ORIGINAL INVESTIGATIONS

The development of postoperative pain in patients with late-stage knee osteoarthritis is associated with impaired metabolism and transport of fatty acids in blood cells

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Objective: *to evaluate differences in the expression of genes associated with β-oxidation and de novo synthesis of fatty acids (FAs) in the blood of patients with the late stage of knee osteoarthritis (OA) before total knee arthroplasty (TA) depending on the development of postoperative pain (POP) in order to determine the molecular mechanisms responsible for the development of chronic POP.*

Material and methods. *Blood of 50 patients with stage III–IV knee OA complaining of constant pain and joint dysfunction was analyzed prior to TA. The control group consisted of 26 healthy individuals. Pain intensity was assessed using a visual analogue scale (VAS) and the BPI questionnaire. In addition, pain, stiffness and physical functioning were assessed using WOMAC index and the presence of neuropathic pain was assessed using the DN4 and PainDETECT questionnaires. The development of POP was assessed 3 and 6 months after TA. Total RNA isolated from blood was used to determine the expression of ACLY, ACC1, MLYCD, FASN and CPT1A genes by real-time quantitative reverse transcriptase-polymerase chain reaction.*

Results and discussion. *POP ≥30 mm by VAS was detected in 17 patients. Before TA, the expression of most of the analyzed genes was significantly increased compared to controls, while the expression of the FASN gene was comparable in patients with OA and healthy individuals. There were no differences in clinical and functional parameters between the groups of patients with and without POP. Before surgery, patients who subsequently developed POP had significantly higher expression of ACLY and CPT1A genes than patients who were satisfied with the results of TA. At the same time, no differences in the expression of ACC1, MLYCD and FASN were found in the groups analyzed.*

Conclusion. *The development of POP is associated with an increased supply of FAs to the mitochondria caused by overexpression of the CPT1A gene, as well as with the accumulation of acetyl-CoA, a product of high expression of the ACLY gene, which can be measured in the blood of OA patients before TA.*

Keywords: *knee osteoarthritis; prediction of postoperative pain; gene expression; fatty acid metabolism; blood.*
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Osteoarthritis (OA) of the knee joint (KJ) is characterized by loss of articular cartilage structure, remodeling of the subchondral bone, synovial inflammation and osteophyte formation [1]. The disease is associated with factors such as obesity, age, injury, gender and/or ethnicity [2]. Currently suffering from OA 7% of the world's population complaining on joint pain comprise a third of population over 65 years old [3], which is almost 500 million people, and from 1990 to 2019 this number increased by 48% [4]. Although OA is a leading cause of disability, there are currently no drugs that modify the disease [2]. In the conservative treatment of knee OA, non-steroidal anti-inflammatory drugs (NSAIDs), hyaluronic acid, glucocorticoids and symptomatic delayed-release drugs are mainly used [5]. Their effect is due to the suppression of inflammation and pain, which is the main clinical symptom that limits ability to work and patients daily self-care. In the late stages of OA, severe constant pain serves as one of the most important indications for total joint replacement (TJR). TJR is the most common method of surgical treatment of OA worldwide, the number of such surgeries increases every year and is expected to increase 7 times by 2030 [6]. Meanwhile, after TJR, pain persists in 10–40% of patients [7]. In connection with this, elucidation of the reasons influencing the outcome of TJR, would make it possible to provide OA patients with a more realistic information about the results of the surgery and optimize preoperative preparation, which is especially important due to the high cost of TJR [8].

Our previous studies predicting the development of postoperative pain (POP) showed that high expression of genes associated with inflammation, extracellular matrix degradation and apoptosis activity, can serve as an important biomarker of the formation of POP in OA [9]. Moreover, clinical parameters patients with OA were positively correlated with biopsychosocial factors (gender, age, psychological state) and expression of the studied genes [9]. Because these biomarkers are associated with metabolic disorders in OA [10], our subsequent studies were devoted to studying the association of POP with metabolic conversions of carbohydrates in patients with OA. A higher rate of glycolysis and a shortage of energy have been shown, probably due to higher activity of uncoupling of oxidation and phosphorylation in patients with POP [11].

