DOI:10.23888/PAVLOVJ20202815-12

СОПОСТАВИТЕЛЬНЫЙ АНАЛИЗ ИЗМЕНЕНИЙ СОСТОЯНИЯ МЕТАБОЛИЗМА КОСТНОЙ ТКАНИ И ЦИТОКИНОВОГО ПРОФИЛЯ У ПАЦИЕНТОВ С НЕСТАБИЛЬНОСТЬЮ ЭНДОПРОТЕЗА ПОСЛЕ ПЕРВИЧНОЙ АРТРОПЛАСТИКИ КОЛЕННОГО СУСТАВА

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Цель. Определить взаимосвязь между уровнями sRANKL и BMP-2, IL1β, TNFα, IL4 в сыворотке крови и определить их роль в патогенезе нестабильности эндопротеза у пациентов после первичной артропластики коленного сустава.

Материалы и методы. Ретроспективно 80 пациентов были разделены на 2 группы: в 1-ю вошли 40 пациентов с остеолизом и асептической нестабильностью эндопротеза коленного сустава, возникшими в сроки до 12 месяцев после операции; во 2-ю – 40 пациентов с имплантат-ассоциированным воспалением, развившимся в сроки от 4 недель до 12 месяцев после первичной артропластики коленного сустава; 20 доноров-добровольцев составили контрольную группу. Содержание sRANKL (пг/мл, Biomedica, Austria), BMP-2 (пг/мл, Ray Bio, USA), а также цитокинов – TNFα (пг/мл), IL1β (пг/мл) и IL4 (пг/мл) (ЗАО «Вектор-Бест», г. Новосибирск, РФ) в сыворотке крови определяли методом иммуноферментного анализа. Сопоставительный анализ статистически значимых показателей проводили с помощью определения R-коэффициента корреляционных рангов Спирмена.

Результаты. У пациентов 1-й группы через 1 мес. после операции обнаружены положительные связи средней силы между уровнем sRANKL и концентрациями BMP-2, TNFα и IL4. Через 12 мес. сохранялись положительные связи изучаемых параметров, однако отсутствовала связь с IL4. У пациентов 2-й группы через 1 мес. после хирургического вмешательства отмечали появление умеренных отрицательных связей sRANKL с BMP-2 и TNFα. Через 12 мес. сохранилась отрицательная связь средней силы sRANKL с BMP-2, кроме того возникли новые умеренные связи: отрицательная – BMP-2 с IL1β, положительные – sRANKL с IL1β и с TNFα, IL1β с IL4.

Заключение. Зарегистрировано, что нарушение метаболических процессов костной ткани, окружающей имплантат, с преобладанием провоспалительных цитокинов, активирующих остеокластогенез, могут являться патогенетическими факторами формирования нестабильности эндопротеза у пациентов после первичной артропластики коленного сустава.

Ключевые слова: *коленный сустав; первичная артропластика; нестабильность эндопротеза; метаболизм костной ткани; цитокины.*

DOI:10.23888/PAVLOVJ20202815-12

COMPARATIVE ANALYSIS OF THE CHANGE OF BONE TISSUE METABOLISM CONDITION AND CYTOKINE PROFILES IN PATIENTS WITH ENDOPROSTHESIS INSTABILITY AFTER PRIMARY KNEE ARTHROPLASTY

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Aim. To define relations between serum concentrations of sRANKL and BMP-2, IL-1β, TNFα, IL-4 as well as their role in endoprosthesis instability pathogenesis in patients following primary knee arthroplasties.

Materials and Methods. 80 patients were retrospectively divided into 2 groups: there were 40 patients with osteolysis and aseptic instabilities of knee endoprosthesises that had developed before 12 months after the surgery in the 1st group; the 2nd group was made up of 40 patients with implantat-associated inflammations that had developed in 4 weeks to 12 months after primary knee arthroplasties. 20 volunteer donors made up the control group. The enzyme-linked assay was used to define serum content of sRANKL (pg/ml, Biomedica, Austria), BMP-2 (pg/ml, Ray Bio, USA), cytokines TNFα (pg/ml), IL-1β (pg/ml) and IL-4 (pg/ml) (Vector-Best, CJSC, Novosibirsk, Russian Federation). The comparative analysis of statistically significant indicants was performed defining Spearman rank correlation coefficient.

