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Evaluation of the influence of inflammation markers and body mass index on the level of pain syndrome after joint replacement

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Abstract

Aims: To evaluate the relationship between the severity of pain in the early postoperative period after total joint replacement and the levels of laboratory markers of inflammation and body mass index.

Methods: A prospective cohort study involved 21 patients (15 women, 6 men) with an average age of 65.3±7.65 years after total hip (n=18) or knee (n=3) replacement with an assessment of pain syndrome using a visual analogue scale in the early postoperative period and a study of its relationship with laboratory parameters (leukocytes, platelets, ESR) before and after the surgery.

Results: Females, compared to males, had a higher BMI (30.98±4.82; 26.90±2.96; p=0.070), higher preoperative ESR levels (24.93±9.04; 15.33±3.20; p=0.021), and a significant increase in platelet count on the third postoperative day (289.00 [235.50; 345.00]; 190.00 [186.25; 218.50]; p=0.029). Patients with grade I obesity noted more severe pain in the early postoperative period compared to patients with normal weight (8.67±1.21; 6.00±1.00 p=0.0138), although the differences between the groups diminished within days. Correlation analysis revealed a moderate positive relationship between leukocyte level and VAS pain scores particularly on the third (r≈0.38, p=0.009 and fifth (r ≈0.45, p<0.05) postoperative days.

Conclusion: The findings demonstrate that gender differences, BMI, and the severity of pain affect several clinical and laboratory parameters relevant to clinical practice. The systemic inflammatory response, as evidenced by changes in platelet counts and ESR, plays an important role in the pathogenesis of postoperative pain, with notable gender differences

Keywords: Total joint replacement; Postoperative pain syndrome; Inflammatory markers; Osteoarthritis

1. Introduction

Total hip and knee replacement is one of the most effective methods of restoring mobility in patients with severe forms of osteoarthritis and other degenerative-destructive joint diseases [1] . Despite the significant improvement in quality of life after surgery, one of the key factors influencing the process and duration of the rehabilitation period remains postoperative pain syndrome, which can persist for several weeks or months [2]. Female gender, severe preoperative pain, Body mass index (BMI), concomitant medical and psychiatric diseases, according to the literature, are associated with an increased risk of severe postoperative pain syndrome [3] .

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BMI is an important factor influencing the postoperative period, since obesity is associated with chronic inflammation and increased production of proinflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), which can modulate nociceptive processes and increase pain severity [4] , [5]. A number of studies demonstrate that obese patients more often experience intense pain in the postoperative period, which may be associated with changes in central nociception and neuroinflammation [6]. However, the effect of BMI on pain syndrome after total hip and knee replacement remains ambiguous, since some studies did not reveal reliable differences in pain levels in patients with different body weights [6].

Inflammatory markers such as leukocytes, ESR, and platelet count are important indicators of the body's inflammatory response to the surgery [7]. Elevated leukocyte count and ESR in the early postoperative period may indicate activation of the systemic inflammatory response, which may potentially contribute to increased pain [7]. Platelets, in addition to their key role in blood clotting, are also involved in inflammatory processes and the release of proinflammatory mediators, which may affect to the pain perception [8]. However, there is no consensus in the literature on the relationship between changes in these indicators and the severity of pain in the postoperative period. In view of the above, the study of factors influencing the severity of postoperative pain in patients after total joint replacement is a relevant task. This article examines the relationship between the intensity of pain syndrome after total hip and knee arthroplasty and such indicators as BMI, leukocyte level, ESR and platelets, in order to identify potential predictors of an unfavorable course of the early postoperative period.

2. Methods

A prospective cohort study was conducted to investigate the association of pain syndrome in patients after total hip and knee replacement in the early postoperative period with BMI, complete blood count (leukocyte count, platelet count, and erythrocyte sedimentation rate (ESR). The study group included 21 patients of both genders, of whom 6 (28.6%) were men and 15 (71.4%) were women. The mean age of patients was 65.30±7.65 years. All patients underwent total hip (n=18) or knee (n=3) replacement. The severity of pain syndrome was assessed by the visual analogue scale (VAS) on 1st (PS1), 3rd (PS 3), 5th (PS 5) and 10th (PS 10) days after the surgery. Laboratory parameters (leukocyte, platelet levels and ESR) were determined the day before and on 3rd and 5th days after the surgery. Patients were stratified into four groups depending on BMI values: normal body weight (18.5–24.9 kg/m^2), overweight (25.0–29.9 kg/m^2), grade I obesity (30.0–34.9 kg/m^2) and grade II obesity (35.0–39.9 kg/m^2). The characteristics of the study groups are presented in Table 1.

