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Development and risk factors of chronic pain due to trauma to the anterior cruciate ligament and/or meniscus of the knee joint

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Abstract

Aim – to evaluate the incidence and risk factors of chronic post-traumatic pain in patients who suffered an anterior cruciate ligament (ACL) and/or knee joint meniscus (CC) injury.

Material and methods. The study group consisted of 148 patients (48.0% women, 37.9 ± 13.1 years old) who had suffered an injury to the PC and/or meniscus of the CS, confirmed by magnetic resonance imaging (MRI). The inclusion criterion was moderate/severe pain (≥4 on the numerical rating scale, NRS 0-10) 1 month after the injury. Patients were examined after 3, 6, and 12 months with an assessment of pain (NRS) and the KOOS index, signs of neuropathic pain (painDETECT), anxiety and depression (HADS a and HADS d), central sensitization index (CSI), pain catastrophization (PCS), fibromyalgia symptoms (FiRST), fatigue (FACIT). An MRI scan was performed after 6 and 12 months. The plasma concentrations of a number of biomarkers (HCRP, NTX, ADAMTS-5, COMP, MMP3, MMP9, MMP13, substance P) were studied.

Results. After 3 months, pain with movement ≥4 NRS was observed in 58 (39.2%) patients. These patients formed the group with chronic post-traumatic pain (CPTP+), patients with lower pain intensity or absence (≤4 NRS) formed the control group (CPTP-). In patients with CPTP+, compared with the CPTP- group, pain at rest and at night was significantly higher (p <0.001). A significant difference in pain during movement, at rest, and at night, as well as all KOOS scales, remained between the CPTP+ and CPTP- groups after 6 and 12 months. In the CPTP+ group, there was a tendency to a higher frequency of signs of neuropathic pain, anxiety and depression, central sensitization index, pain catastrophization scale and fatigue, however, the difference with the CPTP- group was unreliable. The concentration of biomarkers in the CPTP+ and CPTP- groups did not differ. There was a significant association between CPTP and the female sex (odds ratio = 3.18; 95% confidence interval 1.606-6.297, p<0.001), meniscus injury (OR = 2.132; 95% CI 1.07-4.252, p=0.03), osteitis (OR = 5.734; 95% CI 2.106-15.609, p<0.001) and synovitis (OR = 2.35; 95% CI 1.186-4.656, p=0.013) according to MRI, surgery (reduced the risk of CPTP, OR = 0.385; 95% CI 0.195-0.759, p<0.005), initially severe pain (≥7 NRS, OR = 5.553; 95% CI 1.696-18.179, p=0.002), signs of highly probable CS (CSI ≥40, OR = 3.915; 95% CI 1.147-13.368, p=0.021) and severe depression (HADS ≥ 11, OR = 4.12; 95% CI 1.672-21.983, p=0.05).

Conclusion. CPTP occurs in almost 40% of patients after knee joint meniscus injury. Risk factors for CPTP are female gender, meniscus injury, osteitis and synovitis (MRI data), initially severe pain, central sensitization, and depression.

Keywords: anterior cruciate ligament/meniscus injury, chronic post-traumatic pain.

Conflict of interest: nothing to disclose.

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Развитие и факторы риска хронической боли после травмы передней крестообразной связки и/или мениска коленного сустава

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Аннотация

Цель – оценить частоту развития и факторы риска ХПТБ у пациентов, перенесших травму передней крестообразной связки (ПКС) и/или мениска коленного сустава (КС).

Материал и методы. Исследуемую группу составили 148 пациентов (женщины 48,0%, 37,9 ± 13,1 года), перенесших травму ПКС и/или мениска КС, подтвержденную магнитно-резонансной томографией (МРТ). Критерием включения была умеренная/выраженная боль (≥4 по числовой рейтинговой шкале, ЧРШ 0–10) через 1 месяц после травмы. Пациенты обследовались через 3, 6 и 12 месяцев с оценкой боли (ЧРШ) и индекса KOOS, признаков невропатической боли (PainDETECT), тревоги и депрессии (HADS a и HADS d), центральной сенситизации, ЦС (CSI), катастрофизации боли, КБ (PCS), симптомов фибромиалгии, ФМ (FiRST), утомляемости (FACIT). Через 6 и 12 месяцев проводилась МРТ. Была исследована плазменная концентрация ряда биомаркеров (вчСРБ, NTX, ADAMTS-5, COMP, ММП3, ММП9, ММП13, субстанция Р).

