2</sup> , Me [25th; 75th percentiles]	24 [21; 28]	28 [25; 31.6]	<b>0.04</b>
Hip circumference, cm, Me [25th; 75th percentiles]	100 [94; 107]	108 [100; 116]	<b>0.04</b>
WOMAC, мм, Me [25-й; 75-й перцентили]:			
stiffness subscale	20 [0; 50]	102.5 [75; 135]	<b>&lt;0.001</b>
function subscale	145 [55; 270]	925 [557; 1100]	<b>&lt;0.001</b>
Total Index	248 [90; 410]	1245 [872; 1510]	<b>&lt;0.001</b>
KOOS, %, Me [25-й; 75-й перцентили]:			
Symptoms	79 [71; 88]	59 [47; 75]	<b>&lt;0.001</b>
Daily Living Function	90 [76; 96]	53 [44; 76]	<b>&lt;0.001</b>
Sport/Recreation Function	75 [40; 85]	28 [15; 42]	<b>&lt;0.001</b>
Quality of Life	69 [50; 81]	35 [25; 56]	<b>&lt;0.001</b>
Total	79 [63; 88]	44 [37; 67]	<b>&lt;0.001</b>
DN4. points, Me [25th; 75th percentiles]	1 [0; 2]	1 [1; 4]	<b>0.02</b>
Patient's global health assessment, mm, Me [25th; 75th percentiles]	29.5 [10; 50]	60 [47; 80]	<b>&lt;0.001</b>
Radiographic stage, %:			0.3
0	1.07	0	
I	82.8	68.75	
II	16.1	31.25	
Synovitis, %:			
history	31.1	75	<b>0.008</b>
clinically significant synovitis at examination, %	13.9	50	<b>&lt;0.001</b>
Limited knee flexion, %	19.3	50	<b>0.01</b>
Osteophytes (ultrasound), %	10.75	50	<b>&lt;0.001</b>
Metabolic syndrome, %	25.8	56.25	<b>0.03</b>
Menopause, %	35.48	68.75	<b>0.01</b>
Triglycerides, mmol/L, Me [25th; 75th percentiles]	0.93 [0.67; 1.24]	1.4 [0.82; 2.1]	<b>0.02</b>

In the Spearman correlation analysis, significant associations ( $p < 0.05$  for all cases) were confirmed between joint pain 40 mm and various factors associated with OA and metabolic disorders (Table 4).

The factors that showed the strongest correlation with knee pain in early-stage OA and the lowest intercorrelation with each other were included in the discriminant analysis. This analysis was performed using a stepwise backward elimination method, excluding variables with minimal impact or low significance. The results of the discriminant analysis are presented in Table 5.

Using the obtained discriminant function coefficients, a formula was developed to accurately predict the likelihood of developing knee pain 40 mm in early-stage OA:

Prediction of pain development (40 mm on the VAS) in a patient with early-stage knee OA =  $(0.012 \times \text{functional limitation by WOMAC}) + (3.03 \times \text{presence of metabolic syndrome}) + (3.38 \times \text{osteophytes on ultrasound}) + (2.14 \times \text{clinically significant synovitis})$  14.1. *where functional limitation by WOMAC is given in mm; metabolic syndrome (0 = absent, 1 = present); osteophytes on ultrasound (1 = absent, 2 = present); clinically significant synovitis (1 = absent, 2 = present).*

If the total prognostic score is greater than or equal to 14.1, the probability of developing pain 40 mm on the VAS for a given patient is 90.8%.

The predictive performance of the model was assessed using ROC analysis (Fig. 1).

The area under the ROC curve was 0.898 (95% CI: 0.794–1.002), indicating very good predictive accuracy and an excellent balance between sensitivity and specificity for forecasting pain development in early-stage OA.

Thus, discriminant analysis revealed that the most significant risk factors for the development of pain in early-stage knee OA are: functional limitation according to the WOMAC index, clinically detected synovitis, the presence of metabolic syndrome, and the presence of osteophytes on ultrasound examination.