Exclusion criteria: history of diabetes mellitus, autoinflammatory and autoimmune diseases. Inclusion criteria: stage 3-4 according to Kelgren-Lawrence, operated according to the standard protocol, ineffectiveness of conservative therapy, absence of signs of inflammation according to the general blood test in the preoperative period. The study was approved by the Ethics Review Committee of the Bashkir State Medical University, and signed informed consent was obtained from all of the participants.

2.1. Statistical processing

GraphPad software was used for statistical data processing. Prism, version 8.0 (GraphPad Software, San Diego, CA, USA). The analysis included testing the data for compliance with normal distribution, calculating mean values and standard deviations, median values and interquartile range, and using parametric and nonparametric statistical analysis methods depending of the distribution of the variables. The level of statistical significance was considered reliable at $p<0.05$.

3. Results

Overall, after the surgery it found that women participating in the study were significantly older than men (68.0 [66.5;73.5] versus 56.0 [44.25; 61.75]; p=0.008). In addition, men had significantly higher height indicators (171.83±6.59 versus 158.60±6.74; p< 0.001), but body weight did not differ significantly between the groups (p=0.611). BMI values in women showed a tendency towards higher values (30.98±4.82 versus 26.90±2.96; p=0.070). Descriptive characteristics of the study group depending on gender are presented in Table 1.

Table 1 Descriptive characteristics of the study group., BMI - body mass index, * - statistical significance at p<0,05

Indicators	Female (N=15)	Male (N=6)	p
Age, years	68.0 [66.5; 73.5]	56.0 [44.25; 61.75]	0.008*
Height, cm	158.60±6.74	171.83±6.59	< 0.001*
Weight, kg	80.00 [70.00; 85.00]	83.50 [71.50; 85.75]	0.611
BMI, kg/m^2	30.98±4.82	26.90±2.96	0.070

The results of the influence of gender on the quantitative indicators are presented in Table 2. Laboratory parameters analysis revealed a significant difference in platelet count on a 3rd day after the surgery, with significantly higher levels in women compared to men (289.00 [235.50; 345.00] vs. 190.00 [186.25; 218.50]; p=0.029). However, on a 5th day, the differences between the groups disappeared (p=0.697). Women also had significantly higher ESR before the surgery (24.93±9.04 mm/h vs. 15.33±3.20 mm/h; p=0.021). At the same time, pain scores on the visual analogue scale did not differ between men and women at any observation time point.

Table 2 Comparative statistics of laboratory parameters and pain syndrome depending on gender. ESR - erythrocyte sedimentation rate, * - statistical significance is marked p<0.05

Indicators		Female (N=15)	Male (N=6)	p
Platelets, 10^9/l	Before	212.00 [200.50; 264.00]	211.00 [183.75; 233.75]	0.755
	3rd day	289.00 [235.50; 345.00]	190.00 [186.25; 218.50]	0.029*
	5th day	324.00 [307.50; 372.50]	371.50 [276.75; 416.75]	0.697
White blood cells, 10^9/l	Before	11.33±2.36	12.32±4.87	0.535
	3rd day	7.59±2.62	8.92±2.63	0.309
	5th day	6.80 [6.10; 9.25]	9.10 [8.00; 10.20]	0.243
ESR, mm/h	Before	24.93±9.04	15.33±3.20	0.021*
	3rd day	37.27±12.19	27.00±6.00	0.066
	5th day	35.47±11.95	40.33±15.67	0.449
Pain syndrome, points	1st day	7.07±2.49	5.33±2.34	0,160
	3rd day	5.00 [2.00; 5.50]	4.00 [1.75; 4.75]	0.607
	5th day	3.47±2.67	1.83±1.72	0.185