Disturbances in energy metabolism in blood cells in patients with OA associated with POP may be caused also by the presence of metabolic syndrome, the role of which in the development and progression of knee OA has been identified relatively recently

[12]. Metabolic syndrome represents a heterogeneous disease characterized by central obesity, arterial hypertension, dyslipidaemia, elevated fasting glucose levels or diabetes mellitus, which also predisposes to the development of OA [13]. Indeed, excess body weight (index body weight – BMI – >25 kg/m^2) and obesity (BMI >30 kg/m2) have long been recognized as major risk factors of OA of KJ [14]. Moreover, a high BMI is accompanied by greater pain intensity [15]. Therefore, it is important to know how disturbances in lipid metabolism and POP are interrelated. Lipid macronutrient metabolism is associated with fatty acid (FA) metabolism, which includes catabolic processes that generate energy and anabolic processes that produce the building blocks for synthesis of other compounds [16]. During catabolism FAs produce energy, mainly in the form of adenosine triphosphate (ATP), when completely oxidized to CO2 and water through β-oxidation and in the Krebs cycle [17]. In this case, free long-chain (LC) FAs penetrate into cells involving specific transport proteins, such as the FA transport protein SLC27 family [18], and are further converted into a molecule of acyl-coenzyme A (acyl-CoA), which is transported into the mitochondrial matrix using palmitoyl-CoA transferase. Later, in the process of β-oxidation of acyl-CoA in the mitochondrial matrix, the long carbon chains of fatty acids are fragmented into a series of two-carbon (acetate) units that, in combination with CoA, form acetyl-CoA molecules, which condense with oxaloacetate to form citrate and enter into the Krebs cycle [17]. At the same time, de novo synthesis of FAs from acetyl-CoA occurs outside the mitochondria, in the cytosol. For this purpose, cytosolic citrate (formed by condensation of acetyl-CoA with oxaloacetate) is removed from the cycle Krebs and is transported through the inner mitochondrial membrane into the cytosol [19], where it is cleaved by ATP citrate lyase (ACLY) into acetyl-CoA and oxaloacetate. Oxaloacetate returns to mitochondria in the form of malate [20]. Cytosolic acetyl-CoA is carboxylated by acetyl-CoA carboxylase (ACC) to malonyl-CoA, which is the first step in the synthesis FA catalyzed by FA synthase (FASN) [21]. Regulation of de novo FA synthesis process is carried out through ACC and malonyl-CoA decarboxylase (MLYCD), which convert malonyl-CoA into acetyl-CoA and carbon dioxide and, thus, catalyze the reverse ACC reaction [22].

The purpose of the study is to evaluate differences in expression of genes associated with β-oxidation and de novo synthesis of FAs in blood of patients with late stage OA KJ before TJR depending on the development of POP and to determine the molecular mechanisms, responsible for the formation of chronic POP.

Material and methods

The prospective study included 50 patients with OA who met the ACR (American College of Rheumatology) criteria [23], which in 2018–2019 were followed up at the Federal State Budgetary Institution "Research Institute of Rheumatology named after V.A. Nasonova" (NIIR named after V.A. Nasonova) and undergone TJR. The average age of the patients was 67.6±7.5 years. Before TJR, all of them had a constant pronounced pain 60–70 mm according to VAS and dysfunction of the knee joint (according to opinion of the doctor and the patient), III–IV radiological stage of OA according to Kellgren–Lawrence [24], in all cases there was no effect of conservative therapy for a period of more than 6 months. Non-inclusion criteria: any previous TJR operations; 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 medications containing estrogen, progesterone, glucocorticoids, bisphosphonates and alfacalcidol. The control group consisted of 26 healthy individuals comparable in age to patients of the main group (average age – 65.8±7.3 years), which had no significant concomitant pathologies and OA. The study protocol was approved by the local ethical committee of V.A. Nasonova NIIR (protocol No. 32 from 12/20/2018), informed consent was obtained from all the patients. Before surgery, pain intensity was determined using a visual analogue scale (VAS), and the Brief Pain Inventory (BPI) [25] and WOMAC index [26] were also used. To identify neuropathic pain, the PainDETECT [27] and DN4 (Douleur Neuropathique en 4 Questions) questionnaires [28] were used; and for depression and anxiety – Hospital Anxiety and Depression Scale (HADS) [29]. The development of POP (≥30 mm according to VAS) was assessed 3 and 6 months after TJR and the patient's discharge from the hospital according to the results of a telephone survey.

