ORIGINAL INVESTIGATIONS

Prediction of the development of postoperative pain in patients with late-stage knee osteoarthritis based on the expression of genes for degradation of the extracellular matrix, inflammation and apoptosis in the blood

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About 10–40% of patients with osteoarthritis (OA) are not satisfied with the results of total arthroplasty (TA) of large joints. At the same time, the most common complication associated with the ineffectiveness of TA is postoperative pain (PP).

Objective: *to identify genes whose expression in the peripheral blood before TA is associated with an increased risk of PP developing.*

Patients and methods. *Before TA, the blood of 50 patients with late-stage knee OA was examined; the control group consisted of 26 healthy individuals. The level of pain was assessed using the visual analog scale (VAS), the BPI short questionnaire, and the WOMAC index; the presence of neuropathic pain was assessed using the DN4 and PainDETECT questionnaires. The development of PP was determined 3 and 6 months after TA. The levels of matrix metalloproteinase protein (MMP) 9 and tissue inhibitor of metalloproteinase (TIMP) 1 were quantified by ELISA. Total RNA isolated from blood was used to determine the expression of caspase 3, MMP9, TIMP1, cathepsins K and S, tumor necrosis factor (TNF) α, interleukin (IL) 1β, and cyclooxygenase 2 genes using a quantitative real-time reverse transcriptase polymerase chain reaction.*

Results and discussion. *PP according to VAS ≥30 mm was noted in 17 patients. Before TA, these patients had significantly increased expression of cathepsins K and S, caspase 3, TIMP1, IL1β, and TNFα genes compared to other patients with OA. ROC analysis revealed a statistically significant relationship between the expression of these genes and the likelihood of developing pain after TA.*

Conclusion. *High expression of genes associated with degradation of the extracellular matrix (catepsins S and K, TIMP1), inflammation (IL1β, TNFα), and apoptosis (caspase 3) can serve as an important biomarker for the development of PP in patients with knee OA. To confirm the value of preoperative gene expression testing in predicting the onset of PP, further studies involving large cohorts of patients are needed.*

Key words: *knee osteoarthritis; prediction of postoperative pain; gene expression; peripheral blood.*

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Osteoarthritis (OA) is one of the most common diseases of the musculoskeletal system. According to the Global Burden of Disease Study, more than 500 million people suffered from OA in 2019 [1]. Effective and safe treatment of this disease is one of the priorities of medical science.

The modern concept of OA therapy involves an integrated approach using a combination of non-pharmacological and pharmacological methods (with mandatory consideration of comorbidity). This approach improves the patient's condition by reducing or completely eliminating pain, increasing functional and professional activity, optimizing the psychological state and overall quality of life.

However, in some patients, despite conservative treatment, progression of the disease is noted, which leads to the need for total joint arthroplasty (TA). Primary arthroplasty is a widely used and effective method of surgical treatment of OA of large joints. In the Russian Federation, according to the reports of the Federal State Budgetary Institution "National Research Center for Traumatology and Orthopaedics named after N.N. Priorov" of the Ministry of Health of Russia, in the period from 2014 to 2018, the number of primary TA of the knee joint (KJ) increased from 36,843 to 47,945, which reflects the global trend [2, 3]. Thus, in 2017, 911,000 endoprosthetics of this joint were performed in the USA, 191,000 in Germany, and 125,000 in the UK [3].

At the same time, not in all cases there is a high level of satisfaction with the results of TA – about 10–40% of patients note the ineffectiveness of this type of treatment. One of the main reasons for this is the development of postoperative pain (PP) [4], the main predictors of which have not yet been elucidated. The occurrence of pain and its severity can be influenced by the patients' expectations from the operation, their age, gender, ethnicity, marital and socioeconomic statuses, psychological characteristics, mental health, etc. In recent years, there is increasing evidence that increased anxiety, depression, sleep disturbance, catastrophization of pain, subjectively perceived injustice are directly related to the chronicity of pain after TA of the KJ.

A recently published systematic review including 181 clinical studies demonstrated that depression and anxiety are the main

causes of long-term pain and functional impairment after TA [5]. In addition, PP itself is heterogeneous (nociceptive, neuropathic, and neuroplastic/dysfunctional) and often has a mixed origin, which requires a consultation of related specialists and the use of centrally acting drugs from the group of anticonvulsants or antidepressants.

