

Venher Ihor K., Kostiv Sviatoslav Ya., Khvalyboha Dymytrii V. Risk factors for venous thrombosis in patients with endoprosthetics of hip joints. *Journal of Education, Health and Sport*. 2021;11(09):875-885. eISSN 2391-8306. DOI <http://dx.doi.org/10.12775/JEHS.2021.11.09.102> <https://apcz.umk.pl/JEHS/article/view/JEHS.2021.11.09.102> <https://zenodo.org/record/5765457>

The journal has had 5 points in Ministry of Science and Higher Education parametric evaluation. § 8.2) and § 12.1.2) 22.02.2019.  
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The authors declare that there is no conflict of interests regarding the publication of this paper.

Received: 25.08.2021. Revised: 12.09.2021. Accepted: 30.09.2021.

## Risk factors for venous thrombosis in patients with endoprosthetics of hip joints

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**Funding:** "This research received no external funding"

**Conflicts of Interest:** "The authors declare no conflict of interest."

Materials of the study meet the requirements of the rules and principles of bioethics (in accordance with the basic provisions of the GSP (1996) of the Council of Europe Convention on Human Rights and Biomedicine (dated 04.04.1997), the Declaration of the World Medical Association on the Ethical Principles of Conducting Scientific Medical Research with Human Participation (1964-2000), and the Ministry of Health of Ukraine Order No. 281 of 01.11.2000, the Code of Ethics of the Scientist of Ukraine (2009)) and were approved by the Bioethics Committee of I. Horbachevsky Ternopil National Medical University (protocol №52, 04.03.2019).

### Abstract

**Background.** Important part of orthopaedic surgery is endoprosthetics of hip joints, which eliminates pain syndrome, restores the amplitude of movements and the support ability of the lower limb. But there is a number of complications; venous thromboembolism among them occupies a leading place.

**Material and methods.** 219 patients with a mean age of  $64.7 \pm 3.8$  years were operated. In 137 (62.1%) observations, total cement hip replacement was performed for

osteoarthritis. 82 (37.4%) patients received total and unipolar cement hip replacement for cervical femoral neck fractures.

**Results.** Clinical manifestations of non-specific connective tissue dysplasia were detected in 83 (37.9%) patients, which were confirmed by the laboratory determination of the level of general, bound and free oxyproline. In the postoperative period, the thrombotic process in the venous system of the inferior vena cava was diagnosed in 23 (10.5%) observations. Operative intervention on the hip joint in patients with nonspecific dysplasia of connective tissue in 11 (13.3%) cases was complicated by the development of venous thrombosis. In patients without non-specific connective tissue dysplasia, postoperative thrombosis in the system of the inferior vena cava was diagnosed in 12 (8.8%) observations.

**Conclusions.** Patients with osteoarthrosis of the hip joint and the femoral neck fracture accompanied by the non-specific dysplasia of the connective tissue are characterized by expressed levels of endothelial dysfunction and increased activity of the blood-coagulation system.

**Key words: thromboembolism; endoprosthesis; dysplasia.**

**Introduction.** Significant occurrence of diseases of the joints of the lower extremities leads to the search for effective methods of treatment. Among them endoprosthesis of the joints have leading position. It allows to eliminate pain syndrome, to restore the amplitude of movements and support ability of the lower limb [1]. During endoprosthesis, a number of complications often occurs, among which VTEC remain relevant [2]. To prevent venous thromboembolic complications, direct anticoagulants are used predominantly. The factors that predispose a high risk of venous thromboembolism in patients at endoprosthesis of the joints are taken into account [3]. But there is no significant decrease of frequency of development of VTEC [4].

### **Materials and Methods**

219 patients with a mean age of  $64.7 \pm 3.8$  years were operated. In 137 (62.1%) observations, total cement hip replacement for osteoarthritis was performed. 82 (37.4%) patients received total and unipolar cement hip replacement for cervical femoral neck fractures. Operative intervention was carried out under subdural anesthesia with the use of bupivacaine.