Результаты. Через 3 месяца боль при движении ≥4 ЧРШ отмечена у 58 (39,2%) пациентов. Эти пациенты составили группу с ХПТБ (ХПТБ+), пациенты с меньшей интенсивностью или отсутствием боли (≤4 ЧРШ) – контроль (ХПТБ-). У пациентов ХПТБ+ в сравнении с группой ХПТБ- была достоверно выше боль в покое и ночью (p <0,001). Достоверное различие боли при движении, в покое и ночью, а также всеми шкалами KOOS сохранялось между группами ХПТБ+ и ХРТБ- через 6 и 12 месяцев. В группе ХПТБ+ была тенденция к большей частоте признаков невропатической боли, тревоги и депрессии, ЦС, КБ и усталости, однако различие с группой ХПТБ- было недостоверным. Концентрация биомаркеров в группах ХПТБ+ и ХПТБ- не различалась. Отмечена достоверная связь между ХПТБ и женским полом (отношение шансов, ОШ = 3,18; 95% доверительный интервал, ДИ 1,606-6,297, p<0,001), травмой мениска (ОШ = 2,132; 95% ДИ 1,07-4,252, p=0,03), остеитом (ОШ = 5,734; 95% ДИ 2,106-15,609, p<0,001) и синовитом (ОШ = 2,35; 95% ДИ 1,186-4,656, p=0,013) по МРТ, проведенной операцией (снижала риск ХПТБ, ОШ = 0,385; 95% ДИ 0,195-0,759, p<0,005), исходно сильной болью (≥7 ЧРШ, ОШ = 5,553; 95% ДИ 1,696-18,179, p=0,002), признаками высоко вероятной ЦС (CSI ≥40, ОШ = 3,915; 95% ДИ 1,147-13,368, p=0,021) и выраженной депрессией (HADS ≥ 11, ОШ = 4,12; 95% ДИ 1,672-21,983, p=0,05).

Заключение. ХПТБ возникает у почти 40% пациентов после травмы КС. Факторы риска ХПТБ – женский пол, травма мениска, остеит и синовит (данные МРТ), исходно сильная боль, ЦС и депрессия.

Ключевые слова: травма передней крестообразной связки/мениска, хроническая посттравматическая боль

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КС – коленный сустав; ПКС – передняя крестообразная связка; ПТОА –посттравматический остеоартрит; ХПТБ – хроническая посттравматическая боль; ЧРШ – числовая рейтинговая шкала; ОА – остеоартрит; ОШ – отношение шансов; ЦС – центральная сенситизация; ФМ – фибромиалгия.

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INTRODUCTION

Injuries are a serious medical and social problem, one of the main reasons of death, disablement, and considerable decrease of quality of life in the modern world [1]. According to official statistics, the ‘external causes’ (including injuries) in the Russian Federation in 2020 ranked fourth among causes of death (139,600), after cardiovascular diseases (938,500), neoplastic diseases (295,900), and COVID-19 (144,700). The absolute number of injuries was 8.92 million cases, of which 6.17 were injuries of upper and lower extremities [2].

In the structure of injuries of the lower extremities, the injuries to the knee joint (KJ) and ankle joint prevail, whose cumulative incidence rate is over 50% from the total number of injuries to the skeletomuscular system [3]. The most frequent traumatic injuries of the knee joint are the meniscal tear and the anterior cruciate ligament tear (ACL) [4, 5].

Notwithstanding the wide range of conservative and surgical methods of treatment of injuries, their sequelae are often adverse. Injury complications may present themselves as a permanent loss of capacity, neurological and infectious complications, post-traumatic osteoarthritis (PTOA), and chronic post-traumatic pain (CPTP) [6–10].

Chronic post-traumatic pain is a syndrome characterized by moderate or significant pain in the area of the sustained injury that persist for three or more months after the injury [11]. This is a frequent complication: after injuries of the knee

joint, depending on their severity, CPTP sets on in 10–50% patients. CPTP significantly affects the general well-being, affects physical and social activity, affects quality of life, and incurs significant expenses on treatment and rehabilitation [6–10].

Besides, the CPTP may be regarded as the first manifestation of the emerging PTOA. The international experts' council Optimizing Knee Health after Injury (OPTIKNEE) identified the PTOA of the knee joint thus: "structural or symptomatic osteoarthritis developing after a traumatic injury of the knee joint". PTOA of the knee joint is considered symptomatic in the presence of a clinic picture matching the criteria of at least one professional associations working on osteoarthritis, e.g., ACR (American College of Rheumatology), but excludes age limitations regardless of the presence of structural changes identified by instrumental methods [12].

This shows that the CPTP and PTOA are serious challenges of modern medicine that require adequate approaches to prevention and treatment. At the same time, proper management of PTOA is not possible without a clear understanding of the mechanism of its development and without identification of risk factors of the pathology. Therefore, the fundamental task in studying CPTP is the creation of a prognostic model that will analyze a complex of symptoms and assess the probability of development of the pathology, its pathway and phenotypic features.

AIM

To evaluate the incidence rate and risk factors of chronic post-traumatic pain in patients who suffered an anterior cruciate ligament and/or knee joint meniscus injury.