The identification of predictors of the development of PP is an urgent task of traumatology and orthopaedics. Finding out the causes of its occurrence will improve the outcomes of surgical intervention. Currently, there is a search for biochemical and genetic biomarkers that will help predict the development of PP. In particular, it has been shown that many cytokines, chemokines, metalloproteinases (MMPs), adhesion molecules, growth factors, etc. are associated with the intensity of pain in OA: interleukin (IL) 6, IL7, IL8, IL10, IL12, IL13, IL1β, tumour necrosis factor (TNF) α, C-X-C-chemokine ligand (CXCL) 10, interferon (IFN) γ, MMP3, MMP13, C-C-chemokine ligand (MCP) 1, group of highly mobile proteins (HMGB) 1, C-C-chemokine ligand 22 (MDC), ALG1-encoded chitobiosyldiphosphodolichol-beta-mannosyltransferase (MT) 1, macrophage migration inhibitory factor (MIF), TIMP1, C-terminal cross-linked collagen type II telopeptide (CTX) II, cartilage oligomeric matrix protein (COMP), lectin domain C-type containing 11A (SCGF) β, vascular endothelial growth factor (VEGF), transforming growth factor (TGF) β2, vascular cell adhesion protein (cVCAM), cell adhesion molecule (cICAM), protein that cleaves CRP by MMP (CRPM), and brain-derived neurotropic factor (BDNF) [6]. A. Pearle et al. [7] found in OA patients a relationship between the level of CRP in the blood serum and the concentration of IL6 in the synovial fluid, as well as the intensity of pain. There is evidence that high concentrations of TNFα, MMP13 and IL6 in the synovial fluid are predictors of the development of postoperative pain 2 years after arthroplasty [8]. A number of studies have confirmed the existence of a relationship between BDNF, TIMP, and CRPM and neuroplastic as well as neuropathic components of pain [9]. It has been noted that MMP9 and intracellular caspases contribute to the induction of neuropathic pain [10, 11], while the expression of the MMP2 and cathepsin S genes contributes to its maintenance due to the cleavage of the transmembrane chemokine on the surface of neurons [12]. Other authors have shown that changes in TIMP expression in astrocytes are associated with the development of chronic neuroinflammation and hyperalgesia [13]. These data suggest that the determination of the expression of some of these genes can be used as predictors of the development of potential postoperative complications even before TA. It should be emphasized that all of the above proteins and their encoding genes are expressed in the nervous tissue, cartilage, and peripheral blood cells, while cathepsin K expression demonstrates a significant relationship between chondrocytes and blood cells and is considered as an obligate marker of extracellular matrix renewal [14].

The aim of the study was to determine the genes whose expression in the blood of patients with OA is associated with the development of pain after TA of the KJ.

Patients and methods. The prospective study included 50 patients with knee OA who met the ACR criteria (American College of Rheumatology) [15–29], and underwent TA in V.A. Nasonova Research Institute of Rheumatology in 2018–2019. The mean age of the patients was 67.6±7.5 (54–82) years. Before TA, all patients had severe pain and dysfunction of the KJ (reported by both patients and physicians), radiological changes corresponding to stage III–IV of OA (according to Kellgren–Lawrence), in all cases there was no effect of conservative therapy for at least 6 months.

Exclusion criteria were: any previous KJ surgery; the presence of systemic inflammatory rheumatic diseases; oncological, infectious, significant endocrine or other visceral pathology that can cause damage to the musculoskeletal system; aseptic necrosis of the femur or tibia; taking drugs containing oestrogen, progesterone, glucocorticoids, bisphosphonates and alfacalcidol.

The control group consisted of 26 healthy individuals comparable in age to the patients of the main group (mean age 65.8±7.3 [42–74]) years, who did not have significant concomitant pathology and knee OA.

The study was approved by the local ethical committee of V.A. Nasonova Research Institute of Rheumatology. Informed consent was obtained from all study participants.

Before surgery, the level of pain was determined using a visual analogue scale (VAS), the brief pain questionnaire (Brief Pain Inventory, BPI) [16], and the WOMAC index [17]. To identify neuropathic pain, the PainDETECT and DN4 (Douleur Neuropathique en 4 Questions) questionnaires were used [18]; depression and anxiety were assessed using Hospital Anxiety and Depression Scale (HADS) [19].

The development of PP (≥30 mm according to VAS) was assessed 3 and 6 months after the TA and discharge of the patient from the hospital based on the results of a telephone survey.

Quantification of MMP9 and TIMP1 protein levels. Peripheral blood (10 ml) was collected from 07:00 to 09:00 in Vacutainer tubes containing ethylenediaminetetraacetic acid (BDH, UK). Ficoll density gradient was used to fractionate whole blood. Peripheral blood mononuclear cells located in interphase were harvested and washed twice with phosphate-buffered saline. The resulting blood cells were frozen and stored at -80°C until protein extraction. The concentrations of MMP9 (BMS2016-2) and TIMP1 (BMS2018) were determined in isolated PBMCs (peripheral blood mononuclear cells) using commercially available kits (Bender MedSystems GmbH, Austria) for enzyme-linked immunosorbent assay (ELISA) according to the manufacturer's instructions. The results were expressed per μg DNA measured in lysates of PBMCs.