Clinical manifestations of NCTD were detected in 83 (37.9%) patients. This was confirmed by laboratory determinations of the level of general, bound and free oxyproline. The method of P.N. Sharaev for a calibrated curve was used.

In all observations mechanical prophylaxis of VTEC by elastic compression of the lower extremities was used. Pharmacological prevention of VTEC was performed using LMWH (enoxaparin).

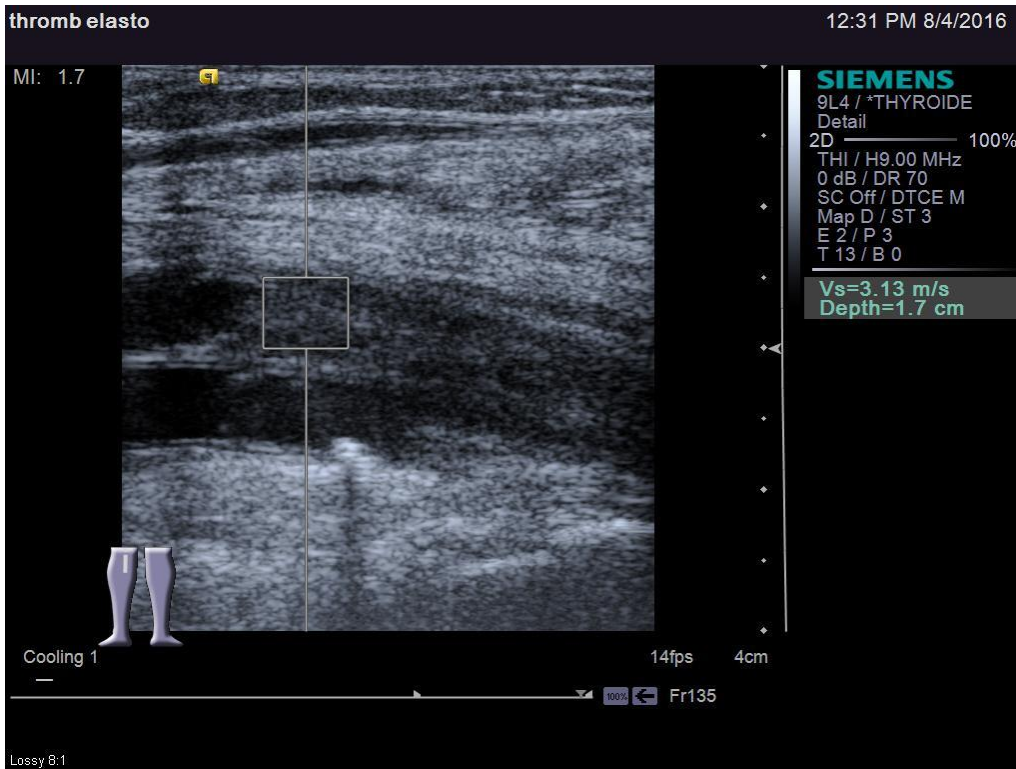
In the postoperative period, the thrombotic process in the venous system of IVC was diagnosed in 23 (10.5%) observations. Operative intervention on the hip joint in patients with NCTD in 11 (13.3%) cases was complicated by the development of venous thrombosis. In patients without NCTD, postoperative thrombosis in the venous system of IVC was diagnosed in 12 (8.8%) observations. In 21 patients, postoperative thrombosis was detected in the deep venous system of IVC and only in two observations in the superficial venous system.

Monitoring of the thrombotic process in the venous system of the inferior vena cava was performed by duplex ultrasound scans of the vessels of the lower extremities by Sonoscape S8exp with a frequency of 5-12 MHz and 2.5-4 MHz from the first day of the postoperative period. In the first day of the postoperative period, in two patients we diagnosed the thrombotic processes in the deep veins of the IVC system, on day 2 - in 5 observations, on the 3rd day - in one patient, on 6, 7 and 8 days – in 3, 5 and 2 cases, respectively, and on 11 and 12 days - in one and two patients, respectively. In the superficial venous system of the lower limb, the thrombotic process was detected in two observations at 6 and 10 days of the postoperative period.