Total RNA isolation and reverse transcription (RT) reaction

To determine gene expression, total RNA was isolated from 100 μl of whole blood immediately after its collection 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 performed 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

We used ready-made primers and probes for TaqMan analysis (Applied Biosystems, USA) for human genes: *ACLY* (Hs00982738_m1), *ACC1* (Hs01046047_m1), *MLYCD* (Hs00918031_m1), *FASN* (Hs01005622_m1) and *CPT1A* (Hs00912671_m1). Endogenous β-actin served as control. Quantitative assessment of gene expression was carried out using the real time polymerase chain reaction (PCR) (Quant Studio 5, Applied Biosystems, USA). A volume of 1 μl of RT product was subjected to Real-time PCR in 15 μl general reaction mixture containing 7.5 μl TaqMan Universal PCR Master Mix (Applied Biosystems, USA), sense and antisense primers 900 nM, probe 50 nM and template cDNA. After one stage at 50 °C for 2 min and 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 annealing and extension at 60 °C). Relative mRNA expression was determined by the ΔΔCT method, which is described in detail described in the manufacturer's instructions (Applied Biosystems, USA). The ΔCT value was calculated by subtracting the CT value for the housekeeping gene β-actin from the value CT for each sample. ΔΔCT was then calculated by subtracting the ΔCT value for the control (each healthy patient) from the ΔCT value for each OA patient. Every PCR was performed in duplicate. Three controls were invariably negative for each reaction.

Statistical data processing was performed using Statistica 10 for Windows and SPSS version 22 (IBM, USA), including generally accepted methods of parametric and nonparametric analysis. For statistical analysis, when the data deviated from the normal distribution, Spearman's rank correlations were used. Since one of the groups included less than 30 patients, nonparametric method was

used for intergroup calculations Mann-Whitney test. Comparison of percentages was performed using a two-tailed Z test. Differences were considered statistically significant at $p<0.05$.

Results

Clinical characteristics of patients with OA.

The average age of patients with OA (n=50) was 67.6±7.5 years, the median duration of the disease was 9.5 [5; 14.5] years. The patients had stage III–IV OA according to the Kellgren–Lawrence classification (35 stage III and 15 stage IV), as well as an increased BMI (on average 30.5±3.8 kg/m²). The total WOMAC score ranged from 300 to 1435 mm (average, 1064±225 mm), while the intensity of general pain reached an average of 222.8± 62.6 mm, total functional impairment, 746.5 ± 159.6 mm, total stiffness, 93.9±24.6 mm. During the 6 months before TJR, all patients experienced constant pain in the knee joint. The majority of OA patients reported mild pain at rest (average 31.3±2.2 mm), and 2 patients reported severe pain at rest (80 mm). According to the BPI questionnaire, the average pain intensity before surgery in the examined cohort was 4.8±1.1. When assessing neuropathic pain using the DN4 questionnaire, its median was 2 [1; 2.5]. One patient had neuropathic pain according to the DN4 questionnaire (>4 points). The average score on the PainDETECT questionnaire was 6.0±4.1, 1 patient had neuropathic pain (>18 points). According to HADS, 3 (0.06%) patients had abnormal anxiety (>11 points), and 14 (28%) had borderline levels of anxiety (8–10 points). In addition, 9 (18%) patients had depression (total score: 11–15), 14 (28%) had a borderline state (8–10 points) on the scale depression HADS [9]. 3 months after TJR, 17 (34%) patients had POP (average 34.3±2.3 mm according to VAS), which persisted by the 6th month of observation (on average , 38.6±2.5 mm according to VAS). Depending on the presence or absence of POP, patients were divided into two groups: with POP (group 1, n=17) and without POP (group 2, n=33).