Isolation of total RNA and reverse transcription (RT) reaction. To determine gene expression, total RNA was isolated from 100 μl of whole blood immediately after it was obtained using the Extract RNA reagent (Evrogen, Russia) in accordance with the manufacturer's recommendations. Total RNA had A260/290>1.9. The RT reaction was carried out using the MMLV RT kit containing M-MLV reverse transcriptase, random hexanucleotide primers, and total RNA, in accordance with the manufacturer's recommendations (Evrogen, Russia).

Quantitative real-time PCR. TaqMan ready to use primers and probes (Applied Biosystems, USA) were used for the analysis of gene expression of human genes: cathepsin S (Hs00175407_m1), cathepsin K (Hs00166165_m1), caspase 3 (Hs00263337_m1), TNFα (Hs00174128_m1), IL1β (Hs00174097_m15), MMP9 (Hs00234579_m1), TIMP1 (Hs00171558_m1). β-actin was used as an endogenous control. Gene expression was quantified by real-time polymerase chain reaction (PCR) (Quant Studio 5, Applied Biosystems, USA). A volume of 1 μl of the RT product was subjected to real-time PCR in 15 μl of the total reaction mixture containing 7.5 μl of TaqMan Universal PCR Master Mix (Applied Biosystems, USA), 900 nM sense and antisense primers,

Table 1. Comparative characteristics of patients with OA before TA of the KJ

Index	1 group (n=17)	2 group (n=33)	*p*
Age, years, Me [25; 75 percentile]	70 [64; 75]	68 [61; 72]	0.70
OA stage, n (%):			
III	12 (71)	23 (70)	0.94
IV	5 (29)	10 (30)	0.94
BMI, kg/m^2, Me [25; 75 percentile]	32.4 [27.1; 34.5]	29.1 [27.3; 32,1]	0.31
Body weight, n (%):			
normal	1 (6)	2 (6)	100
overweight	5 (29)	17 (51.5)	0.14
Obesity class 1	10 (59)	11 (33.5)	0.08
Obesity class 2	1 (6)	3 (9)	0.71
Disease duration, years Me [25; 75 percentile]	8 [5.5; 12]	10 [5; 14]	0.90
ESR, mm/h, Me [25; 75 percentile]	8,5 [5.5; 19]	12 [10; 25]	0.27
Pain (VAS), mm, Me [25; 75 percentile]	60 [60; 70]	70 [60; 70]	0.89
DN4 score, Me [25; 75 percentile]	2 [1.5; 3]	2 [1; 2]	0.24
PainDETECT, Me [25; 75 percentile]	7 [4; 9]	4 [2; 9]	0.28
HADS anxiety, Me [25-й; 75-й percentile]	7 [4,5; 9,5]	5.5 [3,5; 7,5]	0.07
HADS depression, Me [25; 75 percentile]	8.5 [6; 10,5]	7 [6; 9]	0.25
BPI (pain severity), Me [25; 75 percentile]	4.5 [3.9; 5.4]	5.5 [4.5; 5.8]	0.07
WOMAC, mm, Me [25; 75 percentile]: total	1130 [1020;1260]	1150 [950; 1200]	0.99
Total pain	230 [195; 260]	230 [205; 270]	0.72
Total stiffness	100 [75; 110]	100 [80; 115]	0.65
FN	820 [710; 855]	760 [685; 830]	0.48
AH, %	65	30	<0,01
Cardiovascular disease, %	6	15	0.35

Note. BMI - body mass index; FN - functional insufficiency.

50 nM probe, and template cDNA. After one step at 50°C for 2 min and an initial activation at 95°C for 10 min, the reaction mixtures were subjected to 40 amplification cycles (15 s at 95°C for denaturation and 1 min for annealing and elongation at 60°C). Relative mRNA expression was determined by the ΔΔCT method, which is described in detail in the manufacturer's instructions (Applied Biosystems, USA). The ΔCT value was calculated by subtracting the CT value for the β-actin housekeeping gene from the CT value for each sample. The ΔΔCT was then calculated by subtracting the ΔCT value for the control (each healthy patient) from the ΔCT value for each OA patient. Each PCR was performed in duplicate. Three controls were consistently negative for each reaction.

Statistical data processing was performed using Statistica 10 for Windows and SPSS version 22 (IBM, USA), including conventional methods of parametric and nonparametric analysis. For statistical analysis of normally distributed data, Pearson's rank correlations and unpaired Student's t-test were used to compare controls and subgroups of patients with OA. ROC curve analyses are presented as areas under the curve (AUC) and 95% confidence intervals (CI). The diagnostic performance of gene expression values was assessed using sensitivity and specificity at cut-off points. A two-tailed Z-test was used to compare percentages. Differences were considered statistically significant at $p<0.05$.

Results. Comparative analysis of baseline clinical parameters of patients with OA who developed or did not develop PP after 3–6 months. Three months after TA of the KJ, 17 (34%) of 50 patients had PP (mean value 34.3±2.3 mm according to VAS), which persisted by the 6th month of follow-up (38.6±2.5 mm according to VAS). Depending on the presence or absence of PP, patients were divided into two groups: with PP (Group 1, n=17) and without PP (Group 2, n=33). Comparison of both groups before surgery did not reveal significant differences in most parameters (Table 1). It was noted that arterial hypertension (AH) was recorded significantly more often in persons with PP.