### Discussion

Studies specifically focused on pain and the factors associated with its severity in early-stage OA are extremely limited. Most available data are concentrated on advanced stages of the disease, where pain typically has a multifactorial nature. This considerably complicates direct comparison of our findings with existing studies.



## ORIGINAL INVESTIGATIONS

**Table 4. Correlation between knee pain  $\geq 40$  mm and factors associated with OA and metabolic disturbances**

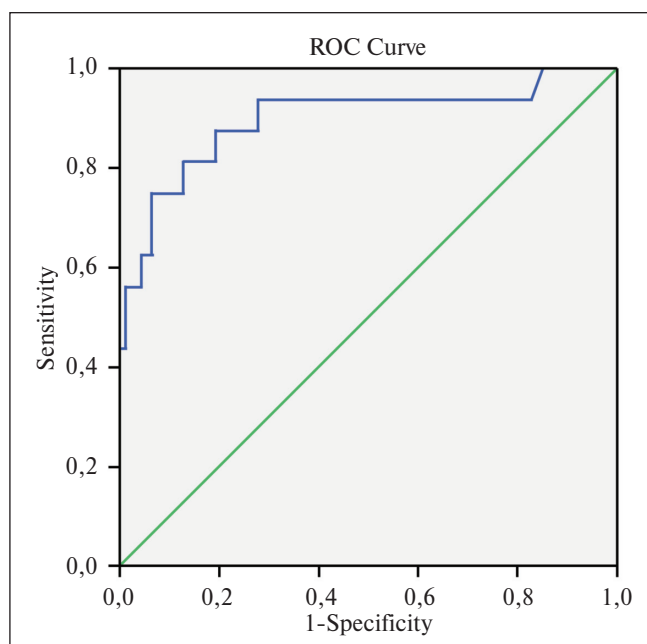
Parameter	r	p
Age, years	0.21	<b>0.02</b>
BMI, kg/m <sup>2</sup>	0.19	<b>0.04</b>
Hip circumference, cm	0.2	<b>0.03</b>
Synovitis: clinically significant history of synovitis	0.3 0.3	< <b>0.001</b> <b>0.001</b>
Limited knee flexion	0.25	<b>0.007</b>
WOMAC: stiffness subscale, mm function subscale, mm total index, mm	0.5 0.48 0.5	< <b>0.001</b> < <b>0.001</b> < <b>0.001</b>
KOOS: symptoms, % daily living function, % sport/recreation function, % quality of life, % total, %	-0.3 -0.4 -0.4 -0.4 -0.4	< <b>0.001</b> < <b>0.001</b> < <b>0.001</b> < <b>0.001</b> < <b>0.001</b>
DN4	0.23	< <b>0.001</b>
Patient's global health assessment, mm	0.4	< <b>0.001</b>
Osteophytes (ultrasound)	0.4	< <b>0.001</b>
Menopause	0.26	<b>0.005</b>
Coronary artery disease	0.23	<b>0.01</b>
Metabolic syndrome	0.23	<b>0.01</b>
Triglycerides, mmol/L	0.2	<b>0.02</b>

**Table 5. Coefficients of the discriminant function for pain prediction model in early OA**

Factor	Discriminant coefficient
WOMAC function subscale	0.012
Osteophytes (ultrasound)	3.38
Metabolic syndrome	3.03
Clinically significant synovitis	2.14

**Note:** The model's predictive accuracy according to the classification matrix is 90.8%

In this study, clinical, metabolic, and structural changes identified using instrumental methods and associated with pain were investigated. Correlation analysis revealed statistically significant associations between knee pain intensity and the following factors: age, BMI, clinical examination findings (presence of clinically significant synovitis, limited knee flexion), medical history (history of synovitis), severity of knee stiffness, radiographic disease stage, total WOMAC index, KOOS scores, the patient's global health self-assessment, the presence of neuropathic pain signs, as well as ultrasound parameters (presence of osteophytes and cartilage thickness). Additionally, knee pain was shown to correlate with comorbid conditions — such as metabolic syndrome, arterial hy-

**Fig. 1. ROC curve of sensitivity/specificity ratio of the predictive model for moderate/severe pain development in early-stage knee OA (AUC=0.898)**

pertension, obesity, hypertriglyceridemia, and menopause — as well as with laboratory parameters including glycated hemoglobin, fasting glucose, triglycerides, alkaline phosphatase, and cartilage oligomeric matrix protein (COMP).