Comparison of clinical characteristics of patients of both groups before surgery was described in detail in our previous study [9]. However, no significant differences in most parameters were observed. However, in people with POP hypertension was recorded significantly more often, which was detected in 11 (65%) patients of the 1st group and 10 (30%) patients of the 2nd group (odds ratio, OR 4.2; 95% confidence interval, CI 1.22–14.6; p=0.019). Cardiovascular diseases were present in 6 patients: 1 patient of group 1 had atherosclerosis and 5 patients of group 2 - atherosclerosis, cardiosclerosis, coronary heart disease, atrial fibrillation. In addition, the following trends were observed: patients of group 1 were slightly more likely to suffer from grade 1 obesity (p=0.08) and anxiety, according to the HADS questionnaire (p=0.07). The severity of pain before surgery was slightly higher in patients of group 2 (p=0.07) [9].

Gene expression in blood

The levels of most of the genes studied were significantly increased in both groups of patients with OA compared to controls. At the same time, the expression of the *FASN* gene in both groups of OA patients did not differ from that in healthy people (Fig. 1). In patients with POP it was revealed a statistically significant increase in *ACLY* gene levels (p=0.0001) and *CPT1A* (p=0.01), as well as a trend towards higher *ACC1* gene expression (p=0.06) compared to in patients without BE. Intergroup differences in levels *MLYCD* (p=0.12) and *FASN* (p=0.23) genes were not detected.