Expression of genes in the blood. In group 1, a statistically significant increase in the expression of cathepsin S (p=0.0006), cathepsin K (p=0.007), caspase 3 (p=0.002), TIMP1 (p=0.017), IL1β (p=0, 01) and TNFα (p=0.006) compared with patients of the 2nd group was observed

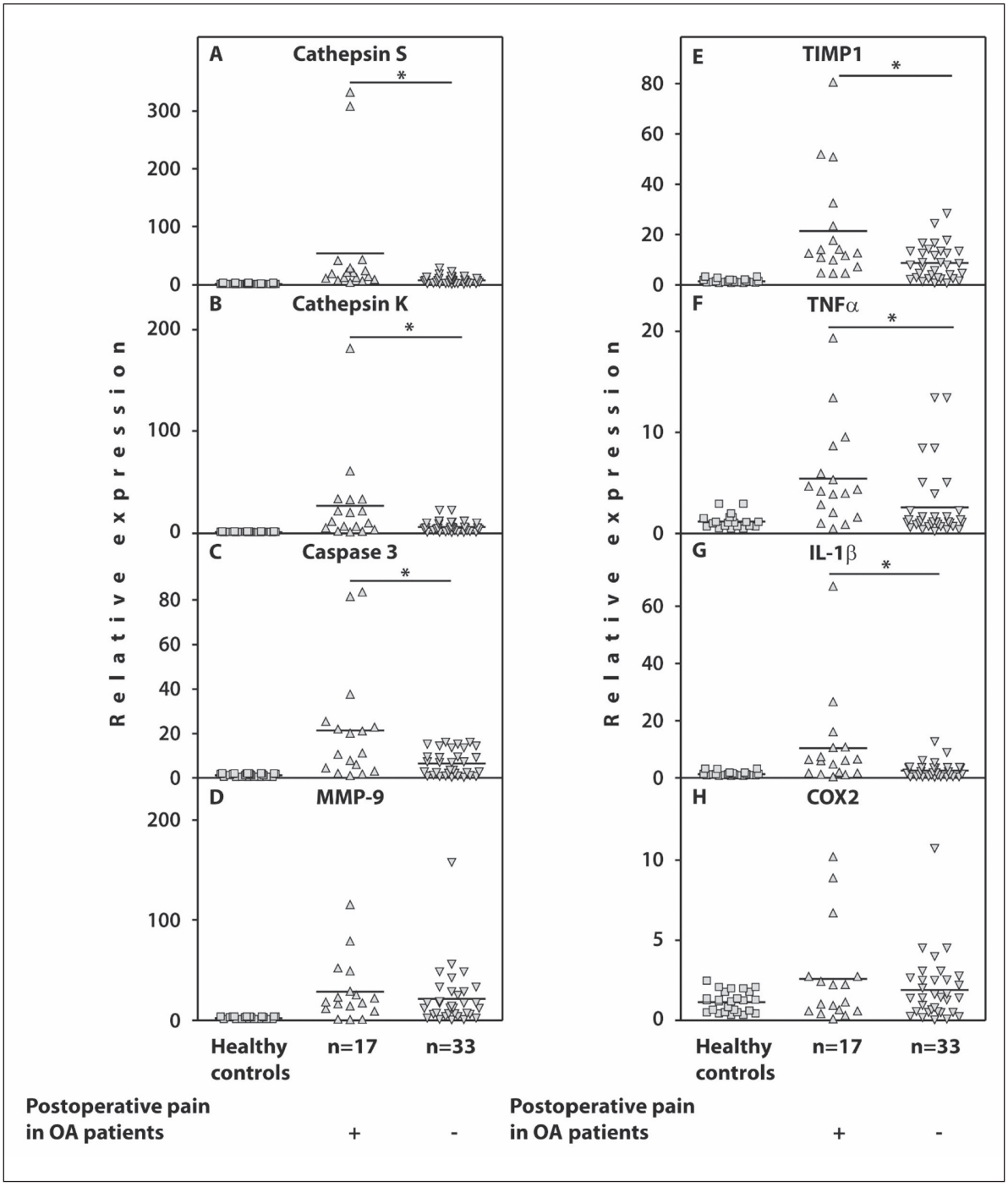

Fig. 1. *Relative expression of cathepsin S (A), cathepsin K (B), caspase 3 (C), MMP9 (D), TIMP1 (E), TNF α (F), IL1β (G), and COX2 (H) genes determined with using real-time PCR in the blood of patients who developed (n=17) or did not develop (n=33) PP compared with healthy individuals (n=26). Gene expression levels in healthy individuals are taken as 1.0, which is necessary for relative quantification in accordance with the real-time PCR protocol.*
** – significant differences between the studied groups of patients with OA*

(Fig. 1). Intergroup differences in the expression of the MMP9 and COX2 genes were not revealed.