The results of subsequent discriminant analysis allowed us to identify the main predictors associated with pain: the degree of functional limitation according to the WOMAC index, the presence of osteophytes on ultrasound, metabolic syndrome, and clinically detectable synovitis. Based on the discriminant coefficients, we proposed a formula capable of predicting pain development in patients with early-stage knee OA with high accuracy (90.8%). The strong predictive performance of the model was confirmed by ROC analysis: the area under the curve (AUC) was 0.898 (95% CI: 0.794–1.002), indicating high diagnostic value.

Our findings demonstrate that pronounced pain in patients is closely associated with functional limitation as assessed by the WOMAC index. This is consistent with the results reported by D. Cubukcu et al., who identified a significant association between pain and functional impairment in patients with OA ( $p < 0.01$ ), confirming their interdependence [13]. Notably, in their study, radiographic changes (according to the K-L scale) did not have a significant effect on either pain or functional limitation ( $p > 0.05$ ). This result is particularly important for early-stage OA, where radiographic signs of the disease are minimal or entirely absent.

Our data on the significant role of osteophytes detected by ultrasound in the development of pain in early-stage OA are supported by numerous studies demonstrating the high sensitivity of ultrasound in their detection [14–16]. Many studies have shown that ultrasound is comparable to radiography in identifying osteophytes and, in some cases, even superior due to its ability to detect smaller and early changes that may not be visible on radiographs.

For example, in the study by J. Koski, it was shown that ultrasound detects more osteophytes than radiography in both the medial (65% vs 48%) and lateral (70% vs 60%) compartments of

## ORIGINAL INVESTIGATIONS

the knee joint [17]. Moreover, a correlation was established between the presence of osteophytes detected by ultrasound and degenerative cartilage changes confirmed arthroscopically, highlighting the clinical value of this method, especially at early disease stages. Another study demonstrated a significant correlation between the presence of osteophytes identified by ultrasound and pain intensity in patients with OA [18]. These findings confirm that ultrasound not only detects structural changes but also allows for a more precise assessment of their clinical significance in the context of pain.

In the study by Z-J. He et al., conducted within the framework of the Osteoarthritis Initiative (OAI) and involving patients at various stages of OA, factors influencing the development of knee pain were described [19]. Individual components of metabolic syndrome (MS), such as BMI and diabetes mellitus (DM), showed an association with pain in the univariate analysis. BMI was identified as a significant factor associated with knee pain development (OR=1.06;  $p<0.001$ ); however, its influence was not significant in the multivariate model (OR=1.005;  $p=0.494$ ). In contrast, DM remained significant as an independent risk factor for pain (OR=1.27;  $p=0.039$ ). Furthermore, the contribution of MS to pain development was confirmed in another study, which found that the accumulation of MS components was associated with higher pain intensity (OR=3.7; 95% CI 1.5–5.9;  $p=0.001$ ), independent of patient age and BMI [20]. Multiple regression analysis showed that hyperglycemia and elevated triglyceride levels significantly exacerbated pain ( $p=0.009$  and  $p=0.04$ , respectively), while waist circumference and systolic blood pressure correlated with functional impairment as measured by the Lequesne index

( $p=0.04$  and  $p=0.01$ , respectively). Our findings, which demonstrate that MS as a whole is a significant factor, are consistent with these data and underscore the importance of investigating its cumulative impact on pain syndrome.

