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Analysis of the relationship between degenerative changes in the joint under conditions of hip osteoarthritis with hemostasis disorders in patients based on the results of a biochemical study

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Venous thromboembolism is one of the serious complications that occurs after total hip arthroplasty (THA). Among the risk factors may be the presence of disorders of hemostasis and fibrinolysis in patients before surgical intervention. The aim of study to identify the influence of hip osteoarthritis III–IV stages on the hemostasis of patients before performing THA. Methods. A prospective study was conducted with the participation of 60 patients with hip ostheoarthritis III–IV stages and 30 healthy volunteers (control group). Blood and urine samples were obtained from all participants (in patients — one day before THA). Prothrombin time (PT), activated partial thromboplastin time (APTT), fibrinogen, fibrinolytic activity (FA), soluble fibrin monomer complexes (SFMCs), glycoproteins, sialic acids, chondroitin sulfates (CS), acid and alkaline phosphatases, β lipoproteins were determined in the blood; in urine — oxyproline, uronic acids, Ca and P. The Pearson correlation coefficient (r) was calculated to determine the relationship between markers of hemostasis and connective tissue metabolism. Results. Compared with the control group, the level of alkaline phosphatase in the blood of patients with hip ostheoarthritis level of glycoproteins ($r = 0.97$; $p < 0.05$), cholesterol ($r = 0.91$; $p < 0.05$); the level of SFMCs was correlated with the level of glycoproteins ($r = 0.99$; $p < 0.05$), CS ($r = 0.94$; $p < 0.05$). Conclusions. In patients with hip ostheoarthritis III-IV stages the levels of connective tissue markers (glycoproteins, CS) correlate with the levels of hemostasis markers (fibrinogen, SFMCs). This is of clinical significance for the timely prevention of the development of thromboembolic complications in patients to whom THA is recommended. Key words. Hip replacement, fibrinolysis, fibrinogen, chondroitin sulfates, soluble fibrin monomer complexes.

Венозний тромбоемболізм є одним із серйозних ускладнень, яке виникає після тотального ендопротезування кульшового суглоба (ТЕКС). Серед чинників ризику може бути наявність порушень гемостазу та фібринолізу в пацієнтів до хірургічного втручання. Мета. Виявити вплив наявності коксартрозу III–IV ст. на гемостаз хворих до виконання ТЕКС. Методи. Проспективне дослідження проведено за участю 60 пацієнтів із коксартрозом III–IV ст. та 30 здорових добровольців (контрольна група). У всіх учасників отримали зразки крові та сечі (у пацієнтів — за добу до ТЕКС). У крові визначали протромбіновий час (ПТ), активований частковий тромбопластиновий час (АЧПЧ), фібриноген, фібринолітичну активність (ФА), розчинні фібрин-мономерні комплекси (РФМК), глікопротеїни, сіалові кислоти, хондроїтинсульфати (ХС), кислу і лужну фосфатази, β-ліпопротеїни; у сечі — оксипролін, уронові кислоти, Са та Р. Коефіцієнт кореляції Пірсона (r) розрахований для визначення взаємозв'язку між маркерами гемостазу і метаболізму сполучної тканини. Результати. Порівняно з контрольною групою в крові хворих на коксартроз рівень лужної фосфатази був вищий у 1,5 рази ($p < 0,05$), кислої — у 1,2 разу ($p < 0,05$), β-ліпопротеїдів — у 1,5 разу ($p < 0,05$); глікопротеїнів, сіалових кислот і ХС — в 1,6; 1,7; 5,1 разу відповідно ($p < 0,001$). Рівень фібриногену в пацієнтів був вищим у 1,2 разу, ФА — в 1,6 ($p < 0,001$) за показники контролю. У сечі пацієнтів рівень гідроксипроліну був вищим у 1,7 разу, Са — в 1,4 ($p < 0,05$), а фосфору — нижчим в 1,5 разу ($p < 0,05$). У хворих рівень фібриногену корелював із рівнем глікопротеїнів ($r = 0,97$; $p < 0,05$), ХС ($r = 0,91$; $p < 0,05$); рівень РФМК — із рівнем глікопротеїнів ($r = 0,99$; $p < 0,05$), ХС ($r = 0,94$; $p < 0,05$). Висновки. У пацієнтів із коксартрозом III–IV ст. рівні сполучнотканинних маркерів (глікопротеїни, ХС) корелюють із рівнями маркерів гемостазу (фібриноген, РФМК). Це має клінічне значення для своєчасної профілактики розвитку тромбоемболічних ускладнень у хворих, яким рекомендоване ТЕКС. Ключові слова. Артропластика кульшового суглоба, фібриноліз, фібриноген, хондроїтинсульфати, розчинні фібрин-мономерні комплекси.