Levels of MMP9 and TIMP1 proteins in blood cells. To further study the clinical significance of assessing the relative expression of the studied genes in the blood of patients with advanced OA, the levels of MMP9 and TIMP1 proteins in the blood cell fraction were analysed. The levels of TIMP1 protein in the examined individuals with PP were significantly higher than in patients without pain, while the concentrations of the MMP9 protein did not differ significantly in the studied groups (Fig. 2).

Correlation analysis of gene expression with clinical and radiological parameters. Correlation analysis revealed a positive re-

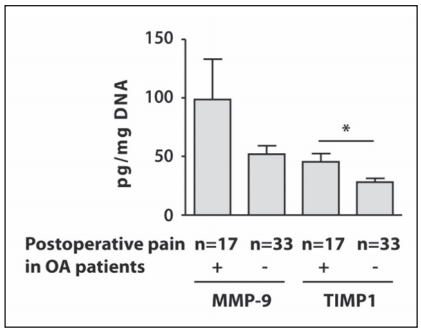

Fig. 2. *MMP9 and TIMP1 protein concentrations measured by ELISA in blood cells of patients with advanced OA who developed (n=17) or did not (n=33) PP. * – significant differences between the studied groups of patients*

lationship between OA stage, PainDETECT index, and pain at night (Table 2). BPI pain severity and HADS anxiety scores correlated with total WOMAC score. In addition, a positive relationship was demonstrated between the DN4 and PainDETECT scores and these scores and depression as measured by the HADS questionnaire.

Significant associations between the expression of the examined genes and many clinical and radiological parameters were confirmed (n=50). In particular, a positive relationship was found between BMI and gene expression of cathepsin S (r=0.307, p=0.03), cathepsin K (r=0.335, p=0.01), caspase 3 (r=0.307, p=0, 03), MMP9 (r=0.439, p=<0.01) and TIMP1 (r=0.329, p=0.02). TIMP1 gene expression negatively correlated with VAS pain scores (r=-0.317, p=0.02) and total WOMAC value (r=-0.290, p=0.04). DN4 parameters were positively associated with TNFα (r=0.330, p=0.02) and IL1β (r=0.496, p=<0.01) gene expression. IL1β gene expression also positively correlated with PainDETECT parameters (r=0.313, p=0.04).

To assess the prognostic value of the expression of these genes, we performed a ROC analysis (Fig. 3), which confirmed a statistically significant relationship between the expression of the studied genes before TA with the likelihood of developing PP: the threshold values for the expression of the studied genes were: 9.09 for cathepsin S (AUC =0.835; 95% CI 0.721–0.949; p=0.000), 5.96 for cathepsin K (AUC=0.743; 95% CI 0.589–0.898; p=0.005), 7.67 for caspase 3 (AUC=0.732; 95 % CI 0.577–0.886; p=0.008), 9.12 for TIMP1 (AUC=0.741; 95% CI 0.603–0.879; p=0.006), 1.88 for TNFα (AUC=0.738; 95% CI 0.589–0.887; p=0.006) and 3.3 for IL1β (AUC=0.763; 95% CI 0.615–0.91; p=0.003).

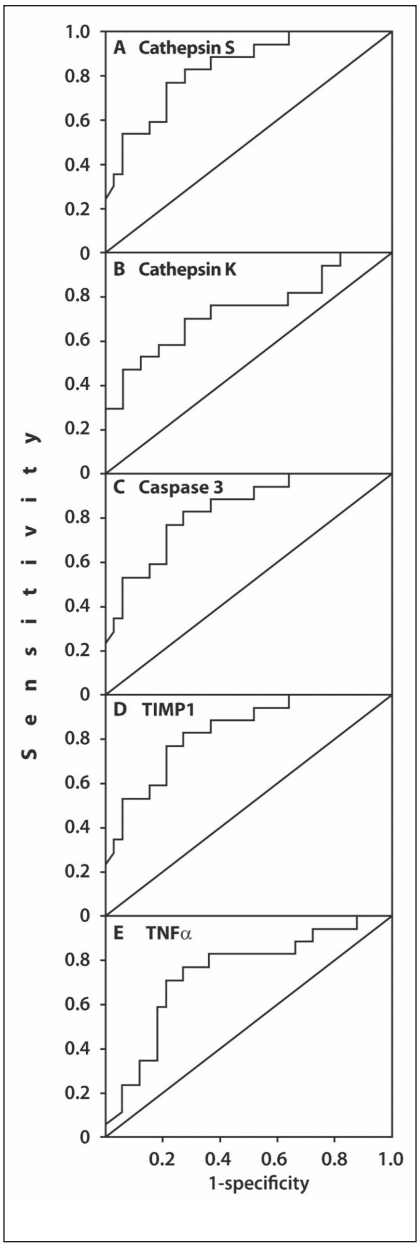

Fig. 3. *Areas under the curve (AUC) demonstrating the relationship between gene expression in the blood of patients with advanced OA and development (n=17) or did not development (n=33) PP*