At the second stage of the study, the subjects were divided into groups depending on BMI into 4 categories, including patients with normal body weight (comparison group), overweight, obesity grade I and obesity grade II) and the general blood test parameters were re-evaluated. The data are presented in Table 3. Analysis of the parameters depending on the BMI category showed that the platelet level at different time points did not have statistically significant differences between the groups (p>0.05). Leukocytes at different time points also did not demonstrate significant differences between patients with different BMI values (p>0.05). When assessing the pain syndrome, it was found that on the 1st day after the surgery, patients with grade I obesity had significantly more pronounced pain (8.67 ± 1.21 points; p = 0.0138) compared to patients with normal weight, but by the 3rdand 5th days the differences between the groups had leveled out.

Table 3 Comparative analysis of variables depending on BMI. BMI - Body Mass Index, ESR - erythrocyte sedimentation rate mm/h, * - marked statistical significance p < 0.05, PLT - platelets, 10^9/l, WBC - white blood cells, 10^9/l, 0 – before the surgery, PS – pain syndrome

Indicators		**BMI**			
		Normal (N=3)	**Overweight (N=8)**	**Obesity I (N=6)**	**Obesity II (N=4)**
Age, years		67.00 [53.00; 71.00]	62.00 [57.75; 69.25] p=0.898	70.50 [68.00; 73.00] p=0.244	66.00 [65.75; 68.75] p=0.439
PLT	0	236.00 [206.50; 285.50]	197.50 [180.00; 212.75] p=0.227	229.00 [209.00; 275.25] p=>0.999	227.00 [206.75; 274.00] p=0.857
	3rdday	227.00 [221.00; 381.00]	195.50 [186.75; 259.25] p=0.278	251.00 [239.00;287.75] p=0.425	324.50 [295.00; 365.75] p=0.914
	5th day	462.67±159.19	309.62±71.63 p=0.055	360.67±79.53 p=0.190	318.75±13.94 p=0.333
WBC	0	12.53±1.12	10.10±2.28 p=0.118	12.85±4.83 p=0.916	12.10±2.21 p=0.771
	3rd day	9.33±0.55	7.44±1.75 p=0.107	9.77±2.78 p=0.803	5.33±2.70 p=0.552
	5th day	10.40 [7.90; 10.50]	7.15 [6.15; 8.85] p=0.222	9.25 [6.75; 11.97] p=0.916	6.90 [6.28; 7.03] p=0.333
ESR	0	30.67±14.01	19.50±8.99 p=0.144	23.00±5.51 p=0.381	20.00±7.79 p=0.228
	3rd day	31.00±20.81	37.12±11.04 p=0.529	31.83±8.16 p=0.559	35.00±13.24 p=0.971
	5th day	40.00 [36.00; 50.50]	30.50 [25.25; 38.25] p=0.222	42.50 [29.75; 52.25] p=0.857	33.00 [32.00; 36.50] p=0.666
PS	1st day	6.00±1.00	6.38±2.67 p=0.822	8.67±1.21 p=0.013*	4.25±2.50 p=0.311
	3rd day	3.33±2.08	4.00±2.67 p=0.563	4.83±1.60 p=0.250	2.00±2.45 p=0.514
	5th day	1.00 [1.00; 2.00]	3.50 [0.75; 4.25] p=0.551	4.00 [3.00; 5.00] p=0.059	1.00 [0.00; 4.00] p=0.800
	10th day	0.00 [0.00; 0.00]	0.50[0.00; 1.00] p=0.363	0.00 [0.00; 2.25] p=0.500	0.00 [0.00; 0.75] p=>0.999

Then the patients were divided into two groups depending on the severity of pain syndrome according to the VAS on the 3rd day of the postoperative period into groups with intense pain syndrome (VAS 6-10 points) and non-intense pain syndrome (VAS 0-5 points). Table 4 presents comparative statistics of quantitative variables in the study groups. When comparing patients with intense and non-intense pain syndrome, assessed on the 3rd day after the surgery, no significant differences in age, height, body weight and BMI were found. Laboratory parameters of the complete blood count also

did not demonstrate statistically significant differences, with the exception of the initial ESR values, which were significantly lower in the group of patients with intense pain syndrome (p=0.007).