Key words. Hip replacement, fibrinolysis, fibrinogen, chondroitin sulfates, soluble fibrin monomer complexes

Introduction

Venous thromboembolism, which occurs in 0.6–1.5 % of cases, is one of the serious complications after total hip replacement [1]. The low incidence is conditioned by the use of anticoagulants after surgery to prevent venous thromboembolism [2, 3], and in its absence, the possibility of complications increases to 50 %. At the same time, the use of modern anticoagulants, such as factor Xa inhibitors, has a side effect in the form of clinically significant bleeding [4]. In this regard, it is important to search for factors that influence the development of venous thromboembolism, in particular, to study the prerequisites for a hypercoagulable state, which is one of the causes of venous thromboembolism [5] and may result from hyperactivity of platelets in some patients [6]. In patients with coxarthrosis, as a result of degenerative changes in articular cartilage and subchondral bone, various metabolic compounds are released into the blood, which probably affect the hemostasis system. In particular, glycosaminoglycans are components of cartilage tissue, and some of them (heparin) have an anticoagulant effect [7]. Other glycosaminoglycans, such as chondroitin sulfates, heparan sulfates, and hyaluronate, can have a similar therapeutic effect [8]. Chronic inflammation in the joint under the conditions of osteoarthritis [9] also negatively affects hemostasis [10, 11], which was shown in a study involving patients before total hip or knee replacement [12]. In clinical studies, the presence of disorders in the fibrinolytic system before surgical intervention was found in persons who underwent total hip replacement [13, 14].

The search for interrelationships between the hemostasis system and metabolic disorders on the part of the connective tissue will allow us to gain new knowledge about the mechanisms of coagulopathy development in coxarthrosis and reduce the risk of thromboembolic complications after endoprosthetic repair. Timely detection of disorders in the hemostasis system based on biochemical studies and indicators of fibrinolysis in patients with coxarthrosis is a prerequisite for their effective and adequate pharmacotherapy with direct and indirect anticoagulants and thrombolytic drugs to prevent the development of thromboembolic complications.

The purpose of the study: to reveal the effect of stage III–IV coxarthrosis on hemostasis of patients before total hip replacement.

Material and methods

The study was carried out in accordance with modern bioethical norms; the design was discussed and approved at a meeting of the Bioethics Committee at the State Institution Professor M. I. Sytenko Institute of Spine and Joint Pathology of the National Academy of Medical Sciences of Ukraine (Protocol No. 224 of 13.06.2022).

The prospective study was conducted in 2018–2020. Among the patients who applied to the institution, 60 individuals with stage III–IV coxarthrosis according to Kellgren-Lawrence were selected, who were scheduled to undergo total hip replacement. 30 volunteers without signs of orthopedic diseases were included in the control group. Exclusion criteria were diseases of the kidneys, liver, tumors, blood coagulation disorders, taking aspirin or other antiplatelet agents. Patients with coxarthrosis did not differ in age and body mass index (BMI) from volunteers of the control group (Table 1).

Biochemical methods

Blood and urine samples were taken from all study participants for biochemical tests. A blood sample of 5 ml was taken from patients with coxarthrosis one day before total hip replacement and from healthy volunteers in vacuum tubes of Vacutest® (BioLine, Ukraine) with a coagulation activator and separating gel. After that, the collected blood serum was centrifuged for 15 minutes (2,000 rpm).