Results. Positive statistically valid relations of average force between concentrations of sRANKL and BMP-2, TNFα, IL-4 were found in patients of the first group in 1 month after surgeries. In 12 months positive relations of the parameters under study subsisted although the relation with IL-4 absented. The emerging of moderate negative statistically significant relations of sRANKL with BMP-2 and TNFα was observed in patients of the 2nd group in 1 month after surgeries. In 12 months negative relations of average force between sRANKL and BMP-2 subsisted, also new moderate relations emerged: negative relation of BMP-2 with IL-1β as well as positive of sRANKL with IL-1β and TNFα, IL-1β with IL-4.

Conclusion. We found that the disorder of metabolic processes in bone tissue surrounding the implantat with the predominance of osteoclastogenesis activating pro-inflammatory cytokines might be the pathogenic factors of endoprosthesis instability development in patients following primary knee arthroplasty.

Keywords: *knee joint; primary arthroplasty; endoprosthesis instability; bone tissue metabolism; cytokines.*

Large-joint replacement surgery is a costly, technologically complicated procedure that has the risk of development of post-surgery complications including post-traumatic endoprosthesis dislocations, periprosthetic infecting, instability of the constructions and loss of their functionality. According to literature data, endoprosthesis aseptic instability may result from osteoclast hyperfunction leading to osteolysis of paraimplantat bone [1]. The key role in the development of infectious inflammatory process in the area of surgical intervention is being played by microorganism with their ability to form special biofilms on the surfaces of the implantats [2]. The bacterial toxin activates mononuclear cells of various

DOI:10.23888/PAVLOVJ20202815-12

morphology and functional specialization resulting in systemic and local hyperproduction of cytokines in the area of inflammation [3]. Contemporary researchers have established the involvement of cell interaction mediators, cytokines and growth factors into the processes of bone resorption and modeling in the area of the implanted construction. The key cytokine stimulating resorptive processes is the receptor activator of nuclear factor kappa-B ligand (RANKL) [4]. Osteogenesis proceeds due to growth factors (cytokines) synthesis. One of their representatives is bone morphogenetic protein-2 (BMP-2) [5]. Interleukin-1β (IL-1β) is a pro-inflammatory cytokine and is the first representatives of the family of structurally related cytokines. Its production is a response to the microbial toxins action and has pro-osteoclastogenic activity. Tumor necrosis factor-α (TNFα) is a long known pro-inflammatory cytokine. It intensifies production of other inflammatory mediators and is also a factor of the bone metabolism resorptive component with both direct and intermediate actions to osteoclastogenesis. Interleukin-4 (IL-4) belongs to anti-inflammatory cytokines, its function is to block both spontaneous response and induced production of IL-1β and TNFα synthesized by monocytes and macrophages in the inflammation area [6].

Pathogenetic mechanisms of the development of endoprosthesis instability are characterized with the change in bone metabolism as well as excessive production of mediators including cytokines [7]. It appears important to perform comparative analysis of bone metabolism indicant levels as well as cytokines in serum of patients with endoprosthesis instabilities after primary knee arthroplasty.

The *objective of the study* is to define interrelation between sRANKL and BMP-2 levels, and the contents of IL-1β, TNFα, IL-4 in serum as well as their role in endoprosthesis instability pathogenesis in patients after primary knee arthroplasty.

Materials and Methods

80 patients of both sexes after primary knee arthroplasty were the subjects of the research. The patients suffering complications were retrospectively divided into 2 groups. The 1st group included 40 patients with osteolysis and knee endoprosthesis aseptic instabilities that had emerged before 12 months after surgeries. The 2nd group was also made up of 40 patients with implant-associated inflammations that had developed in 4 weeks to 12 months after primary knee endoprosthesis replacements. There were 20 volunteer donors in the control group. The median cubital vein puncture was performed for all patients in early morning hours before the meals to take 5 ml blood samples. The blood was then left at room temperature to clot; it was later centrifuged at 2000 rev/min for 10 minutes to receive serum. The enzyme-linked assay was used to define serum content of sRANKL (pg/ml, Biomedica, Austria), BMP-2 (pg/ml, Ray Bio, USA) as well as TNFα (pg/ml), IL-1β (pg/ml) and IL-4 (pg/ml) (Vector-Best, CJSC, Novosibirsk, Russian Federation) cytokines in accordance with their use guidelines.

The results of the study were analyzed with AtteStat software designed as Microsoft Excel addin. The obtained data was processed using nonparametric statistics methods and Mann–Whitney U-test for two independent samplings. The comparative analysis of statistically significant indicants was performed with the help of Spearman rank correlation coefficient, at that the values of $R<0.3$ attested for loose relation between the features under study, the values of $R>0.3<0.7$ attested for average relation and >0.7 attested for strong relation. The certainty index (p) was calculated and defined as statistically reliable at values of $p<0.05$. The preformed research was approved by the Ethics Committee of Federal State Budgetary Educational Institution of Higher Education Saratov State Medical University n.a. V.I. Razumovsky (research protocol №6 of February 06, 2018).