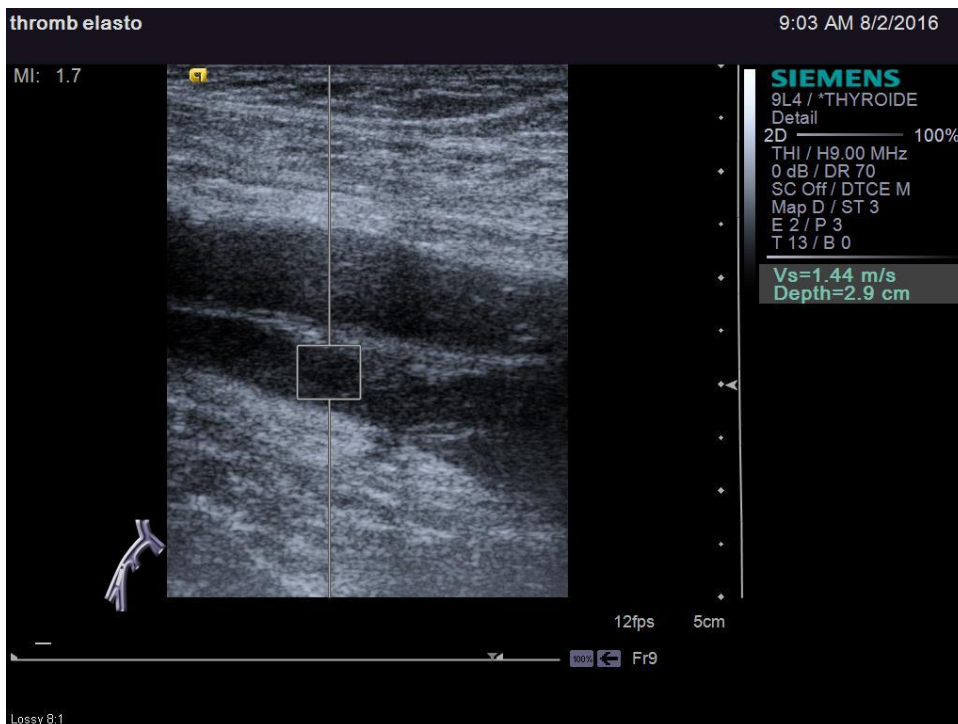
8 (34.9%) cases of the venous thrombotic processes were diagnosed in the first three days of the early postoperative period in patients with NCTD.

To choose the treatment tactics for venous thrombosis of the IVC system, the determination of thrombogenicity of thrombotic masses was performed. The elastographic properties of the venous thrombus were studied by the ultrasonic system Siemens Acuson S2000 (Germany). At the shear wave expansion speed of 2.5 - 2.6 m/s – there is a high risk of embologeneity of the thromb, at the shear wave expansion speed of 2.7 - 2.9 m/s – there is a moderate risk of embologeneity of the thromb, at the shear wave expansion speed of 3.0 m/s and more there is no threat of embolism.

In two observations on the second day of the postoperative period using the ultrasonic system Siemens Acuson S2000 (Germany) we established the propagation of the shear wave at 2.5 - 2.6 m/s in the thrombotic mass of the vein, which is a significant threat to the development of pulmonary embolism. This was an indication for the urgent surgical intervention to eliminate the threat of TPA. In all other cases anticoagulant therapy was performed.