To measure coagulometric indicators, blood was drawn into a tube with 3.8 % sodium citrate. The ratio of sodium citrate to blood was precisely 1:9 (1 ml of citrate and 9 ml of blood or 0.5 ml of citrate and 4.5 ml of blood). All blood tests were performed using a biochemical semi-automatic analyzer StarDust MC15 (DiaSys Diagnostic Systems, Germany), with measurement limits of (640–920 ± 2) nm. To evaluate

Table 1

Characteristics of study participants

Parameter	Coxarthrosis (n = 60)	Control group (n = 30)
Gender (men)	30 (30)	15 (15)
Age, years	46.1 ± 0.79	46.2 ± 1.22
Height, cm	167.1 ± 0.89	167.0 ± 1.30
Weight, kg	72.4 ± 1.64	69.4 ± 1.77
BMI (kg/m^2)	25.9 ± 0.59	24.9 ± 0.66

Note. Student's t-test; results are presented as mean ± standard error. * — differences are significant compared to the control group, if $p < 0.05$. BMI is the body mass index.

indicators in the urine of all study participants, its 24-hour collection was performed.

The following biochemical indicators were measured in blood serum: glycoproteins, chondroitin sulfates, sialic acids, acid and alkaline phosphatase activity, total protein and calcium, ionized calcium, cholesterol, β-lipoproteins. Soluble prothrombin time (PT), activated partial thromboplastin time (APTT), fibrinogen, fibrinolytic activity (FA), soluble fibrin monomer complexes (SFMC) were determined in blood plasma. The level of uronic acids, hydroxyproline, calcium and phosphorus was evaluated in urine. Glycoproteins, sialic acids, chondroitin sulfates in blood serum, hydroxyoxyproline and uronic acids in urine were measured according to the methods described by us earlier [15]. Activity of acid and alkaline phosphatase, total protein and calcium, ionized calcium, cholesterol, β-lipoproteins, coagulometric indicators in blood, level of calcium and phosphorus in urine were measured according to the instructions for the respective kits.

Statistical analysis

Study results are presented as mean ± standard error. The normality of the distribution was checked using the Kolmogorov-Smirnov method. To determine the effect of coxarthrosis on the biochemical indicators of patients, a comparative analysis was performed using the Student's t-test method. The search for relationships between indicators of hemostasis and connective tissue exchange was performed using Pearson's correlation analysis. Statistical analysis was performed using Statsoft Statistica 6.0 software (Microsoft Windows, USA). Differences were considered statistically significant at $p < 0.05$.

Results and their discussion

Compared with the control group, the level of alkaline and acid phosphatase in the blood of patients with coxarthrosis was 1.5 and 1.2 times higher ($p < 0.05$), respectively, and β-lipoproteins were 1.5 times higher ($p < 0.05$); the level of glycoproteins, sialic acids, chondroitin sulfates 1.6; 1.7; 5.1 times ($p < 0.001$) higher, respectively. Other measured indicators in patients with coxarthrosis did not differ significantly from controls (Table 2).

The values of hemostasis markers in the blood plasma of patients with coxarthrosis were higher compared to the control group: 1.2 times for fibrinogen ($p < 0.001$), 1.6 times for FA and SFMC levels ($p < 0.001$). The parameters of PT and APTT did not significantly differ from the control (Table 3).

In the daily urine of patients with coxarthrosis, the following levels were higher than those of the control group: the level of hydroxyproline 1.7 times ($p < 0.05$), calcium 1.4 times ($p < 0.05$); and phosphorus 1.5 times lower ($p < 0.05$). The level of uronic acids did not differ significantly from the control group (Table 4).

According to the results of the correlation analysis in patients with coxarthrosis, the level of fibrinogen was correlated with the level of glycoproteins ($r = 0.97$; $p < 0.05$) and chondroitin sulfates ($r = 0.91$; $p < 0.05$); the level of SFMC also correlated with the level of glycoproteins ($r = 0.99$; $p < 0.05$) and chondroitin sulfates ($r = 0.94$; $p < 0.05$). In the control group, no significant correlation with the level of glycoproteins or chondroitin sulfates was found either for fibrinogen (for glycoproteins $r = 0.002$; $p > 0.05$; chondroitin sulfates $r = 0.14$; $p > 0.05$) or for SFMC (for glycoproteins $r = –0.29$; $p > 0.05$; chondroitin sulfates $r = –0.17$; $p > 0.05$).