Discussion. Previously, several independent predictors of pain persistence after TA of the KJ have been identified based on the clinical characteristics of patients [20]. At the same time, other studies have shown that preoperative values of clinical and biopsychosocial variables do not predict the development of PP, since pain is a subjective sensation and includes physiological, cognitive, and emotional components [21]. In our work, blood expression of genes associated with the renewal of the extracellular matrix (cathepsins S and K and TIMP1), apoptosis (caspase 3), and inflammation (TNFα and IL1β) was used as a prognostic marker of PP. At the same time, the expression of these genes was significantly higher in patients with OA who developed PP, compared with persons satisfied with the results of TA. The high prognostic value of the expression of these genes in the development of this complication was confirmed by the large area under the ROC curves, which allows them to be used to predict the development of PP. Our results are consistent with previously published observations, according to which an increased concentration of cytokines in the synovial fluid correlates with pain [22] and is an independent predictor of the development of pain after TA of the KJ [9]. In addition, previous studies have shown that increased MMP9 activity contributed to an increase in pain in response to injury, which can be counteracted by TIMP1 activity [23]. Therefore, a significant increase in TIMP1 gene expression in our study, observed in patients who developed pain after surgery, as well as a negative correlation between TIMP1 gene expression and pain indices may additionally indicate a high and uncontrolled overall expression of MMP genes and pro-inflammatory cytokines that respond for maintaining pain. Moreover, the development of PP in the examined patients with OA can be explained by a high blood concentration of cathepsin S before surgery, which blocks the activation of T-lymphocytes and the release of peripheral cytokines [24]. Increased expression of the cathepsin K gene associated with PP may be associated with changes in mechanosensitivity and increased activity of the afferent nerve of the KJ, which has recently been demonstrated in studies on animal models of OA [25], while an increase in caspase expression is the result of an increase in pain sensitivity due to activation of sensory neurons, which was previously observed in patients with diabetes mellitus [26].

In our study, patients of both groups practically did not differ in the degree of X-ray damage to the knee joint, the duration of the disease, the intensity of pain, and the level of ESR. These data indicate that clinical and instrumental determinants are not significant predictors of the development of PP. Similar results were obtained by other authors [27], although in

some studies of OA a relationship was found between a lower level of pain before surgery and a less favourable functional outcome [28]. At the same time, a positive correlation of baseline indicators according to the DN4 questionnaire with the expression of TNFα and IL1β genes in peripheral blood may indicate an exacerbation of symptoms of neuropathic pain in conditions of inflammation, as was suggested in previously published studies [29].

There is evidence in the literature that the presence of comorbid conditions, including AH, is associated with the development of PP [30]. According to our data, AH was also significantly more common in patients of the 1st group. There is no doubt that anxiety and depressive states increase the risk of developing unsatisfactory outcomes after surgery, which has been demonstrated by many studies [5, 28], including ours. In this work, as in the previous studies by other authors [31], a relationship was found between neuropathic pain symptoms and pain intensity in the preoperative period: a positive correlation of pain and DN4 indicators with PainDETECT, depression/anxiety (HADS), and pain severity (BPI). At the same time, a high degree of pain severity according to BPI before surgery was associated with a more favourable prognosis in the postoperative period (significant improvement in terms of pain relief), which was confirmed in other studies [32].

Table 2. Correlation coefficients between clinical and biopsychosocial indicators and their significance, assessed before TA of the KJ (n=50)

Index	Pain at night (VAS), mm	Total pain	Total physical function	Total WOMAC	DN4 scores	HADS depression scores
OA radiological stage	0.442 p=0.04		0.512 p=0.01			
PainDETECT scores	0.525 p=0.01				0.708 p<0.01	0.546 p=0.03
HADS anxiety scores			0.551 p=0.01	0.472 p=0.03		0.678 p<0.01
HADS depression scores					0.312 p=0.03	
BPI pain severity scores		0.628 p<0.01	0.541 p=0.01	0.590 p<0.01		

Conclusion. Therefore, high basal expression of genes associated with the degradation of the extracellular matrix (catepsins S and K, TIMP1), inflammation (TNFα and IL1β), and apoptosis (caspase 3), assessed in the blood of patients with the late stage of OA before KJ arthroplasty, may be an important biomarker for the development of PP. Further studies involving large cohorts of patients are needed to confirm our findings on the importance of preoperative gene expression testing for predicting the development of PP. These data will contribute to the maximum alleviation of the condition of patients with a late stage of OA, who are recommended TA of the KJ.