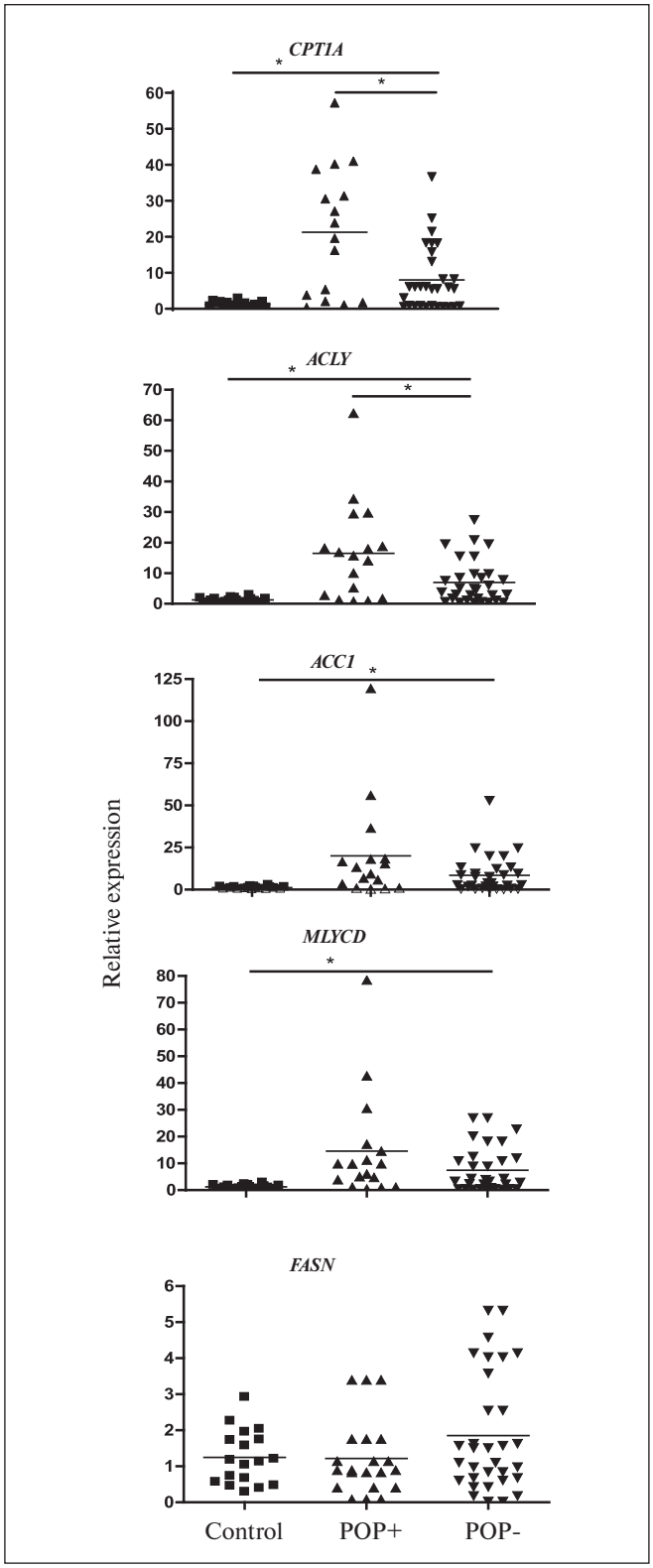

Fig. 1. *Relative expression of CPT1A, ACLY, ACC1, MLYCD and FASN genes determined by real-time PCR in the blood of patients with OA who had (ПБ+; n=17) and did not have (ПБ-; n=33) POP compared to controls (n=26). Gene expression levels in the control were set to 1.0, which is required for relative quantification according to the real-time PCR protocol. * – significant differences between the groups of patients with OA*

Correlation analysis of gene expression with biopsychosocial parameters

A positive correlation was found between PainDETECT index and *ACLY*, *MLYCD*, *FASN* gene level and *CPT1A*, and a trend toward a positive association with expression *ACC1* gene (see table). BPI pain severity also positively correlated with *MLYCD* gene expression and *CPT1A*, and for the *ACLY* gene a similar trend was noted. In addition, positive correlation between the DN4 score and the expression of the *ACLY* and *CPT1A* genes and the tendency towards a positive correlation between this indicator and the level of *MLYCD* and *FASN* genes were observed. *MLYCD* gene expression was also positively correlated with BPI values and tended to be negatively associated with ESR. In addition, this indicator revealed a negative correlation with *ACC1* gene expression and positive, with *FASN* expression. Along with this, most of the examined studied genes showed a high level statistically significant positive correlation with expression previously studied genes of pro-inflammatory cytokines: factor tumor necrosis α (TNFα) and interleukin (IL)1β, cathepsins S and K, and energy metabolism related genes, *AMPK*, *PDH*, *ATP5B*, *PKM2*, *MDH*, *IDH*, *SDHB*, *IDH* and *UCP2* (r=0.5–0.9, p<0.05) [9, 11]. The exception was for the *FASN* gene, the level of which expression was positively correlated only with concentration of *LDHB*, *PDH*, *ATP5B* and *PKM2* genes (r=0.4–0.7, p<0.05), and no correlation was observed with the expression of the rest of the examined genes. To evaluate prognostic value of *CPT1A* and *ACLY* gene expressions, we performed ROC analysis (Fig. 2), which confirmed statistically significant relationship between the expression of these genes before TJR with the likelihood of developing POP: expression threshold for *CPT1A* gene was 16.01 (AUC=0.719; 95% CI 0.588–0.773; p=0.02), and the *ACLY* gene – 11.92 (AUC=0.727; 95% CI 0.647–0.818; p=0.01).