MATERIAL AND METHODS

This study is a part of a prospective scientific study "PHOBOS" ("Factors Defining Chronization of Pain: Evaluation and Systematization") performed from 2022 to 2024 at the V.A. Nasonova Research Institute of Rheumatology. The study group included 148 patients compliant with the *inclusion criteria*: age from 18 to 50; traumatic injury of the anterior cruciate ligament and/or knee joint meniscus confirmed by the magnetic resonance tomography findings (MRI); moderate or significant pain in the knee joint area (>4 on the 0-10 numeric rating scale (NRS), where 0 stands for no pain and 10 for unbearable pain) for ≥1 month after the injury; availability of the patient's informed consent. *The exclusion criteria* were as follows: fracture of the bony structures in the knee joint area (diagnosed as per X-ray data), availability of reliable signs of a rheumatic disease (including earlier diagnosed OA and fibromyalgia), functional disorders of the skeletomuscular system and comorbid conditions precluding regular check-ups required by the study protocol.

All patients included in the study were recommended to wear orthoses, exercise regularly and use non-steroid anti-inflammatory drugs either systemically or locally (ointments and gels) to stop the pain as needed.

The patients were divided into the main group (moderate/severe pain in the knee joint) and the control group (mild pain or no pain in the knee joint) during their second visit, three months after the start of observation.

The criterion for inclusion in the CPTP group (main group) was persistence of moderate or severe pain in the knee joint on activity or at rest (>4 NRS) that persisted for the majority of days within the past 3 months. The studied group consisted mainly of young people with comparable number of males and females who sustained an injury of the ACL, the meniscus, or a combination thereof. Among patients engaged in the study, 48.6% had undergone surgery (ACL restoration, meniscal suture), 51.4% of patients received only conservative treatment. The consolidated initial parameters of patients included in the study follow in **Table 1**.

According to the plan of the work, all patients, at the time of inclusion in the study, underwent a comprehensive examination to identify a group of promising clinical parameters that can be considered subsequently as risk factors for the development of CPTP.

Studies of clinical manifestations of each patients were performed during the first admission, and 3, 6 and 12 months after the injury. To that end, the following indicators were used: pain severity on the NRS in motion, at rest and at

Parameter	Value
Sex (F/M, %)	48.0 / 52.0
Age, years; M±σ	37.9 ± 13.1
Body mass index, kg/m²; M±σ	25.8 ± 5.1
Damage of knee joint structures as per MRI data, %	ACL: 40.0, meniscus: 58.7, combined ACL + meniscus injury: 16.7, ACL + other condition (tendinitis, cysts, ligament strain, etc.): 26.0
Surgery (ACL restoration, meniscal suture, meniscus resection, combined surgeries), %	48.6
Conservative methods of treatment, %	51.4
Pains on activity; Me [25th; 75th percentiles]	5.0 [4.0; 7.0]
Pains at rest; Me [25th; 75th percentiles]	2.0 [0.75; 3.0]
Pain during the night; Me [25th; 75th percentiles]	2.0 [0.0; 3.0]
Functional disorder; Me [25th; 75th percentiles]	4.0 [3.0; 6.0]
KOOS total; M±σ	48.9 ± 17.5
KOOS symptoms; M±σ	59.1 ± 19.6
KOOS pain; M±σ	58.5 ± 16.8
KOOS activity; M±σ	65.0 ± 20.1
KOOS sports; M±σ	33.1 ± 18.7
KOOS quality of life; M±σ	39.8 ± 19.8
PainDETECT; Me [25th; 75th percentiles]	6.0 [3.0; 9.0]
PainDETECT >12, %	10.0
HADS depression; Me [25th; 75th percentiles]	4.0 [1.0; 6.0]
HADS depression >11, %	4.7
HADS anxiety; Me [25th; 75th percentiles]	5.0 [2.0; 7.0]
HADS anxiety >11, %	4.0
CSI; Me [25th; 75th percentiles]	22.5 [14.75; 32.25]
CSI ≥ 40, %	8.6
PCS; Me [25th; 75th percentiles]	12.5 [7.0; 21.0]
PCS >30, %	14.0
FiRST; Me [25th; 75th percentiles]	1.0 [0.5; 2.0]
FiRST >5, %	1.3
FACIT; Me [25th; 75th percentiles]	11.0 [5.0; 19.25]
FACIT 0–13, %	57.3
HAQ; Me [25th; 75th percentiles]	0.375 [0.0; 0.75]

Table 1. *Characteristics of the initial data of patients included in the PHOBOS study (n=148)*

Таблица 1. *Характеристика исходных данных пациентов, включенных в исследование ФОБОС (n=148)*

nighttime; symptom intensity and functional disorders on the Knee Injury and Osteoarthritis Outcome Score – KOOS ('symptoms', 'pain', 'daily activities', 'sports', 'quality of life', 'total' scores); symptoms of neuropathic pain as per the PainDETECT questionnaire; psycho-emotional disorders as per Hospital scale of Anxiety and Depression (HAD); central sensitization (CS) as per the Central Sensitization Inventory (CSI); pain catastrophizing as per the Pain Catastrophizing Scale (PCS); fibromyalgia symptoms as per the Fibromyalgia Rapid Screening Tool (FiRST); fatigue and tiredness as per the Functional Assessment of Chronic Illness Therapy (FACIT).

