Effect of age on the functioning of hemostasis system during hip joint endoprosthesis

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Abstract. The study was performed on 109 osteoarthritis patients who underwent hip joint endoprosthetics; the effect of age on changes in hemostasis system, blood loss level and deep veins thrombosis development in the background of standard prevention with low-molecular heparins were studied. Before the surgery, it was determined that 56 elderly patients (60.3 ± 6.4 years) compared to 53 middle-aged patients (41.8 ± 6.8 years) had a significantly higher initial and postoperative endothelial dysfunction, higher fibrin formation and lower anticoagulant potential; however, it was found that on the background of pharmacological anticoagulant therapy the changes in the hemostasis functioning in elderly patients did not lead to an increase of either blood loss or the number of thromboses. **Keywords:** hemostasis, hip joint endoprosthesis, elderly age, blood loss, thrombosis.

1 Introduction

Increase in life expectancy increases the number of elderly and senile patients with degenerative-dystrophic diseases of lower limbs joints in need of total replacement of large joints. With this, major orthopedic surgeries, in particular reconstructive operations on large joints, involve massive tissue damage that stimulates powerful clotting activation [1,2].

Currently, the influence of age on the hemostasis system functioning has been proven [3,4]. It has been shown that the expression of coagulation proteins, the activity of hemostasis enzymes increases with age [5,6]. The increase in platelet activity, as well as changes in the vascular wall, makes a significant contribution to the strengthening of hypercoagulation state [6,7]. In the process of aging - usually after 50 years - there is decline in the reliability of hemostasis regulation, worsening every decade [8]. This can lead to an increase in the risk of venous thrombosis [9,10]. A significant number of works is devoted to age-related changes in hemostasis system in osteoarthritis patients requiring surgical treatment, but the impact of age on the course of postoperative period in such patients is not studied enough.

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The purpose of the work was to determine the influence of age on changes in the hemostasis system, blood loss level and development of deep vein thrombosis (DVT) after hip joint endoprosthesis (HJE) against the background of standard LMH prevention.

2 Materials and methods

109 patients who underwent primary hip joint endoprosthesis (HJE) were included in the study. Those who had a pathology of the hemostasis system and received anticoagulant or antiplatelet therapy during the week before surgery were not included. The study is approved by the ethics committee. Each person surveyed gave informed consent. All patients were divided into 2 age groups: group 1 (MA - middle age) — 53 patients between the ages of 20 and 50, group 2 (EA - elderly age) — 56 patients between the ages of 51 and 72. The characteristics of groups and the surgery are presented in Table 1. All patients were given standard antithrombotic prophylaxis with low-molecular heparin enoxaparin.

Table 1. Characteristics of groups and surgery

Indicator	group 1 (n=53)	group 2 (n=56)	p
Age, years (min-max)	41.8 ± 6.8	60.3 ± 6.4	<0.001
Gender, male/female	24 / 29	26 / 30	0.905
Prosthesis type, cementless/cemented	51 /2	42 /14	0.002
Type of anesthesia regional/general	27 / 26	34 / 22	0.304
Surgery time, min	120 [95; 150]	115 [95; 150]	0.646

Selection of blood samples for the study was conducted 1 day before surgery, 30 minutes later, on the 1st, 3rd, 7th, 14th day after HJE. Platelet counts were performed in a stabilized EDTA (diosodium salt of ethylenediamintetraacetate) venous blood on an automatic hematology analyzer. Blood samples were also sampled in a specialized test tube with 0.129 M sodium citrate solution. The activity of natural anticoagulants antithrombin and protein C were determined in blood plasma using “ChromoTech-Antithrombin” (Technologiya-Standart) and “Technozym Protein C ELISA “(Technoclone) kits respectively. Determination of plasminogen was carried out using the kit “ChromoTech-Plasminogen” (Technologia—Standart). Platelet activity was determined by the release level of the specific platelet factor β-thromboglobulin from α-granules, which was determined by “Asserachrom β-TG” (Diagnostica Stago) kits. Endothelial markers thrombomodulin and von Willebrand factor were defined by “Human sCD141 ELISA Kit” (Gen Probe Diaclone) and “Technozym vWF:Ag ELISA” (Technoclone) kits respectively. Trombin complexes with antithrombin III (TAT) were defined using “Enzygnost TAT” (Dade Behring) kits as a marker of thrombin formation. The formation and fibrin lysis marker D-dimer were defined by “Technozym D-dimer ELISA” (Technoclone) kits.

The data obtained were processed within the rules of variational statistics. Verification of the sample distribution normality was done using the Shapiro-Wilk test. Comparison of groups was made using the Student t-criterion and the Mann Whitney U-test for samples having and not having distribution normality respectively. The results were expressed as mean ± standard deviation or as median [interquartile range].