Spearman correlation coefficients between biopsychosocial indicators and gene expression and their significance (p), assessed before TA (n=50)

Index	*ACLY*	*ACC1*	*MLYCD*	*FASN*	*CPT1A*
BMI			**0,387 p=0,04**		
DN4	**0,393 p=0,04**		0,325 p=0,09	0,447 p=0,08	**0,409 p=0,03**
PainDETECT	**0,400 p=0,04**	0,359 p=0,07	**0,580 p=0,001**		**0,614 p<0,001**
BPI (Pain severity)	0,335 p=0,09		**0,450 p=0,01**		**0,469 p=0,01**

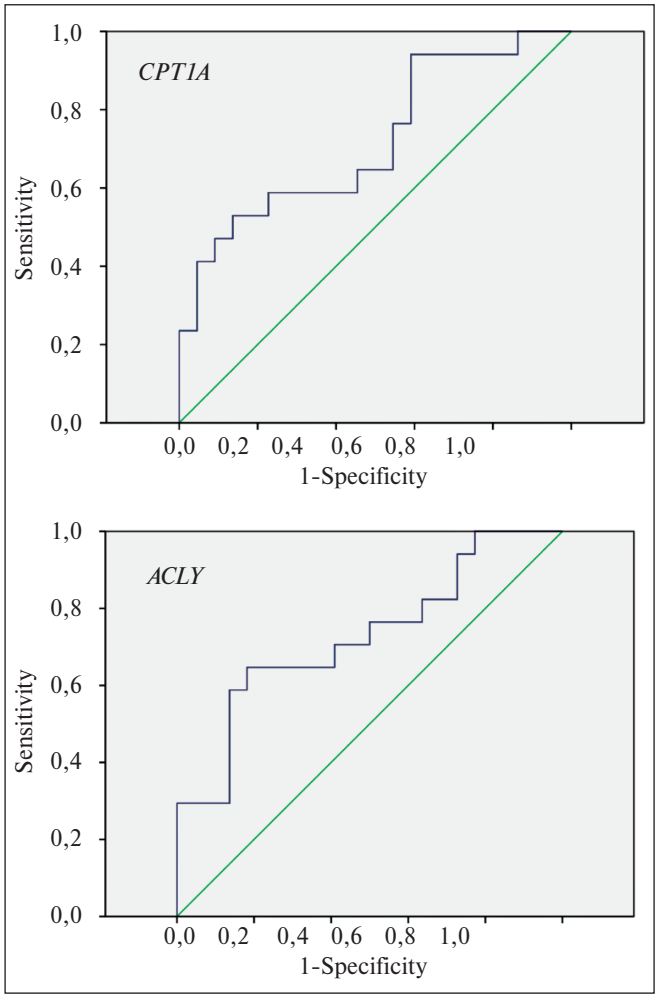

Fig. 2. *Area under the curve (AUC) demonstrating association between CPT1A and ACLY gene expression and the development of POP*

Discussion

The molecular mechanisms that determine the influence of FA metabolism on the development of POP in patients with knee OA are unclear. However, it was shown that a violation of the ratio in the composition of intracellular FAs helps to increase the content of pro-inflammatory lipids, especially in adipose tissue, which is associated with increased pain and dysfunction of the knee joint [30]. But since the immune system plays a significant role in the pathogenesis of OA, soluble (cytokines and chemokines) and cellular (monocytes and macrophages) inflammatory mediators are involved in the destruction articular cartilage, the development of synovitis and impaired bone remodeling [31]. Therefore, our data on statistically significant increase in expression of most of the examined genes related to fatty acid metabolism, with the exception of *FASN*, in the blood of patients from both groups with late stage OA compared with healthy individuals are consistent with the above information on the relationship between disturbances in FA metabolism and clinical manifestations of OA. These violations result in increased expression of the LC-FA transporter *CPT1A* in the mitochondria of patients with knee OA and the production of a large amount of acetyl-CoA during β-oxidation. Additionally, acetyl-CoA is formed in glycolysis, the activity of which is significantly higher in OA patients of both groups than in healthy subjects, as we have shown previously [11]. After condensation of acetyl-CoA with oxaloacetate citrate is formed, which can be oxidized in the Krebs cycle and also transferred to cytosol and cleaved by *ACLY* to form acetyl-CoA and oxaloacetate [19]. As expression *ACLY* in patients with OA is significantly higher than in healthy individuals, then in the cytoplasm of blood cells the concentration of acetyl-CoA increases. At the next stage, acetyl-CoA is carboxylated involving ACC into malonyl-CoA, but the expression