Besides, in patients with coxarthrosis, the level of fibrinogen correlated with the level of SFMC ($r = 0.98$; $p < 0.05$), while this was not found in the control group ($r = 0.06$; $p > 0.05$).

Discussion

A comprehensive laboratory study, which included an assessment of biochemical indicators of the metabolism of connective tissue and the hemostasis system in patients with coxarthrosis before performing total hip replacement, showed a simultaneous violation of hemostasis and an increase in the blood level of markers of inflammatory and destructive processes of cartilage and bone tissue.

Table 2

Markers of connective tissue metabolism in the blood serum of patients with stage III–IV coxarthrosis compared to healthy individuals

Biochemical index	Control group (n = 30)	Coxarthrosis (n = 60)
Total protein, g/l	78.10 ± 1.400	73.29 ± 0.83
Total calcium, mmol/l	2.510 ± 0.040	2.39 ± 0.01
Ionized calcium, mmol l	1.16 ± 0.020	1.17 ± 0.01
Phosphorus, mmol/l	1.46 ± 0.120	1.26 ± 0.02
Alkaline phosphatase, unit/l	165.50 ± 11.050	245.73 ± 7.50*
Acid phosphatase, unit/l	3.75 ± 0.210	4.61 ± 0.12*
Cholesterol, mmol/l	4.97 ± 0.200	4.83 ± 0.14
β lipoproteins, g/l	4.91 ± 0.200	7.39 ± 0.32*
Glycoproteins, g/l	0.68 ± 0.010	1.10 ± 0.01**
Sialic acids, mmol/l	2.00 ± 0.030	3.31 ± 0.16**
Chondroitin sulfates, g/l	0.08 ± 0.004	0.41 ± 0.03**

Note. Student's t-test; results are shown as mean ± standard error. Differences are significant compared to the control group: * — $p < 0.05$; ** — $p < 0.001$.

Table 3

Markers of blood hemostasis in patients with stage III-IV coxarthrosis compared to healthy individuals

Marker	Control group (n = 30)	Coxarthrosis (n = 60)
Prothrombin time, sec	16.40 ± 0.34	15.60 ± 0.74
APTT, sec	29.50 ± 5.00	29.7 ± 1.74
Fibrinogen, g/l	2.52 ± 0.12	3.11 ± 0.30*
Fibrinolytic activity, min	6.53 ± 0.34	10.48 ± 0.25*
SFMC, mg/100 g	3.33 ± 0.05	5.50 ± 0.88*

Note. Student's t-test; results are shown as mean ± standard error. Differences are significant compared to the control group: * — $p < 0.001$. APTT — activated partial thromboplastin time; SFMC— soluble fibrin monomer complexes.

The detected changes in the biochemical parameters of the blood serum are probably due to the presence of degenerative disorders in the joint. The development of coxarthrosis is accompanied by destructive processes in the tissues of the joint, which is confirmed by a significant increase in the activity of alkaline and acid phosphatases (1.5 and 1.2 times respectively) in blood serum compared to healthy individuals. An increase in acid phosphatase activity is associated with degenerative changes in the subchondral bone of the joints, as this enzyme is secreted by osteoclasts during bone resorption. Also, a significant amount of acid phosphatase is contained in platelets, the indicator of which increases in patients with coxarthrosis [11]. Presumably, the increase in acid phosphatase activity occurs due to its release from platelets, as they have procoagulant activity during interaction with thrombin and collagen [16]. The time course of the increase in this indicator may be related to changes in coagulation under the conditions of stage III–IV coxarthrosis.

The indicators of connective tissue metabolism in blood serum (glycoproteins, sialic acids and chondroitin sulfates) in patients with coxarthrosis were significantly higher compared to controls. The level of chondroitin sulfates differed the most (by 5.1 times), which is caused by the degeneration of articular cartilage [17], as they are one of the main components of its matrix.

The established higher level of β-lipoproteins in the blood serum of patients with coxarthrosis compared to the control group indicates a concomitant metabolic syndrome and inflammation in the joint [18, 19]. An increase in the level of β-lipoproteins may be associated with damage to the vascular endothelium and an increase in the risk of thrombosis [20].