During the study process, the following laboratory indicators were evaluated in dynamics (as of the moment of inclusion and 3 months later): hemoglobin level (Hb, g/l), ESR (mm/h), CRP (mg/l), hsCRP (ME/l), NTX, ADAMTS-5, COMP, MMP3 (ng/ml), MMP9 (ng/ml), MMP13 (ng/ml), substance P (pg/ml).

Besides, in 6 and 12 months, MRI of the knee joint was performed to visualize the damage to the meniscus and the ACL, the cartilage, the subchondral bone, presence of effluent to the joint cavity and their objective assessment (degree of synovitis, severity of damage to the ACL and the meniscus, presence of osteitis, etc.). In the course of the study, the MRI scans of the knee joint were compared at the outset, in 6 and 12 months.

Statistical analysis of results of this study was performed in the IBM SPSS Statistics 23 software suite. Quantitative values are presented as averages with the respective standard deviation (M±σ), and in the vase of the lack of the normal distribution within the group, as medians with inter-quartile range Me [25th; 75th percentiles]. Qualitative variables were described with absolute values and respective percentages. In order to analyze the data, statistical tests were used: Pearson's $\chi 2$-test (contingency table analysis), unpaired Student's t-test, for the comparison of quantitative values, Wilcoxon test ($\chi 2$) for related samples, Mann–Whitney test for independent samples, Spearman's rank correlation coefficient. To assess the impact of various factors on the outcome of therapy, odds ratio (OR) calculation with the corresponding 95% confidence interval (CI) was used. Differences were considered statistically significant at $p < 0.05$.

The study was carried out in compliance with the provisions of the Helsinki Declaration of Human Rights. All patients signed informed consent to participate in this work. The study was approved by the local ethics committee of the V.A. Nasonova Research Institute of Rheumatology (Protocol No. 23 dated 23.11.2022).

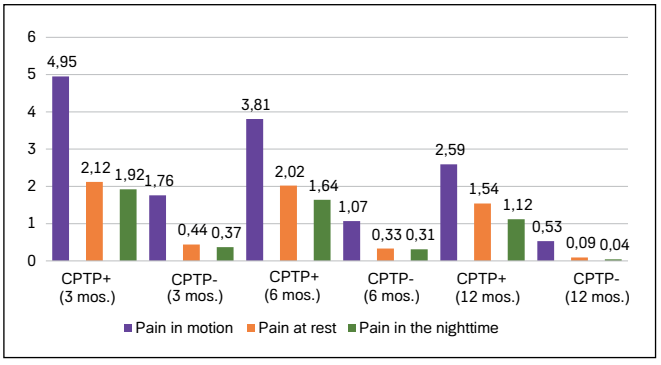

Figure 1. *Pain dynamics in patients with and without CPTP from 3 to 12 months of follow-up.*

Рисунок 1. *Динамика боли у пациентов с ХПТБ и без ХПТБ с 3 по 12 месяц наблюдения.*

RESULTS

Three months after the inclusion, moderate and severe pain in motion (≥4 NRS) was registered in 58 (39.2%) patients. Pursuant to the aim of the study, these patients formed the CPTP group (CPTP+), and patients experiencing less or no pain (≤4 NRS) formed the control group (CPTP-). Besides more intense pain in motion, the CPTP+ patients had reliably more intense pain at rest and in the nighttime as compared to the CPTP- group ($p<0.001$). The reliable difference in the pain intensity in motion, at rest and in the nighttime remained between the CPTP+ and CPTP- groups in the follow-ups after 6 and 12 months (**Fig. 1**).

Manifestations of neuropathic pain, central sensitization and fibromyalgia were found in a minor share of patients at the outset of the study: PainDETECT >12 in 9.8%, CSI ≥40 in 8.7%, FiRST >5 in 1.4%; manifested psycho-emotional disorders, in individual patients: HADS depression >11 in 4.6%, HADS anxiety >11 in 3.9%.