Results and Discussion

Proceeding from the results we were provided with the comparative analysis of indicant levels for bone metabolism condition

DOI:10.23888/PAVLOVJ20202815-12

and cytokines in serum of patients of the 1st group after 1 and 12 months after the surgeries we found a number of statistically valid relations (Table 1).

Table 1

Correlation analysis of bone metabolism indicants and cytokines in patients with aseptic instability of endoprosthesises after primary knee arthroplasty

Indicants	sRANKL	BMP-2	IL-1β	TNFα	IL-4
1 month after surgery					
sRANKL		R=0.44 p=0.031	R=0.29 p=0.178	R=0.52 p=0.009	R=0.40 p=0.051
BMP-2	R=0.44 p=0.031		R=0.02 p=0.920	R=0.11 p=0.606	R=-0.04 p=0.843
IL1β	R=0.29 p=0.175	R=0.02 p=0.924		R=0.05 p=0.811	R=0.32 p=0.116
TNFα	R=0.52 p=0.009	R=0.11 p=0.606	R=0.05 p=0.811		R=0.07 p=0.730
IL4	R=0.40 p=0.052	R=-0.04 p=0.843	R=0.32 p=0.116	R=0.07 p=0.730	
12 months after surgery					
sRANKL		R=0.51 p=0.011	R=-0.09 p=0.648	R=0.42 p=0.041	R=0.29 p=0.169
BMP-2	R=0.51 p=0.011		R=-0.10 p=0.639	R=0.19 p=0.352	R=0.05 p=0.832
IL1β	R=-0.09 p=0.648	R=-0.10 p=0.639		R=0.17 p=0.429	R=-0.28 p=0.191
TNFα	R=0.42 p=0.041	R=0.19 p=0.352	R=0.17 p=0.429		R=0.06 p=0.768
IL4	R=0.29 p=0.169	R=0.05 p=0.832	R=-0.28 p=0.191	R=0.06 p=0.768	

Note: R – Spearman rank correlation coefficient, p – certainty index

Thus, in 1 month after surgeries positive statistically valid moderate relations between the level of sRANKL and BMP-2, TNFα, IL-4 concentrations were found. There was found no significant difference between IL-1β level and all other indicants under study. Positive moderate relation between sRANKL and BMP-2 shows the intensification of bone resorption and its remodeling as the response to surgical intervention; initially it manifests itself with osteolysis intensification [1]. Positive correlations between sRANKL and TNFα as well as IL-4 are most likely related with cytokine regulation of bone resorptive activity in the tissue around the prosthesis in the presence of intensification of the immune system humoral component synthesis which is consistent with the literature evidences [8,9]. In 12 months after surgeries in this group of patients positive moderate relations between sRANKL level and BMP-2 as well as TNFα concentrations subsisted which was indicative of intensification of osteoclasts maturation and differentiation [10]. However no statistically valid relations with other indicants under study were found.

At comparative assessment of correlation for the indicants under study it was found that in the 2nd group of patients in 1 and 12 months after surgeries the presence of infectious inflammatory complications resulted in the change of relations orientation and emergence of the valid change for a number of correlations (Table 2).

DOI:10.23888/PAVLOVJ20202815-12

Table 2

Correlation analysis of bone metabolism indicants and cytokines in patients with implant associated inflammation after primary knee arthroplasty

Indicants	sRANKL	BMP-2	IL1β	TNFα	IL4
1 month after surgery					
sRANKL		R=-0.41 p=0.051	R=0.12 p=0.583	R=-0.39 p=0.051	R=-0.14 p=0.513
BMP-2	R=-0.41 p=0.051		R=-0.22 p=0.292	R=0.23 p=0.272	R=-0.10 p=0.63
IL1β	R=0.12 p=0.584	R=-0.22 p=0.294		R=-0.03 p=0.863	R=0.32 p=0.117
TNFα	R=-0.39 p=0.052	R=0.22 p=0.302	R=-0.03 p=0.864		R=0.11 p=0.623
IL4	R=-0.14 p=0.513	R=-0.10 p=0.63	R=0.33 p=0.117	R=0.11 p=0.624	
12 months after surgery					
sRANKL		R=-0.40 p=0.052	R=0.45 p=0.022	R=0.35 p=0.054	R=0.55 p=0.005
BMP-2	R=-0.40 p=0.052		R=-0.41 p=0.044	R=0.24 p=0.251	R=-0.36 p=0.082
IL1β	R=0.45 p=0.022	R=-0.41 p=0.043		R=-0.12 p=0.561	R=0.59 p=0.002
TNFα	R=0.35 p=0.054	R=0.24 p=0.251	R=-0.12 p=0.561		R=-0.07 p=0.743
IL4	R=0.55 p=0.005	R=-0.36 p=0.082	R=0.59 p=0.002	R=-0.07 p=0.742	