Table 4 Comparative analysis of quantitative variables depending on the pain syndrome on the 3rd day of the postoperative period (intense (6-10 points on VAS) and non-intense (0-5 points on VAS) pain syndrome). VAS – visual analog scale, BMI - Body Mass Index, ESR - erythrocyte sedimentation rate, mm/h, PLT - platelets, 10^9/l, WBC - white blood cells, 10^9/l, 0 – before the surgery, PS – pain syndrome, * - marked statistical significance $p < 0.05$

Indicators		**Non-intensive PS(N=16)**	**Intensive PS(N=5)**	**p**
Age, years		66.00 [62.00; 70.50]	70.50 [62.00; 73.00]	0.832
Height, cm		162.47±8.89	162.17±9.97	0.340
Weight, kg		79.47±11.44	75.00±8.07	0.817
BMI, kg/m^2		30.33±5.38	28.52±2.03	0.409
PLT	0	212.00 [197.50; 239.00]	216.00 [187.00; 270.50]	0.362
	3rd day	290.67±111.63	250.17±57.02	0.537
	5th day	324.00 [307.50; 359.50]	375.00 [294.50; 398.50]	0.377
WBC	0	11.70 [10.25; 12.95]	10.10 [8.38; 12.95]	0.134
	3rd day	7.65±2.60	8.77±2.74	0.648
	5th day	7.00 [5.85; 9.50]	9.00 [6.97; 9.97]	0.913
ESR	0	23.20±9.58	19.67±7.09	0.007*
	3rd day	33.80±13.57	35.67±4.93	0.561
	5th day	38.13±12.59	33.67±14.29	0.805

At the next stage, a correlation analysis was performed between anthropometric parameters, general blood test data and pain syndrome at different time points of the postoperative period. The correlation analysis revealed several statistically significant relationships between laboratory parameters and pain syndrome, presented as a correlation matrix in Figure 1. Among the hematological parameters, the most significant correlation was between the platelet level on 5th day (PLT 5) and ESR on 5th day (ESR 5) ($r=0.742$, $p=0.0014$), which may indicate a significant increase in the inflammatory response during this period. Analysis of the dynamics of the pain syndrome on the VAS scale showed that assessments on the 3rd and 5th days have a moderate ($r=0.587$, $p<0.05$), and strong relationship between the 5th and 10th days ($r=0.727$, $p=0.05$), which indicates the stability of the pain phenomenon in the late postoperative period. Correlation analysis revealed that the level of leukocytes measured on the 3rd day after the surgery (WBC 3) demonstrates a moderately pronounced positive relationship with pain assessments on the VAS scale, especially on the third ($r \approx 0.38$, $p=0.009$) and fifth ($r \approx 0.45$, $p<0.05$) days after the surgery. At the same time, preoperative leukocyte values (WBC 0) show a weak negative correlation with pain syndrome on the tenth day ($r \approx -0.36$, $p>0.05$), and the indicators on the fifth day (WBC 5) have practically insignificant correlations with pain assessments.