**Figure 1.** Thromboelastography of thrombosis of the right popliteal vein



**Figure 2.** Thromboelastography of the thrombosis of the right common femoral vein

The determination of indexes of the coagulation and fibrinolytic system was performed: fibrinogen was determined by gravimetric method according to R.A. Rutberg; activity of the fibrin stabilizing factor (F XIII) – by means of the "set for determination of

FBA-XIII" of the scientific-production firm "SIMKO Ltd" (Lviv); thromboplastic activity of blood - by B. A. Kudryashov and P. D. Ulytina method; Plasma recalcification time - by Bergerhof and Rock method; plasmin, plasminogen, total fibrinolytic activity (TFA) - by V.A. Monastyrska et al. method (1988); time of lysis of euglobin clots - using the "Set for the determination of fibrinolytic blood plasma activity" of the scientific and production firm SIMKO Ltd (Lviv). D-dimer was determined by immunoanalytic method using a coagulometer. The determination of soluble fibrin-monomer complexes was performed using the Tablet method.

The state of the endothelial system was evaluated by determining the level of endothelial dysfunction markers: the concentration of P-selectin, E-selectin, tissue plasminogen activator (t-PA), type 1 vascular endothelium adhesion molecule (sVCA M-1) was determined using the "Bender MedSystems" (Austria) for immune-enzyme analysis. Endothelin-1 concentration was determined using the Biomedica (Canada) kits for immune-enzyme analysis. The reaction was evaluated on a SUNRISE microplate semimetric photometer ("Tecan Austria") using the Hydroflex washing station ("Tecan Austria"). To determine CEC (CEC) we used J.Hiadovec and N.N.Pertishchev et al. method (2001). The level of nitrogen oxide (NO) metabolites, vascular endothelial growth factor (VEGF) was determined by the immune enzyme method using the KHGO111-VTGF analyzer and the Griess reagent.

Due to the surgical trauma and the fact that changes in hemocoagulation begin to occur during the operation [8], indices were determined in the preoperative period, 6 and 12 h after surgery, and in patients with NCTD also at the traumatic stage of the intervention.

There was no control group in the study. The results of laboratory testing of patients were compared with the standard normal values for each index.

Statistical processing of digital data was performed by Excel and STATISTICA software and using parametric and non-parametric methods of estimating the obtained data. The values of the arithmetic mean of the sample (M), its variance and the error of the mean (m) were calculated for all indices. The significance of the difference of values between the independent quantitative values was determined at normal distribution by the Student's t-test, in other cases - by the Mann-Whitney U-test (differences at  $p < 0.05$  were considered significant).

## Results

The study included 136 patients (group I) with hip joint osteoarthritis and femoral neck fracture and 83 patients (group II) with osteoarthritis of the hip joint and femoral neck fracture and associated NCTD.

The state of the endothelial system reflects the pathology of the organism. In patients with osteoarthritis of the hip joint and femoral neck fracture we noted elevated level of all endothelial system markers. At the same time, the level of indicators of endothelium status was more expressed in patients (group II) with pathology of hip joint in the presence of NCDT (Table 1). Thus, at the preoperative stage of treatment, the blood level of CEC was 1.8 times higher ( $P < 0.001$ ), endothelin-1 level was 2.2 times increased ( $P < 0.001$ ), P-selectin and E-selectin levels arose 1.5 ( $P < 0.001$ ) and 1.2 ( $P < 0.05$ ) times comparing to indicators of healthy persons, respectively. There was 1.8 times ( $P < 0.001$ ) increase of blood NO levels and a slight 1.2 times ( $P < 0.05$ ) increase of the VEGF blood contents.

Table 1

Characteristics of the endothelial system in patients with pathology of the hip joint