3 Results

The results of determining the hemostasis system parameters are presented in table 2.

The pre-surgery anticogulant potential of blood plasma in group 2 (EA) was lower than in group 1 (MA), however, levels of both antithrombin and protein C remained within normal in all patients included in study. Lower levels of antithrombin were also identified directly after HJE in group 2 (EA). By the first post-operative day, differences in both age groups in the level of both natural anticoagulants had leveled.

The level of the main component of the plasminogen fibrinolysis system had no significant differences between groups 1 (MA) and 2 (EA) either before surgery or in the postoperative period.

The number of platelets at the pre-operative stage in group 1 (MA) was higher, although the differences did not reach statistical significance. A week after surgery, the reactive build-up of cell data levels was also significantly more pronounced in group 1 (MA).

The activity of beta-thromboglobulin segregation out of alpha granules dramatically increases in the 1st day after surgery in response to surgical intervention, at the same time no significant differences in the level of this protein between groups have been identified.

The blood concentration of the von Willebrand factor was significantly higher in group 2 (EA) compared to group 1 (MA) both before surgery and in the postoperative period. A similar pattern has been found for thrombomodulin.

The activity of thrombin formation determined by the number of complexes formed with antithrombin before surgery and in early postoperative period did not have significant differences between groups, yet in 3 days after HJE the TAT blood concentration was significantly higher in group 2 (EA). In contrast, the concentration of fibrin lysis products - D-dimers - had a higher level already before surgery. After HJE surgery, there was also a higher blood concentration of this fibrin formation marker in group 2 (EA) with differences persisting until the end of the follow-up period.

Intraoperative and general blood loss (including 1st day after surgery) did not have significant differences between groups. Intraoperative blood loss in groups 1 (MA) and 2 (EA) was 600 [350; 750] ml and 500 [350; 800] ml respectively (p=0.975). Total blood loss in groups 1 (MA) and 2 (EA) was 1120 [800; 1400] ml and 1150 [800; 1500] ml respectively (p=0.968)

The number of deep vein thrombosis episodes of the group had no differences. At the end of the follow-up period, deep vein thrombosis (DVT) was identified and confirmed by ultrasound tests in group 1 (MA) in two female patients (aged 45 and 47), in group 2 (EA) — also in two women (ages 52 and 58).

Table 2. Parameters of the hemostatic system, depending on the duration of the operation.

Indicator	Group	Term in regard of surgery					
		Before	After	Day 1	Day 3	Day 7	Day 14
Anti-thrombin	1 MA	104.2 [96.0; 115.2]	85.9 [69.0; 91.6]	83.5 [69.9; 90.9]	94.0 [84.9; 101.0]	105.6 [97.4; 115.6]	101.5 [93.4; 110.9]
	2EA	97.3 [90.6; 111.1]	76.1 [68.6; 83.6]	82.3 [71.6; 87.8]	90.2 [82.7; 95.6]	101.8 [94.6; 112.4]	102.1 [93.6; 112.9]
	p	***0.048***	***0.046***	*0.747*	*0.205*	*0.505*	*0.519*
Protein C	1MA	96.0 [85.0;	73.0 [59.0;	73.4 [59.5;	79.0 [70.6;	95.0 [82.0;	92.2 [81.0;