Statistically reliable difference between the CPTP+ and CPTP- groups was found 3, 6 and 9 months in all scores of the KOOS scale. Other quantitative parameters measured with PainDETECT, HADS, CSI, PSC, FIRST and FACIT

Parameters M+δ. Me [25th; 75th percentiles]	CPTP+ (3 mos.)	CPTP- (3 mos.)	CPTP+ (6 mos.)	CPTP- (6 mos.)	CPTP+ (12 mos.)	CPTP- (12 mos.)
KOOS total*	57.8 ± 18.2	77.3 ± 20.2	60.9 ± 16.7	85.3 ± 21.4	79.0 ± 18.4	88.5 ± 18.8
KOOS symptoms*	57.5 ± 19.4	79.4 ± 16.7	62.8 ± 15.2	85.3 ± 17.4	72.9 ± 19.0	90.4 ± 22.1
KOOS pain*	54.0 ± 13.3	78.5 ± 17.4	63.6 ± 17.2	82.3 ± 20.1	71.9 ± 18.6	90.6 ± 18.5
KOOS activity*	58.9 ± 15.6	82.3 ± 16.7	63.8 ± 20.1	85.1 ± 19.4	71.9 ± 18.2	90.6 ± 21.6
KOOS sports*	39.2 ± 12.4	62.2 ± 18.7	45.1 ± 19.3	69.3 ± 20.3	52.8 ± 17.3	78.6 ± 19.1
KOOS quality of life*	45.7 ± 11.0	68.1 ± 18.1	52.3 ± 14.8	70.0 ± 19.7	67.5 ± 18.4	85.1 ± 22.2
PD	8.0 [6.0: 10.0]	4.5 [3.0; 5.5]	7.0 [5.0; 8.0]	2.0 [3.0; 4.5]	6.0 [4.0; 7.0]	1.0 [0.0; 2.5]
HADS d	4.5 [3.0; 5.5]	2.0 [1.0; 3.0]	5.0 [3.0; 6.5]	2.5 [2.0; 4.0]	4.0 [5.0; 6.0]	2.0 [1.0; 3.0]
HADS a	6.0 [4.0; 8.0]	3.0 [2.0; 4.0]	7.0 [6.0; 8.0]	3.5 [3.0; 4.5]	6.0 [4.0; 7.0]	2.5 [1.0; 3.0]
CSI	26.0 [14.0; 35.0]	16.0 [12.0; 18.0]	21.0 [13.0; 25.5]	9.0 [6.0; 12.0]	15.0 [10.0; 19.0]	4.0 [3.0; 5.0]
PCS	17.0 [14.0; 19.0]	8.0 [6.0; 9.5]	13.0 [11.0; 15.0]	5.0 [3.0; 6.5]	10.0 [7.0; 12.0]	1.5 [0.0; 2.5]
FiRST	1.0 [0.0; 2.0]	0.5 [0.0; 1.0]	1.0 [0.0; 2.0]	0.5 [0.0; 1.0]	1.0 [0.0; 1.5]	0.5 [0.0; 1.0]
FACIT	13.0 [11.0; 17.0]	9.0 [7.0; 11.0]	11.0 [9.0; 13.5]	6.0 [4.0; 8.0]	10.0 [8.0; 12.0]	3.5 [2.0; 5.5]

*Note. * The difference between the CPTP+ and CPTP- groups after 3, 6 and 12 months is statistically reliable in all KOOS parameters ($p < 0.05$).*

Table 2. *Dynamics of clinical parameters in the CPTP+ and CPTP- groups after 3.6 and 12 months*

Таблица 2. *Динамика клинических показателей в группах ХПТБ+ и ХПТБ- через 3, 6 и 12 месяцев*

questionnaires, also differed between the compared groups in the follow-ups after 3, 6 and 12 months, but this difference was not statistically reliable (**Table 2**).

A correlation between the MRI-indicated signs of synovitis and osteoitis showing the persistent joint inflammation and the presence of CPTP was found. The data and the outcomes of recurrent MRI scans after 6 and 12 months showed statistically significant differences in the frequency of synovitis and osteoitis finding in the CPT+ group versus the CPTP- group (**Fig. 2**).

The incidence rate pf MRI signs of synovitis in CPTP patients decreased significantly within the follow-up period: initially, the parameter was found in 67.8% patients, and in 12 months, in 40.7% (p=0.0308). According to the MRI data, the incidence rate of osteisis did not statistically decrease within the tear of follow-up: 28.6% at the outset and 20.3% (p=0.107) by the end of the study.

A credible correlation was found between the development of CPTP and the female gender (OR = 3.18 (95% CI 1.606-6.297), p<0.001),injury of the meniscus (OR = 2.132 (95% CI 1.07-4.252), p=0.03), presence of osteitis (OR = 5.734 (95% CI 2.106-15.609), p<0.001) and synovitis (OR = 2.35 (95% CI 1.186-4.656), p=0.013) as per the MRI data, past surgery (decreasing the risk of CPTP development, OR = 0.385 (95% CI 0.195-0.759), p<0.005), initial severe pain in motion (≥7 NRS, OR = 5.553 (95% CI 1.696-18.179), p=0.002), signs of highly likely central sensitization (CSI ≥40, OR = 3.915 (95% CI 1.147-13.368), p=0.021) and manifested depression (HADS ≥11, OR = 4.12 (95% CI 1.672-21.983), p=0.05).