Index	CEC, of cells $\times 10^4/l$	sVCAM1, ng/ml	P-selectin, ng/ml	E-selectin, ng/ml	t-PA, ng/ml	Endothelin-1, fmol/ml	NO, umol/l	VEGF, pk/ml	
Standard values	4.04±1.09	229.43±35.31	154.82±19.54	40.79±10.13	3.68±0.73	4.12±0.35	21.39±4.71	51.43±5.59	
Group I	Preoperative	5.56±1.23*	257.83±26.61	175.10±23.35	49.65±8.17*	3.10±0.30	5.53±0.37	34.16±5.54	57.05±5.35
	Postoperative, 6 hrs.	7.87±2.89**	357.68±29.85**	173.21±17.94	42.27±8.32	2.53±0.38	7.51±0.41	34.29±5.65	59.12±5.76
	Postoperative, 12 hrs	8.13±3.52**	363.61±31.27**	179.18±18.69	35.69±6.14**	2.25±0.47	6.77±0.45**	37.13±5.13	58.75±8.54
Group II	Preoperative	7.35±1.51*	293.57±28.62*	235.16±25.72*	48.43±6.46	2.58±0.35*	9.11±0.45*	39.21±5.43*	60.11±6.85
	Postoperative, 6 hrs.	9.15±3.71**	397.14±34.18	199.16±71.59	30.67±7.16**	2.45±0.28	12.58±0.56**	43.62±5.17	62.27±6.61
	Postoperative, 12 hrs.	10.81±3.61**	415.17±45.23**	194.58±67.27**	32.74±6.36**	2.31±0.25	13.41±0.54**	45.87±5.39	68.21±6.97

Note: \* - a significant difference between the indicators of norm and indicators before the operation of patients of I and II groups; \*\* - a significant difference between the indicators of patients of groups I and II before the operation and the indicators 6 hrs and 12 hrs after the surgery.

Operative intervention in patients of group II contributes to the formation of severe endothelial dysfunction. This is especially noticeable at twelfth hour of the postoperative

period. The latter occurs due to a 1.5 times increase ( $P < 0.05$ ) of the contents of CEC in blood and a 1.5 times increase ( $P < 0.05$ ) in endothelin-1, a 1.2 times ( $P < 0.05$ ) and 1.5 times decrease ( $P < 0.05$ ) of P-selective and E-selectin levels, respectively, in comparison with the preoperative period. There was also a slight increase of NO contents in blood and 1.3 times ( $P < 0.05$ ) increase of VEGF contents in blood.

At the stage of preoperative preparation of patients, activation of the haemostasis system was observed (Table 2). This is more expressed among patients of the second group. Indicators that characterize the condition of the coagulation system of patients with NCTD were 1.2 times higher than those of the patients without NCTD. In patients with NCTD in the preoperative period, the content of fibrinogen was  $5.07 \pm 0.35$  g/l, (indices in healthy patients were  $3.52 \pm 0.34$  g/l ( $p < 0.05$ )). At the same time, increase of the contents of SCFM in blood was determined to  $0.57 \pm 0.11$  units.extr. ( $P < 0.05$ ). Monomers that appear as a result of the separation of fibrinopeptides A and B from fibrinogen under the influence of thrombin, form macromolecular degradation products of fibrin with it. Trombinaemia was confirmed by the increase up to  $2.61 \pm 0.23$  ng/ l ( $p < 0.05$ ) of FPA content. At the same time, elevated to  $6.92 \pm 2.09$   $\mu$ g/ l (norm  $4.71 \pm 1.58$   $\mu$ g/ml) content of the FDP was detected. It took place on the background of minimal changes of the FBA and in the absence of any changes of level of AT III and PRT.

Table 2

The state of haemostasis in patients with pathology of the hip joint

Index	Preoperative Group I	Preoperative Group II	Norm
Fibrinogen, g/l	$4.16 \pm 0.18$	$5.07 \pm 0.35^*$	$3.52 \pm 0.34$
Soluble complexes of fibrin monomers (SCFM), units.extr..	$0.48 \pm 0.06$	$0.57 \pm 0.11^*$	$0.42 \pm 0.04$
Fibrinopeptide A, ng/ml	$2.04 \pm 0.28$	$2.61 \pm 0.23^*$	$1.82 \pm 0.24$
Fibrin degradation product, mcg/ml	$5.26 \pm 2.14$	$6.92 \pm 2.09^*$	$4.71 \pm 1.58$
Fibrinolytic blood activity, %	$50.63 \pm 0.54$	$54.49 \pm 0.53$	$50.63 \pm 0.46$
Antithrombin III, %	$93.83 \pm 7.56$	$89.77 \pm 8.09$	$96.72 \pm 6.22$
Plasma recalcification time, c	$104.42 \pm 9.68$	$91.67 \pm 10.31$	$110.15 \pm 8.57$

Note: \* - a significant difference between the norm and levels in patients in groups I and II.