		117.0]	87.6]	87.5]	95.2]	102.4]	104.0]
	2EA	86.9 [82.0; 101.0]	71.1 [65.0; 80.9]	68.0 [60.0; 76.0]	80.4 [72.0; 95.0]	94.0 [83.7; 103.0]	92.2 [84.1; 98.7]
	p	*0.082*	*0.916*	*0.545*	*0.978*	*0.896*	*0.508*
Plasminogen	1MA	102.2 [90.5; 118.9]	65.3 [54.4; 80.3]	67.9 [57.3; 79.7]	86.0 [77.9; 102.5]	112.5 [102.6; 131.0]	107.3 [100.6; 122.2]
	2EA	100.1 [90.4; 111.6]	71.0 [63.0; 88.5]	70.6 [59.5; 86.4]	83.8 [68.1; 90.4]	111.7 [101.2; 131.1]	112.5 [104.2; 123.5]
	p	*0.317*	*0.131*	*0.474*	*0.119*	*0.485*	*0.327*
Platelets	1MA	276 [241; 307]	205 [176; 231]	201 [160; 227]	193 [171; 237]	373 [321; 456]	462 [390; 582]
	2EA	265 [213; 297]	206 [169; 236]	200 [153; 222]	189 [162; 220]	341 [254; 407]	448 [402; 568]
	p	*0.086*	*0.862*	*0.424*	*0.474*	***0.049***	*0.802*
Beta thromboglobulin	1MA	31.1 [22.9; 37.1]	64.0 [41.4; 105.1]	54.1 [27.3; 81.9]	28.7 [24.6; 59.5]	34.4 [25.1; 82.1]	32.1 [30.6; 52.0]
	2EA	26.4 [23.0; 37.0]	68.3 [41.9; 79.8]	45.1 [28.9; 52.9]	32.8 [24.7; 47.0]	46.0 [30.0; 58.7]	38.0 [28.0; 43.4]
	p	*0.537*	*0.580*	*0.411*	*0.942*	*0, 845*	*0.964*
Von Willebrand factor	1MA	1.11 [0.87; 1.34]	1.17 [0.99; 1.49]	1.21 [1.05; 1.47]	1.33 [1.06; 1.48]	1.47 [1.19; 1.58]	1.27 [0.92; 1.58]
	2EA	1.38 [1.16; 1.54]	1.41 [1.12; 1.54]	1.54 [1.22; 1.77]	1.63 [1.42; 1.77]	1.51 [1.35; 1.66]	1.49 [1.36; 1.62]
	p	***0.013***	*0.132*	***0.008***	***0.012***	*0.192*	*0.066*
Thrombomodulin	1MA	4.7 [4.1; 5.0]	4.0 [3.5; 4.2]	4.9 [3.9; 6.4]	4.4 [3,6; 5,2]	4.7 [4.1; 5.2]	4.6 [4.2; 5.5]
	2EA	7.5 [5.3; 10.6]	5.6 [4.7; 8.0]	5.7 [4.1; 7.2]	5.8 [5.2; 7.3]	5.6 [5.4; 7.9]	6.2 [5.1; 7.8]
	p	***0.041***	***0.033***	*0.641*	***0.035***	*0.121*	*0.094*
Trombine-antithrombin complexes	1MA	4.5 [2.7; 5.1]	27.9 [20.5; 40.2]	14.2 [11.1; 23.9]	7.5 [6.2; 10.9]	7.2 [5.0; 9.8]	6.2 [4.7; 10.2]
	2EA	3.7 [2.4; 5.5]	34.9 [18.1; 6.8]	11.8 [9.8; 20.0]	11.6 [8.2; 15.5]	6.5 [5.2; 9.2]	6.4 [4.4; 9.4]

	p	*0.465*	*0.212*	*0.313*	*0.120*	*0.934*	*0.987*
D-dimer	1MA	176 [69; 305]	1042 [892; 1429]	1034 [798; 1733]	648 [325; 934]	1172 [828; 1482]	932 [775; 1355]
	2EA	248 [148; 410]	1480 [1025; 2074]	1090 [768; 1664]	779 [399; 1126]	1352 [1122; 1615]	1219 [996; 1657]
	p	***0.034***	***0.046***	*0.895*	*0.121*	*0.054*	***0.005***

4 Discussion

Changes in the hemostasis system are a major problem in larger scale surgeries. Activation of blood clotting and fibrinolysis increased platelet activity and endothelium dysfunction, local reduction of anticoagulation potential play a key role in pathophysiology of cardiorespiratory and vascular complications, may contribute to the breakdown of the delicate balance between thrombosis and bleeding in hip implantation surgeries [11,12].

Older patients with osteoarthritis in need of total large-scale joint replacement are known to have lower anticogulant potential compared to younger patients [3]. In our study it was also shown that older patients had lower pre-operative plasma levels of naturally occurring antithrombin and protein C anticoagulants. In early postoperative period, regardless of age, there was a decrease in the level of these components, but against the background of pharmacological anticoagulant support the level of natural anticoagulants was restored to the original one week later, while the pre-operative differences are leveled.

Plasminegen is a key molecule in the fibrinolysis system, it converts to the plasmin active enzyme by its activators [13]. In addition, plasminogen is involved in healing processes of post-operative wound [14], plays an important role in inflammatory response to surgical damage, in response to infection [15,16]. Previously, a decrease in plasminogen concentration with age was found [17]. However, we did not identify significant effects of age in the studied age groups on plasminogen levels either prior to surgery or in postoperative period.

Age changes in the count and function of platelets are due to changes in the hematopoietic tissue, blood composition and vessel functioning [18,19]. Platelet counts remain relatively stable at 25-60 years of age, but decline in older people [20,21,22]. In pre-operative phase, our study identified only a tendency for lower platelet levels in older patients, but differences gained significance during the reactive build-up period of these cells in response to surgery.