No credible differences between the groups of patients with and without CPTP were found when comparisons were made in the values of BMI, ALC injury, signs of tendinitis, concentration of CRP (standard analysis), initial pain at rest (≥7 NRS) and in the nighttime (≥5 NRS), severity of functional disorder (≥7 NRS), signs of neuropathic pain (PainDETECT questionnaire), anxiety (HADS questionnaire), catastrophization (PCS questionnaire), signs of fibromyalgia (FIRST questionnaire), and fatigue (FACIT questionnaire).

We saw no statistically significant differences in the plasma concentrations of the biomarkers (hsCRP, NTX, ADAMTS-5, COMP, MMP-3, MMP-9, MMP-13 and substance P) in patients with and without CPTP after 3 and 12 months of follow-up. There was no statistically credible correlation between the severity of CPTP and the level of the studies substances.

DISCUSSION

CPTP was identified in 39.3% patients who suffered ACL and/or meniscus rupture. In CPTP patients, throughout the entire follow-up period, greater manifestation of clinical symptoms was seen that were related to the consequences of the injury of the knee joint: pain in motion, at rest and in the nighttime, functional disorders. In each follow-up, credible differences were seen in all sections of the KOOS scale (total score, symptoms, pain, activity, sport, quality of life). Even though after 6 and 12 months the severity of symptoms decreased in many CPTP patients, their numerical value (both in the NRS and KOOS) remained statistically credibly high that those of the patients in the control group.

Despite the fact that the signs of the 'central constituent' of chronic pain were seen only in a minor quantity of patients,

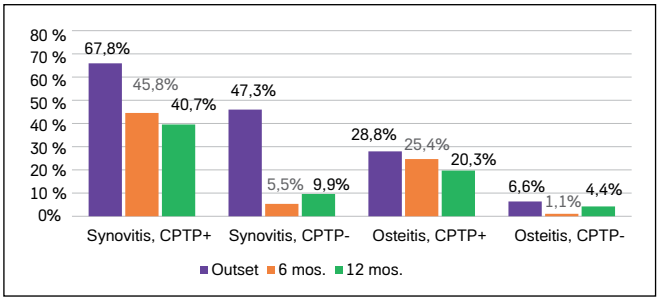

Figure 2. *Dynamics of synovitis and osteitis according to MRI data depending on the presence or absence of CPTP.*

Рисунок 2. *Динамика синовита и остеита по данным МРТ в зависимости от наличия или отсутствия ХПТБ.*

the numerical values of anxiety and depression (HADS), neuropathic pain (PainDETECT), central sensitization (CSI), catastrophization (PCS), fatigue (FACIT) and fibromyalgia (FIRST) were higher on all stages of follow-up in patients with CPTP.

The results obtained by us show that CPTP is a pathophysiological phenomenon related to the specifics of the 'response' of the macro-organism to the injury and associated damage, inflammation and reparative process. At the same time, the formation and the persistence of CPTP may indicate development of PTOA.

The high incidence rate of CPTP in this study may be related to criteria of patient selection for the study. It included only those patients in whom one month after the injury of the knee joint at lease moderately severe pain persisted, which was the reason for seeking medical attention. Our data is close to the results of foreign research of similar topics. Thus, L. Lohmander et al. performed a cohort study of 121 young athletes (average age of 26 years) suffering a rupture of ACL and showed dissatisfaction of 1/3 of respondents with their condition (PASS "-") [13]. S. Van der Graaff et al. followed up 82 patients with ACL rupture and delayed operation; in 29 (35.4%) of which the pain level 3-6 months after the injury was >3 NRS points [14]. C. Anthony et al. assessed the need in opioid analgesics in 4946 patients suffering a knee joint injury and requiring surgical reconstruction of the ACL [15]. Three months before the surgery, 35% of patients had to take opioid analgesics on a regular basis, because they were in intense pain.

We identified a correlation between CPTP and female sex. Higher risk of development of chronic pain in women is confirmed by a meta-analysis of 71 studies performed by H.Andreoletti et al. [16]. This work focused on risk factors of post-surgery pain. One of the main factors was the female sex, OR = 1.34. In the review of S. Mills et al. on the problem of chronic pain it is reported that CPTP is seen more often in women because they describe the sensation of pain in a more pronounced, emotional manner [17].

We also found a correlation between the development of CPTP and structural changes, such as damage to the meniscus, osteitis and synovitis. The contribution of meniscal damage to the development of chronic pain was mentioned earlier in other studies. E.g., C. Maia et al. compared the progress of the primary OA (n=641) and PTOA (n=104) and showed that the presence of meniscal injury is associated with severe pain and disrupts its function [18]. The contribution of meniscal damage to the development of symptomatic PTOA is confirmed in

the study of Y. Lu et al. [19]. The authors followed up 974 patients with injuries of the ACL and meniscus and subsequent reconstruction of the ligament and treatment of the meniscus averagely 7.5 years after the first surgery. They found development of PTOA in 22.1% of the cases. The conclusions of this study confirm that the meniscal damage was a risk factor of development of post-traumatic osteoarthritis.