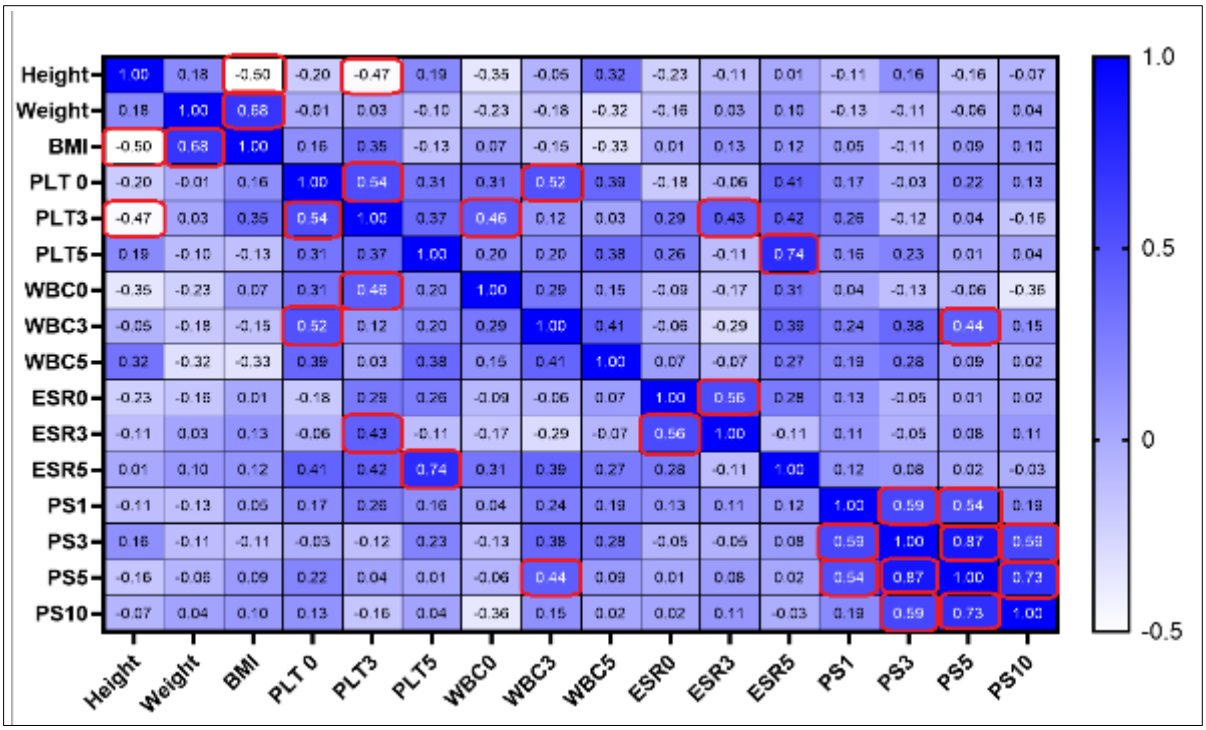

Figure 1 Spearman correlation matrix between clinical and laboratory parameters and pain intensity in the postoperative period. Dark blue indicates strong correlation, light blue indicates weak or no correlation. Red borders indicate statistically significant correlations. BMI – body mass index, PLT 0 – platelets before the surgery, PLT 3 – platelets on the 3rd day, PLT 5 – platelets on the 5th day, WBC 0 – leukocytes before the surgery, WBC 3 – leukocytes on the 3rd day, WBC 5 – leukocytes on the 5th day, ESR 0 – erythrocyte sedimentation rate before surgery, ESR 3 – erythrocyte sedimentation rate on day 3, ESR 5 – sedimentation rate on the 5th day, PS 1 – pain syndrome according to the VAS scale on the 1st day after the surgery, PS 3 - pain syndrome according to the VAS scale on the 3rd day after the surgery, PS 5 - pain syndrome according to the VAS scale on the 5th day after the surgery, PS 10 - pain syndrome according to the VAS scale on the 10th day after the surgery

4. Discussion

The results of the analysis showed that women in the study sample were significantly older than men, had higher BMI values and demonstrated a significant increase in platelet levels on the 3rd day after the intervention. The data obtained are consistent with the results of a number of studies indicating age and hormonal differences in the processes of hemostasis and inflammatory response in men and women [9]. In particular, it is known that in women, especially in the postmenopausal period, the activity of the platelet link of blood coagulation increases, which may explain the identified differences [10]. It was also found that the initial ESR level in women was significantly higher than in men, which may be associated with the influence of estrogen deficiency and metabolic syndrome, activating chronic inflammation [4] , [5]. However, despite the differences in inflammatory parameters, the severity of pain syndrome did not differ between men and women, which confirms the hypothesis about the multifactorial nature of pain sensitivity, including both physiological and psychological aspects [6].