of gene responsible for the rate of the reverse reaction catalyzed by MLYCD is also significantly increased in patients OA compared to controls, which leads to a futile cycle [32]. As a result, the blood cells of all patients with late stage OA accumulate a large amount of acetyl-CoA. It should be noted that in rheumatoid arthritis (RA) it was also observed a movement of significant amounts of acetyl-CoA from mitochondria into the cell cytoplasm to support de novo lipid synthesis [33]. In addition, it was shown that the excess of acetyl-CoA determined pro-inflammatory phenotype of T lymphocytes as a result acetylation of the cytoskeleton [34]. On the contrary, protein deacetylation upon activation of NAD+-dependent deacetylase (SIRT1) with resveratrol slowed down the progression of OA due to its anti-inflammatory effect [35]. In addition, our data on the characteristics of FA metabolism in the blood cells of patients with late stage OA are consistent with previously obtained results from other studies, that have shown that in chronic inflammation, e.g. in RA, the rate of transport of LC-FAs into effector T lymphocytes increases [36]. At the same time, high expression of the *CPT1A* gene may have an anti-inflammatory effect, because activation of *CPT1A* by L-carnitine suppressed synovitis in fibroblasts of rats with knee OA in a model induced by anterior cruciate ligament injury (ACLT) [37]. Interestingly, the expression of the *FASN* gene, which determines de novo rate of FA synthesis, in both groups of OA patients did not differ from the control, possibly due to high expression of the *MLYCD* gene, the product of which prevents further polymerization of malonyl-CoA. Therefore, weak inflammation in OA may be associated with the lack of excess synthesis of LC-FA de novo, that are required for the construction of cell membranes upon activation of T-lymphocyte proliferation [38]. This is also confirmed by the fact that inhibition of the synthesis of LC-FAs suppressed the differentiation of Th17-cells and improved the condition of animals with collagen-induced arthritis [39]. At the same time, the development of POP in patients with a late stage OA is likely associated with a higher degree of imbalance in metabolism of fatty acids, due to significantly higher expression of *CPT1A* and *ACLY* compared with patients satisfied with the results of TJR, which leads to higher concentration of acetyl-CoA in blood cells. This increases the likelihood of non-enzymatic, and therefore uncontrolled, acetylation of protein molecules [40], which increase the proportion of the acetylated fraction [41] and leads to disruption of their functions [42]. The association between FA metabolism and the development of POP is confirmed by positive correlation of *MLYCD* gene expression with BMI, as well as by previous studies showing that weight loss reduced pain in patients with knee OA [43]. Moreover, the positive correlation of the expression of the *MLYCD* and *CPT1A* genes with the severity of pain according to the BPI questionnaire, and the expression of the *ACLY*, *MLYCD* and *CPT1A* genes with the indicators of the neuropathic pain questionnaires in the blood of patients with stage III–IV OA allows us to suggest the possible involvement of neurogenic mechanisms in the development of POP at the late stage of the disease. It should also be noted that, as in the case of our previously studied genes of carbohydrate metabolism, extracellular matrix degradation, inflammation, and apoptosis associated with POP in this cohort of patients [9, 11], there were no qualitative differences in gene expression between the examined patient subgroups. However, exceeding threshold expression levels of the *CPT1A* and *ACLY* genes, which can be determined before TJR, was associated with POP. Therefore, by determining the level of these genes in the blood before surgery, it is possible to predict the development of POP.

Conclusion

Thus, the development of POP in patients with late stage OA is associated with overexpression of the *CPT1A* gene, which increases the entry of FA into mitochondria, as well as with the accumulation of acetyl-CoA, a product of high expression of the *ACLY* gene. These indicators can be assessed in the blood of OA patients before TJR. More detailed studies involving larger cohorts of patients are needed to confirm our findings about the involvement of FA metabolism in the development of POP. The results obtained in this study will contribute to a deeper understanding of the involvement of metabolic processes in the pathogenesis of OA.

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