Effusion to the knee joint and synovitis (proliferative and/or exudative) are widely spread visual symptoms identified in patients both immediately after the joint injury and long after it. The relation of synovitis and clinical symptoms remains a controversial question. Thus, T. Perry et al. studied 174 patients with OA for three years and saw no correlation between the pain as per WOMAC index and thickening of the synovium [20]. At the same time, synovitis of specific areas, viz. Infrapatellar, was associated with severe pain: OR 5.96 (95% CI 1.22-10.7). On the contrary, in the study of G.Wallace et al. found a strong correlation between the synovitis identified by MRI findings and pain in 104 patients with OA [21]. According to the data of a meta-analysis of 18 studies (n=5907 patients), E. Alaia et al. established a relation between clinical and MRI symptoms of OA [22]. Among the latter, synovitis and bone marrow edema were identified as manifestations of osteitis.

In the study of J. Driban et al., who evaluated the MRI data of 121 young patients with injuries of the ALC, found bone marrow edema in 96% patients, but there was no correlation of this MRI-identified symptom with severity of pain: $\beta = -0.09$, $P = 0.25$ [23]. Persistence of the bone marrow edema or its augmentation (increase of area or strengthening of signal from the existing edema without the increase of the osteitis area) according to the MRI data for a long period of time may point at progression of osteodestructive and inflammatory changes, which shows in the persistence or increase of paint in such patients. The study of K. Moradi et al. is demonstrative in this respect: for a period of 4 years, 2430 patients with OA who underwent MRI were followed up. In 1106 patients, the bone marrow edema was found to increase, which was associated with elevated risks of progression of OA as compared to patients in which the intensity of the edema remained the same or decreased: OR 1.3; $P<0.001$ [24].

Development of CPTP is related to initially intense pain (≥7 NRS). In such patients, the level of pain in 6 months credibly correlated with the level of pain at the outset and with functional disorder. Based on this is can be suggested that severe pain and functional disorders point at development of structural disorders, persistence of inflammation and dysfunction of nociceptive system. The significance of initial pain as a risk factor of CPTP development was confirmed in the meta-analysis of 18 studies (n=5372 patients) presented in the article by O. Alkassabi et al. [25].

Another factor influencing progression of CPTP was the presence of depression (HADS ≥11) and highly probable CS (CSI≥40). The severity of CPTP correlated with the numerical value of the central sensitization index (CSI), number of patients with CSI≥40 and number of patients with HADS ≥11.

Despite the absence of the statistically reliable correlation between the progression of CPTP and BMI, severity of neuropathic pain (PainDETECT), anxiety (HADS) and catastrophization (PCS), numeric values of these factors were higher in patients with CPTP in comparison with patients without CPTP. Lack of reliable differences is likely accounted for by the low prevalence of these manifestations in the group generally.

The importance of psycho-emotional disorders, CS and catastrophization in the progression of CPTP was shown in several articles [26–28]. Specifically, the work of S. Heijbel et al. evaluated outcomes of total replacement of the knee joint (TKR) in 8745 patients and found that dissatisfaction with the surgery depended on the presence of depression and anxiety: before the surgery, OR 1.23 (95% CI 1.09-1.40), after the surgery, OR 2.65 (95% CI 2.33-3.00) [26]. The meta-analysis of 32 studies (n=18792) by J. Li et al. concentrated on risk factors of postoperative pain in patients after TKR, and showed the significant contribution of CS, anxiety, and moderate depression [27]. The data of a meta-analysis of 29 studies (n=10360) by U. Olsen et al. demonstrated a correlation between pain progression one year after the surgery and catastrophization: $r=0.36$ (95% CI 0.24-0.47; $p<0.0001$) [28].

The influence of psycho-emotional disorders, catastrophization and CS on the development of CPTP is caused by a decrease in the pain threshold, hyperalgesia, increased pain afferentation, the development of neuroplastic changes and dysfunction of the nociceptive system, which determine an excessive and emotionally charged reaction to pain [29, 30].

We were not able to find a reliable correlation between the level of biochemical markers, namely hsCRP, NTX, ADAMTS-5, COMP, MMP-3, MMP-9, MMP-13 and substance P and progression of CPTP. In some papers, these biomarkers had some correlations with structural changes in the joints in OA (C-terminal telopeptide of type II collagen (CTx-II), COMP, MMP-3) [31, 32]. Some inflammatory cytokines may elevate immediately following the injury and remain in the synovial fluid of the injured joint and plasma of the blood for many months and years (IL-1β, IL-17, IL-6, TNF-α, macrophage inflammatory protein (MIP)-1, MMP, tissue inhibitor of metalloproteinase, TIMP), which may point at chronization of the inflammatory process and progression of PTOA [33]. The meta-analysis of L.Batty et al. showed the predictive value of IL-6, MMP-3, CTx-II in the evaluation of progression of adverse changes after the injury to and reconstruction of the ALC [34]. The article of H. Higuchi et al. reports that elevated concentrations of IL-6, MMP-3 and TIMP-1 in the synovial fluid persisted in persons with ALC injury for six months [35]. The study of K. Elsaid et al. found that in 30 cases of injury of ALC, one year after the injury the synovial fluid still had elevated levels of IL-1β, IL-6, TNF-α, neutrophilic elastase and sulfated glycosaminoglycan. At the same time, the synovial fluid of the opposite non-injured joint did not shoe biomarker levels different from the norm [36].