Note: R – Spearman rank correlation coefficient, p – certainty index

Thus, in 1 month after surgeries negative statistically valid moderate relations between sRANKL concentration and BMP-2, TNFα levels were observed. No significant relations with IL-1β or IL-4 were found besides the aforesaid as well as between the levels of cytokines under study. In the presence of implantat-associated inflammation the condition of metabolic homeostasis of the bone around endoprosthesis worsens acutely. The bacterial toxin takes part in the activation of serum osteoclastogenic factor (TNFα) causing bone catabolism and preventing its remodeling [11]. In 12 months after knee endoprosthesis replacement in this group of patients besides negative moderate relation between sRANKL concentration and BMP-2 level moderate positive relations between sRANKL and IL-1β, TNFα, IL-4 concentrations emerged. The condition triggering bone metabolic imbalances is the derangement of immune mechanisms in the area of chronic biofilm inflammation with the activation of proresorptive cytokines at the intensification of IL-4 synthesis [12]. In addition to the aforesaid relation of BMP-2 to sRANKL it is worth noting that the moderate negative relation between BMP-2 and IL-1β emerged. The excessive IL-1β production in the post-surgery period stimulates the release of sRANKL thus causing significant bone loss. The data we have received are coherent with the data of Russian researches on cytokine role in bone metabolism regulation [13]. Positive relation between IL-1β and IL-4 concentrations also proves the fact of cytokine regulation for inflammatory response suppressing osteogenesis. No valid relations between IL-4 concentration and concentrations of the rest of indicants under study were found.

DOI:10.23888/PAVLOVJ20202815-12

Conclusion

We have found that derangement of metabolic processes in bone tissue around endoprosthesis with the predominance of osteoclastogenesis activating pro-inflammatory cytokines may work as pathogenic factors for endoprosthesis instability development in patients after primary knee arthroplasty.

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Дополнительная информация [Additional Info]

Источник финансирования. Исследование выполнено в рамках инициативного плана, регистрационный номер АААА-А18-118011790046-8. [**Financing of study.** The study is performed as a part of the initiative plan, Registration № АААА-А18-118011790046-8.]

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, о которых необходимо сообщить в связи с публикацией данной статьи. [**Conflict of interest.** The authors declare no actual and potential conflict of interests which should be stated in connection with publication of the article.]

Участие авторов. Галашина Е.А. – концепция и дизайн исследования, написание текста, Ульянов В.Ю. – редактирование, Гладкова Е.В. – сбор и обработка материала, написание текста, Шпиняк С.П. – сбор и обработка материала, статистическая обработка, Бондаренко А.С. – дизайн исследования, сбор и обработка материала. [**Participation of authors.** E.A. Galashina– concept and design of the study, copywriting, V.Yu. Ulyanov – editing, E.V. Gladkova – data acquisition and processing, copywriting, S.P. Shpinyak – data acquisition and processing, statistical processing, A.S. Bondarenko – study design, data acquisition and processing.]

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DOI:10.23888/PAVLOVJ20202815-12

Цитировать: Галашина Е.А., Ульянов В.Ю., Гладкова Е.В., Шпиняк С.П., Бондаренко А.С. Сопоставительный анализ изменений состояния метаболизма костной ткани и цитокинового профиля у пациентов с нестабильностью эндопротеза после первичной артропластики коленного сустава // Российский медико-биологический вестник имени академика И.П. Павлова. 2020. Т. 28, №1. С. 5-12. doi:10.23888/PAVLOVJ20202815-12

To cite this article: Galashina EA, Ulyanov VYu, Gladkova EV, Shpinyak SP, Bondarenko AS. Comparative analysis of the change of bone tissue metabolism condition and cytokine profiles in patients with endoprosthesis instability after primary knee arthroplasty. *I.P. Pavlov Russian Medical Biological Herald.* 2020;28(1):5-12. doi:10.23888/PAVLOVJ20202815-12

Поступила/Received: 08.07.2019
Принята в печать/Accepted: 31.03.2020