Table 4

Markers of excretion of connective tissue metabolites in patients with stage III-IV coxarthrosis compared to healthy individuals

Marker	Control group (n = 30)	Coxarthrosis (n = 60)
Oxproline, mg/day	25,00 ± 1,40	41,60 ± 1,30*
Uronic acids, mg/day	4,50 ± 0,22	4,34 ± 0,32
Calcium, mg/day	125,00 ± 7,90	172,00 ± 8,90*
Phosphorus, mg/day	1,06 ± 0,09	0,71 ± 0,09*

Note. Student's t-test; results are shown as mean ± standard error. Differences are significant compared to the control group: * — $p < 0.05$.

Assessment of the level of excretion of uronic acids, hydroxyproline, calcium and phosphorus in patients with coxarthrosis also revealed differences from the control group. In particular, the level of excretion of hydroxyproline with urine exceeded the control indicator, suggesting an activation of collagen metabolism with a huge predominance of its catabolism. The higher level of calcium and lower level of phosphorus in the urine of patients compared to healthy individuals is probably explained by the disturbance of phosphorus-calcium metabolism.

Evaluation of hemostasis indicators in the blood plasma of patients with coxarthrosis showed higher levels of fibrinogen, SFMC and higher fibrinolytic activity, as well as the absence of a significant difference for indicators of PT and APTT compared to the control group. S. Wanderling with co-authors [14] also showed a 1.2 times higher level of fibrinogen in patients before total hip replacement compared to healthy individuals. In another study, an elevated level of fibrinogen was determined in 20 % of patients before total hip replacement [21]. G. Mitana et al. [22] showed that the level of SFMC correlates with the development of deep vein thrombosis in patients after total knee replacement. Contrary to this, H. Watanabe et al. [23] did not find a significant difference in the level of SFMC in patients before total knee replacement depending on the subsequent occurrence of asymptomatic venous thromboembolism. At the same time, the time course of SFMC in patients before the specified surgical intervention is poorly studied.

Under the conditions of coxarthrosis, the revealed relationship between the indicators of connective tissue markers (glycoproteins, chondroitin sulfates) and indicators of hemostasis (fibrinogen, SFMC) confirms our hypothesis about the relationship between the time course of fibrinolysis indicators and degenerative changes in the bone and cartilage tissues of the joints. The general link that explains the detected

correlation is probably the «plasminogen activator / plasmin» system [24]. It regulates fibrinolysis by converting plasminogen to plasmin, the active form that causes thrombolysis, and also promotes tissue remodeling by destroying the extracellular matrix by activating metalloproteinases [25]. One of the components of this system, which regulates the conversion of plasminogen to plasmin, an inhibitor of plasminogen activator-1, is contained in platelets, leads to increased biosynthesis of metalloproteinases-13, -3, -9 by chondrocytes, affecting the degradation of the cartilage matrix in osteoarthritis [26]. At the same time, the inhibitor of plasminogen activator-1 after release from platelets can participate in inflammation regardless of its effect on plasminogen activators [25]. That is, inflammation in the joint in osteoarthritis causes an increase in the synthesis of metalloproteinases and the entry into the blood of cartilage matrix degradation products (chondroitin sulfates). At the same time, an excessive amount of «acute phase proteins» — glycoproteins that are inhibitors of proteolysis, including fibrinolysis — accumulates in the blood. [27]. Some glycoproteins prevent fibrinolysis by primarily binding the active form of plasminogen — plasmin. [28]. As a result, fibrin is not used as a substrate for plasmin [29], and this probably leads to the accumulation of fibrinogen, SFMC in the blood plasma and an increase in fibrinolytic activity.

Conclusions

In patients with stage III-IV coxarthrosis, the levels of connective tissue markers (glycoproteins, chondroitin sulfates) correlate with the levels of hemostasis markers (fibrinogen, SFMC). This is of clinical importance for the timely prevention of thromboembolic complications in patients who are recommended total hip replacement.

Conflict of interest. The authors declare no conflict of interest.

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ANALYSIS OF THE RELATIONSHIP BETWEEN DEGENERATIVE CHANGES IN THE JOINT UNDER CONDITIONS OF HIP OSTEOARTHRITIS WITH HEMOSTASIS DISORDERS IN PATIENTS BASED ON THE RESULTS OF A BIOCHEMICAL STUDY

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