REFERENCES

1. Global Burden of Disease Collaborative Network. Global Burden of Disease Study 2019 (GBD 2019) results. 2020. http://ghdx.healthdata.org/gbdresults-tool.
2. Андреева ТМ, Огрызко ЕВ, Попова ММ. Травматизм, ортопедическая заболеваемость, состояние травматолого-ортопедической помощи населению России в 2014 году. Москва: НМИЦ ТО им. Н.Н Приорова; 2015.
[Andreeva TM, Ogryzko EV, Popova MM. *Travmatizm, ortopedicheskaya zabolevaemost', sostoyanie travmatologo-ortopedicheskoi pomoshchi naseleniyu Rossii v 2014 godu* [Traumatism, orthopedic morbidity, the state of traumatological and orthopedic care to the population of Russia in 2014]. Moscow: NMITs TO im. N.N Priorova; 2015].
3. Андреева ТМ, Огрызко ЕВ, Попова ММ. Травматизм, ортопедическая заболеваемость, состояние травматолого-ортопедической помощи населению России в 2018 году. Москва: НМИЦ ТО им. Н.Н Приорова; 2019.
[Andreeva TM, Ogryzko EV, Popova MM. *Travmatizm, ortopedicheskaya zabolevaemost', sostoyanie travmatologo-ortopedicheskoi pomoshchi naseleniyu Rossii v 2014 godu* [Traumatism, orthopedic morbidity, the state of traumatological and orthopedic care to the population of Russia in 2018]. Moscow: NMITs TO im. N.N Priorova; 2019].
4. Abdelaal MS, Restrepo C, Sharkey PF. Global Perspectives on Arthroplasty of Hip and Knee Joints. *Orthop Clin North Am*. 2020 Apr;51(2):169-76. doi: 10.1016/j.ocl.2019.11.003. Epub 2020 Feb 6.
5. Wylde V, Hewlett S, Learmonth ID, et al. Persistent pain after joint replacement: prevalence, sensory qualities, and postoperative determinants. *Pain*. 2011 Mar;152(3):566-72. doi: 10.1016/j.pain.2010.11.023. Epub 2011 Jan 15.
6. Nakano N , Shoman H, Olavarria F, et al. Why are patients dissatisfied following a total knee replacement? A systematic review. *Int Orthop*. 2020 Oct;44(10):1971-2007. doi: 10.1007/s00264-020-04607-9. Epub 2020 Jul 8. 8.
7. Pearle A, Scanzello C, George S, et al. Elevated high-sensitivity C-reactive protein levels are associated with local inflammatory findings in patients with osteoarthritis. *Osteoarthritis Cartilage*. 2007 May;15(5):516-23. doi: 10.1016/j.joca.2006.10.010. Epub 2006 Dec 5.
8. Gandhi R, Santone D, Takahashi M, et al. Inflammatory Predictors of Ongoing Pain 2 Years Following Knee Replacement Surgery. *Knee*. 2013 Oct;20(5):316-8. doi: 10.1016/j.knee.2012.10.015. Epub 2012 Nov 14.
9. Fayet M, Hagen M. Pain characteristics and biomarkers in treatment approaches for osteo-