Based on the discriminant analysis, we also established that the presence of synovitis plays a significant role in the development of pain at early stages of OA. The data obtained are consistent with findings reported in the literature. For example, according to the study by E. Sanchez-Lopez et al., the presence of synovitis is an important factor influencing pain severity in OA, even when radiographic changes are minimal [21]. Moreover, beyond exacerbating pain, synovitis also plays a significant role in structural joint damage and disease progression. Thus, the identified risk factors and the proposed predictive formula may serve as a basis for developing individualized preventive and therapeutic strategies for patients with early-stage OA.

## Conclusion

The results of this study confirmed the significant contribution of several factors – such as functional limitation according to the WOMAC index, the presence of osteophytes detected by ultrasound, metabolic syndrome, and clinically significant synovitis – to the development of pain in early-stage knee OA. These findings highlight the need for a comprehensive approach to pain management that includes therapy aimed at reducing inflammation and improving patients' functional activity, as well as addressing comorbid conditions. Future studies involving larger patient samples may help clarify the role of additional factors, identifying new targets for the prevention and treatment of OA.

## REFERENCES

- GBD 2021 Osteoarthritis Collaborators. Global, regional, and national burden of osteoarthritis, 1990–2020 and projections to 2050: a systematic analysis for the Global Burden of Disease Study 2021. *Lancet Rheumatol*. 2023 Aug;5(9):e508–e522. doi: 10.1016/S2665-9913(23)00163-7.
- Caneiro JP, O'Sullivan PB, Roos EM, et al. Three steps to changing the narrative about knee osteoarthritis care: a call to action. *Br J Sports Med*. 2020 Mar;54(5):256–258. doi: 10.1136/bjsports-2019-101328. Epub 2019 Sep 4.
- Altman R, Asch E, Bloch D, et al. Development of criteria for the classification and reporting of osteoarthritis. Classification of osteoarthritis of the knee. Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Association. *Arthritis Rheum*. 1986 Aug;29(8):1039–49. doi: 10.1002/art.1780290816.
- Luyten FP, Denti M, Filardo G, et al. Definition and classification of early osteoarthritis of the knee. *Knee Surg Sports Traumatol Arthrosc*. 2012 Mar;20(3):401–406. doi:10.1007/s00167-011-1743-2.
- Luyten FP, Bierma-Zeinstra S, Dell'Accio F, et al. Toward classification criteria for early osteoarthritis of the knee. *Semin Arthritis Rheum*. 2018 Feb;47(4):457–463. doi:10.1016/j.semarthrit.2017.08.006.
- Migliore A, Scire CA, Carmona L, et al. The challenge of the definition of early symptomatic knee osteoarthritis: a proposal of criteria and red flags from an international initiative promoted by the Italian Society for Rheumatology. *Rheumatol Int*. 2017 Aug;37(8):1227–1236. doi:10.1007/s00296-017-3700-y.
- McAlindon TE, Cooper C, Kirwan JR, et al. Knee pain and disability in the community. *Br J Rheumatol*. 1992 Mar;31(3):189–192. doi:10.1093/rheumatology/31.3.189.
- Creamer P, Hochberg MC. The relationship between psychosocial variables and pain reporting in osteoarthritis of the knee. *Arthritis Care Res*. 1998 Feb;11(1):60–65. doi:10.1002/art.1790110110.
- Verbrugge LM. Physical and social disability in adults. In: Hibbard H, Nutting PA, Grady ML, editors. *Primary Care Research: Theory and Methods*. RockvilleMD: Agency for Health Care Policy and Research, U.S. Department of Health and Human Services; 1991. P. 31–57.
- Bidaut-Russell M, Gabriel SE. Adverse gastrointestinal effects of NSAIDs: consequences and costs. *Best Pract Res Clin Gastroenterol*. 2001 Oct;15(5):739–753. doi:10.1053/bega.2001.0232.
- Altman RD, Gold GE. Atlas of individual radiographic features in osteoarthritis, revised. *Osteoarthritis Cartilage*. 2007;15 Suppl A:A1–56. doi:10.1016/j.joca.2006.11.009.
- King LK, Mahmoudian A, Waugh EJ, et al. "You don't put it down to arthritis": A qualitative study of the first symptoms recalled by individuals with knee osteoarthritis. *Osteoarthr Cartil Open*. 2023 Dec 16;6(1):100428. doi:10.1016/j.jocarto.2023.100428.
- Cubukcu D, Sarsan A, Alkan H. Relationships between pain, function and radiographic findings in osteoarthritis of the knee: a cross-sectional study. *Arthritis*. 2012;2012:984060. doi:10.1155/2012/984060
- Okano T, Filippucci E, Di Carlo M, et al. Ultrasonographic evaluation of joint damage in knee osteoarthritis: feature-specific comparisons with conventional radiography. *Rheumatology (Oxford)*. 2016 Nov;55(11):2040–2049. doi:10.1093/rheumatology/kew304.
- Abraham AM, Pearce MS, Mann KD, et al. Population prevalence of ultrasound features of osteoarthritis in the hand, knee and hip at age 63 years: the Newcastle thousand families birth cohort. *BMC Musculoskelet Disord*. 2014 May 19;15:162. doi:10.1186/1471-2474-15-162.
- Nevalainen MT, Kauppinen K, Pylväläinen J, et al. Ultrasonography of the late-stage knee osteoarthritis prior to total knee arthroplasty: comparison of the ultrasonographic,