Biomarker concentration may correlate with signs of joint inflammation identified on MRI scans. In the article of Z. Zhu et al., biomarkers of 193 patients with active OA were studied. It was found that the increase of concentration of IL-6, IL-17 and IL-23 correlated with bone marrow edema [37].

However, some studies do not confirm data on the correlation between the level of biomarkers and progression of CPTP. For example, C. Lisee et al. studied the correlation between development of symptoms after the injury to and restoration of ACL and levels of MCP-1, COMP, MMP-3 and

CTx-II in 30 patients. After six months of the study, there was no correlation between the symptoms and concentration of biomarkers [38]. The systematic review of O. O'Sullivan et al. presented the data of 8 studies (n=879 patients), in which the correlation between concentration of IL-1, IL-6, TNF-α, COMP and some other biomarkers with clinical and structural changes in PTOA was not confirmed. The authors concluded that the differences in methods do not allow comparison of the results of different studies, and the overall weak connection between laboratory and clinical data [39].

The absence of correlations between biomarkers and clinical manifestations in our study may indicate both methodological problems with the analysis of biomarkers (a small number of observations, a heterogeneous group), and a true absence of differences in their concentrations associated with the peculiarities of the choice of the study cohort (all patients initially had severe pain and a similar spectrum of structural changes in the knee joint).

CONCLUSION

Thus, some of the main risk factors for the development of CPTP are intense pain, as well as the presence of structural changes: meniscus damage, synovitis and osteitis according to MRI data. There is no doubt that in the early stages of the post-traumatic process, it is such objective factors, indicating the presence of damage and inflammation, that play a leading role in the development of chronic post-traumatic pain. Later, they are joined by elements of dysfunction of the nociceptive system and psycho-emotional disorders. Although we were unable to detect statistical significance of the influence of catastrophization, fibromyalgia symptoms, depression and anxiety, there is an obvious tendency for these parameters to be more frequent in patients with CPTP. Therefore, it makes sense to take into account the signs of dysfunction of the nociceptive system and psycho-emotional disorders, which can be considered an important element in predicting the negative trajectory of the course of PTP and the development of PTOA.

ADDITIONAL INFORMATION	ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ
Ethical review. This work was carried out in compliance with human rights defined by the Helsinki Accords. All patients gave informed consent to participate in the study. The study was approved by the Ethics Committee of the V.A. Nasonova Research Institute of Rheumatology (Protocol No. 8 dated 10/25/2022).	***Этическая экспертиза.*** Настоящая работа проводилась с соблюдением прав человека, определенных Хельсинкским соглашением. Все пациенты дали информированное согласие на участие в исследовании. Исследование было одобрено этическим комитетом ФГБНУ «НИИ ревматологии им. В.А. Насоновой» (протокол № 8 от 25.10.2022).
Study funding. The work was carried out using budgetary funding for the implementation of the state assignment on topic FURS-2022-0009 (state assignment number 1021062512064-0).	***Источник финансирования.*** Работа выполнена за счет средств бюджетного финансирования на выполнение государственного задания по теме FURS-2022-0009 (номер государственного задания 1021062512064-0).
Conflict of interest. The authors declare that there are no obvious or potential conflicts of interest associated with the content of this article.	***Конфликт интересов.*** Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с содержанием настоящей статьи.
Contribution of individual authors. A.A. Byalik: collection of database, writing of the text of article. S.A. Makarov: patient selection. A.E. Karateev, E.I. Byalik, V.A. Nesterenko, D.M. Kudinsky: idea of study, editing of article. V.E. Byalik: statistical processing of results. The authors gave their final approval of the manuscript for submission, and agreed to be accountable for all aspects of the work, implying proper study and resolution of issues related to the accuracy or integrity of any part of the work.	***Участие авторов.*** А.А. Бялик – сбор базы данных, написание текста статьи. С.А. Макаров – отбор пациентов. А.Е. Каратеев, Е.И. Бялик, В.А. Нестеренко, Д.М. Кудинский – идея исследования, редактирование статьи. В.Е. Бялик – статистическая обработка результатов. Все авторы одобрили финальную версию статьи перед публикацией, выразили согласие нести ответственность за все аспекты работы, подразумевающую надлежащее изучение и решение вопросов, связанных с точностью или добросовестностью любой части работы.

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