arthritis pain. *Pain Manag.* 2021 Jan;11(1): 59-73. doi: 10.2217/pmt-2020-0055. Epub 2020 Oct 30.
10. Clark AK, Yip PK, Grist, et al. Inhibition of Spinal Microglial Cathepsin S for the Reversal of Neuropathic Pain. *Proc Natl Acad Sci U S A.* 2007 Jun 19;104(25):10655-60. doi: 10.1073/pnas.0610811104. Epub 2007 Jun 5.
11. Berta T, Park CK, Xu ZZ, et al. Extracellular caspase-6 drives murine inflammatory pain via microglial TNF-alpha secretion. *J Clin Invest.* 2014 Mar;124(3):1173-86. doi: 10.1172/JCI72230. Epub 2014 Feb 17.
12. Kawasaki Y, Xu ZZ, Wang X, et al. Distinct roles of matrix metalloproteases in the early- and late-phase development of neuropathic pain. *Nat Med.* 2008 Mar;14(3):331-6. doi: 10.1038/nm1723. Epub 2008 Feb 10.
13. Gardner J, Borgmann K, Deshpande MS, et al. Potential mechanisms for astrocyte-TIMP-1 downregulation in chronic inflammatory diseases. *J Neurosci Res.* 2006 May 15;83(7):1281-92. doi: 10.1002/jnr.20823.
14. Tchetina EV, Makarov SA, Kuzin AN. Coordinated expression of the genes associated with cell growth (mTOR), collagen degradation (cathepsin K), and lipid metabolism (fatty acid synthase) in the peripheral blood and articular cartilage of the end-stage osteoarthritic patients. *Ann Rheum Dis.* 2013;72(Suppl 3):694.
15. Kellgren JH, Lawrence JS. Radiological assessment of osteoarthrosis. *Ann Rheum Dis.* 1957 Dec;16(4):494-502. doi: 10.1136/ard.16.4.494.
16. Cleeland CS, Ryan KM. Pain assessment: global use of the Brief Pain Inventory. *Ann Acad Med Singap.* 1994 Mar;23(2):129-38.
17. Bellamy, N. WOMAC Osteoarthritis Index: A User's Guide.London: University of Western Ontario; 1995.
18. Freynhagen R, Baron R, Gockel U, Tolle TR. PainDETECT: a new screening questionnaire to identify neuropathic components in patients with back pain. *Curr Med Res Opin.* 2006 Oct;22(10):1911-20. doi: 10.1185/030079906X132488.
19. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand.* 1983 Jun;67(6):361-70. doi: 10.1111/j.1600-0447.1983.tb09716.x.
20. Lewis GN, Rice DA, McNair PJ, et al. Predictors of persistent pain after total knee arthroplasty: a systematic review and meta-analysis. *Br J Anaesth.* 2015 Apr;114(4):551-61. doi: 10.1093/bja/aeu441. Epub 2014 Dec 26.
21. Barroso J, Wakaizumi K, Reckziegel D, et al. Prognostics for pain in osteoarthritis: Do clinical measures predict pain after total joint replacement? *PLoS One.* 2020 Jan 8;15(1): e0222370. doi: 10.1371/journal.pone.0222370. eCollection 2020.
22. Li L, Li Z, Li Y, et al. Profiling of inflammatory mediators in the synovial fluid related to pain in knee osteoarthritis. *BMC Musculoskelet Disord.* 2020 Feb 14;21(1):99. doi: 10.1186/s12891-020-3120-0.
23. Knight BE, Kozlowski N, Havelin J, et al. TIMP-1 Attenuates the Development of Inflammatory Pain Through MMP-Dependent and Receptor-Mediated Cell Signaling Mechanisms. *Front Mol Neurosci.* 2019 Sep 20;12:220. doi: 10.3389/fnmol.2019.00220. eCollection 2019.
24. Eckert WA 3rd, Wiener JJM, Cai H, et al. Selective Inhibition of Peripheral Cathepsin S Reverses Tactile Allodynia Following Peripheral Nerve Injury in Mouse. *Eur J Pharmacol.* 2020 Aug 5;880:173171. doi: 10.1016/j.ejphar.2020.173171. Epub 2020 May 11.
25. Nwosu LN, Gowler PRW, Burston JJ, et al. Analgesic effects of the cathepsin K inhibitor L-006235 in the monosodium iodoacetate model of osteoarthritis pain. *Pain Rep.* 2018 Oct 5;3(6):e685. doi: 10.1097/PR9.0000000000000685. eCollection 2018 Nov.
26. Hulse RP, Beazley-Long N, Ved N, et al. Vascular endothelial growth factor-A165b prevents diabetic neuropathic pain and sensory neuronal degeneration. *Clin Sci (Lond).* 2015 Oct 1;129(8):741-56. doi:10.1042/CS20150124.
27. Katz NP, Paillard FC, Ekman E. Determining the clinical importance of treatment benefits for interventions for painful orthopedic conditions. *J Orthop Surg Res.* 2015 Feb 3;10:24. doi: 10.1186/s13018-014-0144-x.
28. Lungu E, Vendittoli PA, Desmeules F. Preoperative Determinants of Patient-reported Pain and Physical Function Levels Following Total Knee Arthroplasty: A Systematic Review. *Open Orthop J.* 2016 Jun 23;10:213-31. doi: 10.2174/1874325001610010213. eCollection 2016.
29. Mai L, Zhu X, Huang F, et al. p38 Mitogen-Activated Protein Kinase and Pain. *Life Sci.* 2020 Sep 1;256:117885. doi: 10.1016/j.lfs.2020.117885. Epub 2020 May 30.
30. Lingard EA, Katz JN, Wright E, et al. Kinemax Outcomes Group. Predicting the outcome of total knee arthroplasty. *J Bone Joint Surg Am.* 2004 Oct;86(10):2179-86. doi: 10.2106/00004623-200410000-00008.
31. Kurien T, Arendt-Nielsen L, Petersen KK, et al. Preoperative Neuropathic Pain-like Symptoms and Central Pain Mechanisms in Knee Osteoarthritis Predicts Poor Outcome 6 Months After Total Knee Replacement Surgery. *J Pain.* 2018 Nov;19(11):1329-41. doi: 10.1016/j.jpain.2018.05.011. Epub 2018 Jun 18.
32. Rehman Y, Lindberg MF, Arnljot K, et al. More Severe Radiographic Osteoarthritis Is Associated With Increased Improvement in Patients' Health State Following a Total Knee Arthroplasty. *J Arthroplasty.* 2020 Nov;35(11): 3131-7. doi: 10.1016/j.arth.2020.06.025. Epub 2020 Jun 17.

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