Significant changes of coagulation system occur during the intraoperative period of surgical treatment of the patient. At the traumatic stage of surgical intervention the formation of a hypercoagulative condition of blood occurs. During this period, the fibrinogen level in the blood exceeded the preoperative level by only 10.2%, then the blood contents of SCFM was 1.4 times ( $p < 0.05$ ) increased, the contents of FPA was 1.7 times ( $P < 0.001$ ) increased, the

contents of FDP was 1.9 times increased (P <0.001). It took place on the background of reduced fibrinolytic activity of blood, reduced contents of AT III in blood, decrease of PRT (Table 3).

The maximum level of hypercoagulation was reached at 6 hrs of early postoperative period. At this time, the blood fibrinogen level 1.3 times (p <0.05) exceeded the preoperative rate, and the contents of SCFM in blood was 2.1 (P <0.001) times increased, the content of FPA and FDP – 2.7 and 2.8 (P <0.001) times, respectively. It happened at the 1.3 times decrease (p <0.05) of fibrinolytic activity of blood, the decrease of the contents of AT III, and a slight decrease of PRT.

Table 3

The intraoperative state of haemostasis in patients with hip arthritis and NCTD

Index	Preoperative	Traumatic stage	3hr. p/o	6hr. p/o	12 hr. p/o
Fibringen, g/l	5.07±0.35	5.59±0.46	5.82±0.49	6.54±0.48*	6.43±0.47*
SCFM, units.extr.	0.57±0.11	0.81±0.11*	1.23±0.19**	1.24±0.18**	0.97±0.21**
FPA, ng/ml	2.61±0.23	4.51±0.36*	7.05±0.35*	6.94±0.43*	6.39±0.48*
FDP, mcg/ml	6.92±2.09	13.47±3.56*	18.25±4.41*	19.12±4.38*	14.89±4.78*
FBA, %	54.49±3.53	43.75±4.13	42.19±4.16*	43.41±4.23*	45.72±4.27*
AT III, %	89.77±6.09	84.12±6.55	81.24±5.49	84.54±5.75	85.56±5.68
PRT, sec	91.67±7.31	80.57±7.33	82.65±7.72	84.59±7.37	89.28±8.19

\* p <0.05 in comparison with preoperative values.

\*\* p <0.001 in comparison with preoperative values

Operative intervention significantly influenced the aggregation state of patients' blood. So at the traumatic stage of surgical intervention and up to 6 hrs of early postoperative period, the platelet aggregation rate significantly increased with a slight decrease in platelet aggregation time. In the same period, there was a decrease in the activity of the fibrinolytic blood system. The indicated level of anticoagulant system with a tendency to exacerbation was maintained until 3 hrs of early postoperative period. From 6th hour of early postoperative period, a gradual increase in the activity of the fibrinolytic blood system was observed.

The results of the study of haemostasis in patients with NCTD at the intraoperative stage of surgical intervention at the increase of hypercoagulative properties of blood, strengthening its aggregation ability with a depressed state of the fibrinolytic blood system indicate the development of conditions for the formation of thrombotic process in the venous system. It can be promoted by a high level of endothelial dysfunction, which increases in the conditions of surgical intervention.



## Discussion

A number of complications often occurs at endoprosthesis. VTEC among them remain relevant [1]. Patients with surgical interventions on the large joints of the lower extremities require anticoagulant prophylaxis [2]. Both the classical factors of the Virchow triad, and the specific factors, which are specific for the endoprosthesis of the hip joint [3], as well as individual factors of the patient's risk and pathology of large joints are taken into account [4]. However, in the use of thromboprophylaxis, the incidence of thrombosis of deep veins after the hip replacement is 0.8 to 9.0%, pulmonary embolism - from 1.4 to 6.0% [5]. The latter gives the right to suppose that during the thromboprophylaxis factors with different etiopathogenetic origin are not taken into account, but there is a direct or indirect activation of procoagulant FBAs in their presence. Thus, much attention should be paid to nonspecific dysplasia of the connective tissue [6].