When analyzing the parameters depending on BMI, it was found that body weight affects the severity of pain in the early stages (1st day), but by the 3rd and 5th days the differences were leveled out. A number of studies indicate that obesity is associated with chronic inflammation and altered nociceptive response, which may explain the more pronounced pain sensitivity in obese patients [11] , [12]. However, the absence of differences at later stages may indicate gradual adaptation and involvement of central pain modulation mechanisms. On the other hand, BMI did not affect the platelet level and ESR, which is somewhat at odds with previously published data on hypercoagulability and chronic inflammation in obesity [13] , [14]. This effect is probably leveled out due to the relatively small sample and the absence of severe obesity in most patients.

Patients with intense pain syndrome on the 3rd day had more severe pain sensations in the subsequent periods (the 5th and the 10th days), which confirms the previously described patterns of pain persistence and the formation of chronic

pain syndrome [15]. However, contrary to expectations, pain severity did not correlate with inflammatory markers such as leukocytes and ESR. This may indicate the predominance of central pain mechanisms in this category of patients, where inflammation plays a less significant role compared to neuraxial cytokines [6]. It has previously been shown that in the acute period of pain syndrome, an increase in the level of inflammatory cytokines such as IL-6, TNF-α and CRP can correlate with pain intensity [7]. However, in our study, no significant relationship was observed between ESR and pain syndrome, which may be due to the limited sensitivity of ESR in assessing acute inflammation and a small sample of patients.

Analysis of the dynamics of laboratory parameters showed that the platelet level increased by the 5th day, while the leukocyte levels remained relatively stable. The increase in platelet count may be associated with a response to inflammation and tissue stress, which is supported by data on compensatory activation of megakaryopoiesis in response to tissue damage [8].

ESR showed a tendency to increase in the postoperative period, which is a typical response of the body to the inflammatory process. Similar changes were noted in a number of studies devoted to the analysis of inflammatory reactions after surgical interventions [7] . A moderate positive relationship between the erythrocyte sedimentation rate (ESR) on the 5th day and pain intensity on the 1st day may indicate the role of the inflammatory process in the formation of pain syndrome, which confirms the importance of monitoring inflammatory markers in the management of patients in the postoperative period, but this rather reflects a systemic inflammatory response than local changes associated with nociception. Thus, the obtained data emphasize the importance of early control of inflammation and adequate pain relief in the postoperative period, as well as the need for further research into the mechanisms of the influence of inflammatory processes on pain syndrome.

5. Conclusion

The obtained results demonstrate that gender differences and BMI may influence the levels of laboratory markers of inflammation. Women had a higher level of platelets on the 3rd day and an initial increase in ESR. Obesity of the I degree affects the severity of pain in the early stages, but does not significantly affect inflammatory markers. The obtained data also suggest that the severity of the inflammatory response, especially on the 5th day after the surgery, plays an important role in the formation of persistent pain in patients who underwent knee and hip arthroplasty. The revealed moderate correlations between inflammatory markers and pain assessments emphasize the role of systemic inflammation in the pathogenesis of postoperative pain and justify the need for timely control of the inflammatory response.

Limitations of the study

This study has several limitations that must be considered when interpreting the results. First, the limited sample size reduces the generalizability of the findings to a wider patient population. Second, because the study was conducted at a single center, the results may not be fully applicable to other institutions that use different approaches to postoperative patient management. A third important limitation is the lack of long-term follow-up, which precludes assessing the impact of the differences identified on long-term outcomes.

In addition, not all potentially significant factors were taken into account in the analysis. Although the study included analysis of gender and BMI, such aspects as comorbidities, analgesic therapy and level of physical activity were not considered, which could have affected the results. Heterogeneity of surgical interventions should also be taken into account: the lack of a detailed analysis of their nature may affect the inflammatory response and severity of pain. Another limitation is the subjectivity of pain assessment, since the VAS scale was used, which depends on individual patient perception. This may lead to variability in data and reduce the accuracy of assessments. Thus, further studies with an expanded sample, multicenter design and a longer follow-up period are needed to confirm the obtained results, which will clarify the identified patterns and their impact on postoperative outcomes.

Compliance with ethical standards

Disclosure of conflict of interest

The authors declare that they have no competing interests.

Statement of ethical approval

The study was approved by the Ethics Review Committee of the Bashkir State Medical University, and signed informed consent was obtained from all of the participants.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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