## ORIGINAL INVESTIGATIONS

radiographic and intra-operative findings. *Sci Rep*. 2018 Dec 10;8(1):17742. doi:10.1038/s41598-018-35824-3.

17. Koski JM, Kamel A, Waris P, et al. Atlas-based knee osteophyte assessment with ultrasonography and radiography: relationship to arthroscopic degeneration of articular cartilage. *Scand J Rheumatol*. 2016;45(2):158-164. doi:10.3109/03009742.2015.1055797.

18. Serban O, Porojan M, Deac M, et al. Pain in bilateral knee osteoarthritis – correlations

between clinical examination, radiological, and ultrasonographical findings. *Med Ultrason*. 2016 Sep;18(3):318-325. doi:10.11152/mu.2013.2066.183.pin.

19. He ZJ, Li SL, Zou JH, et al. Pain-related risk factors among radiologic stages of knee osteoarthritis: data from the Osteoarthritis Initiative. *Arthritis Care Res (Hoboken)*. 2023 Jun;75(6):1333-1339. doi:10.1002/acr.24997.

20. Abourazzak F, Talbi S, Lazrak F, et al. Does metabolic syndrome or its individual

components affect pain and function in knee osteoarthritis women? *Curr Rheumatol Rev*. 2015;11(1):8-14. doi: 10.2174/1573397111666150522093337.

21. Sanchez-Lopez E, Coras R, Torres A, et al. Synovial inflammation in osteoarthritis progression. *Nat Rev Rheumatol*. 2022 May; 18(5):258-275. doi:10.1038/s41584-022-00749-9.

Received/Reviewed/Accepted  
07.02.2025/21.04.2025/27.04.2025

**Conflict of Interest Statement**

This article was prepared within the framework of a research project (state assignment №1021051403074-2).

The investigation has not been sponsored. There are no conflicts of interest. The authors are solely responsible for submitting the final version of the manuscript for publication. All the authors have participated in developing the concept of the article and in writing the manuscript. The final version of the manuscript has been approved by all the authors.

Khalmetova A.R. <https://orcid.org/0000-0002-0447-4110>

Lila A.M. <https://orcid.org/0000-0002-6068-3080>

Taskina E.A. <https://orcid.org/0000-0001-8218-3223>

Alekseeva L.I. <https://orcid.org/0000-0001-7017-0898>

Savushkina N.M. <https://orcid.org/0000-0001-8562-6077>

Kashevarova N.G. <https://orcid.org/0000-0001-8732-2720>

Strebkova E.A. <https://orcid.org/0000-0001-8130-5081>

Alekseeva O.G. <https://orcid.org/0000-0003-1852-1798>