Patients with hip osteoarthritis, femoral neck fracture with NCTD are characterized by an elevated degree of endothelial dysfunction, a greater activity of the haemocoagulation system compared to patients without NCTD. Thus, in the preoperative stage, the blood level of markers of endothelial dysfunction in patients with NCTD is 1.5-2.2 times ( $P < 0.001$ ) higher comparing with patients without NCTD. This causes 1.2 times higher activity of the haemocoagulation system of blood of patients.

Patients with pathology of the hip joint with NCTD develop an elevated degree of endothelial dysfunction at the intraoperative stage which leads to hypercoagulation. These changes of the endothelial system and the haematocoagulation system create conditions for VTEC.

Endoprosthesis of the hip joint belongs to a high-risk group of VTEC and requires anticoagulation prophylaxis. A number of modern recommendations offer pharmacological prophylaxis for the prevention of VTEC at the endoprosthesis of large joints. The use of low molecular heparins, synthetic inhibitors of Xa and IIa factors of blood coagulation or antagonists of vitamin K is recommended for this aim [7]. However, the rate of development of VTEC in the postoperative period remains at the previous level.

In order to reduce the postoperative DVT, attention should be paid to intraoperative changes in the haemocoagulation state of operated patients. [8] There are reports [9] about the diagnosis of the thrombotic process in the IVC system after the end of the surgical intervention.

During the surgical intervention for the pathology of the hip joint from the second half of the traumatic phase and in the first 2-3 hours of the early postoperative period, an increase

of the level of hypercoagulation due to fibrin-monomeric complexes is observed. It is the unfractionated heparin that has a predominant influence on the IIa factor (thrombin - fibrinogen) of the haemocoagulation cascade. And thromboprophylaxis should be started straight after the end of the surgical intervention with the prescription of non-fractional heparin and should be continued until the first injection of LMWH, which has a predominant influence on the Xa factor of the blood coagulation system [10].

The use of oral form of unfractionated heparin is promising [11]. This has become possible due to the combination of unfractionated heparin and the molecule N [8 (2-hydroxybenzene) amine] carrier – sodium caprylate. The third phase of coagulation cascade study showed that oral heparin reduces the incidence of postoperative thrombotic formation.

### **Conclusions**

1. Patients with osteoarthritis of the hip joint and femoral neck fracture and non-specific dysplasia of the connective tissue are characterized by expressed levels of endothelial dysfunction and increased activity of the haematocoagulation system.

2. In the postoperative period after endoprosthetics of hip joints in patients with osteoarthritis of the hip joint and femoral neck fracture and non-specific dysplasia of the connective tissue, VTEC were diagnosed in 13.3% of observations, in patients with osteoarthritis of the hip joint and femoral neck fracture in the absence of nonspecific dysplasia of the connective tissue VTEC were detected in 8.8% of cases.

3. The thromboprophylaxis of VTEC in patients with endoprosthetics of hip joints should be started right after the onset of surgical intervention with the prescription of non-fractional heparin, which has predominant effect on the IIa FBA of the haemocoagulation cascade and should be continued until the first injection of LMWH, which has a dominant influence on Ha-factor of haemocoagulation system.

### **Abbreviations**

VTEC	venous thromboembolic complications
NCTD	non-specific connective tissue dysplasia
SCFM	soluble complexes of fibrin-monomers
FDP	fibrin degradation product
FPA	fibrinopeptide A
FBA	fibrinolytic blood activity
AT III	antithrombin III
PRT	plasma recalcification time
DVT	deep vein thrombosis
IVC	inferior vena cava
LMWH	low molecular weight heparins
TPA	thromboembolism of the pulmonary artery

TFA	total fibrinolytic activity
VEGF	vascular endothelial growth factor
IVC	inferior vena cava
CEC	Circulating endothelial cells

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