The effect of age on platelet function is less clear. Platelet reactivity is thought to increase in middle age, but there is little evidence of changes in platelet response in older age [19]. We found no significant age-related differences in platelet activity during the pre-operative stage. After endoprosthetics surgery, platelet activity increases significantly [11]. Kim Y. et al. [23] showed that the incidence of DVT in patients with continued moderate/high platelet activity was significantly higher than in patients with low platelet activity: 21.7% and 1.0% respectively. In our study, platelet activity increased significantly immediately after surgery and persisted during the first day, by 3 days in most of the examined patients the alpha-granules secretion was approaching its original level regardless of age.

Already at the pre-operative stage, the activity of hemocoagulation was increased in patients with osteoarthritis [24,25]. Traumatic surgeries involve extensive tissue damage, this in turn stimulates the powerful activation of thrombin formation at the site of damage. The treatment of bone tissue in the implant bed formation for the prosthesis components

caused a sharp increase in thrombin formation markers; methylmethacrylate triggers the expression of tissue factor on monocytes, change in the shape and function of endothelial cells, non-thrombogenic endothelial coating transformes into a highly thrombogenic surface that triggers the transformation of fibrinogen into fibrin. Increased fibrinolytic activity has been detected synchronously with massive intraculmonary coagulation activation, but this process is impeded several hours after the surgery by antifibrinolytic activity of plasminogen activator inhibitor type 1 (PAI-1) [12, 26, 1]. In our study, formation of thrombine-antithrombin - a marker of which is the formation of thrombine-antithrombin complexes - was increased 10-15 times at the end of surgery compared to the initial level. The increase and gradual decrease in core coagulation enzyme formation activity was similar in both age groups.

Being products of degradation of insoluble fibrin, D-dimers have two peaks of postoperative increase. The first maximum was reached on the 1st day after HJE and was due to the strong fibrin formation ensuring bleeding arrest [27, 28]. Repeated increase as in the study of Waśko MK et al. was observed a week after surgery; this increase in D-dimer levels is associated with fibrinolysis in the process of vascular reparation. Previously, the level of coagulation and fibrinolysis activity which reflects D-dimer has been shown to correlate positively with age [29]. We found that formation activity and fibrin lysis was significantly higher in older patients both at pre-operative stage and after HJE.

Low-molecular heparin enoxaparin not only reduces coagulation activity, but also proportionally enhances fibrinolysis activity [30]. It can be assumed that in elder patients the increase in fibrin formation activity is compensated by an increase in its lysis activity aided by the LMH use.

Vascular endothelium is the central regulator of hemostasis [31]. Endothelial cells are able to maintain a state in which platelet adhesion and activation, coagulation, inflammation, leukocyte activation is suppressed. This condition of the endothelial surface is supported by various mechanisms, one of which is the production of thrombomodulin - an endothelial membrane protein acting as cofactor in activation of anticoagulant protein C. Endothelial dysfunction increases with age [32], synthesis of prostacyclines and antiaggregation activity of the vessel wall decreases [33]. Reflection of endothelium dysfunction may be the increase in the multi-dimensional adhesive glycoprotein expression of von Willebrand factor linking platelets to vascular damage site also [34]. Plasma thrombomodulin is also used to assess the degree of damage to endotheliocytes; its release from the endothelial surface is increased in various pathologies due to increased proteolytic activity on the endothelium surface [35]. Our study showed that in patients with osteoarthritis requiring total hip replacement the severity of endothelium damage increases significantly with age, which is indicated by a significant increase in both endothelial markers.

With damage (particularly in surgery) the endothelial surface changes its properties helping to bleeding arrest. Our study showed that this is reflected in the increase of the adhesive glycoprotein of the von Willebrand factor expression and in the level reduction of the anticoagulant thrombomodulin system component. At the same time, significant pre-operative age differences remain in the postoperative period.

5 Conclusion

Older patients compared to middle-aged patients who underwent hip endoprosthesis surgery, had a significantly higher initial and postoperative endothelial dysfunction, higher fibrin formation level and lower anticoagulant potential. However, against the background of the perioperative pharmacological anticoagulant therapy, changes in the hemostasis

functioning in elderly patients did not lead to either an increase in the blood loss level, nor to an increase in the number of thromboses.

References

1. Green, A. S. Lawrie, R. Patel, R. C. Stephens, I. J. Mackie, A. Chitolie, F. S. Haddad, S. J. Machin, Thromb Res, **130(5)**, 775-9 (2012) doi: 10.1016/j.thromres.2011.12.023
2. Y. S. Lee, Y. K. Lee, S. B. Han, C. H. Nam, J. Parvizi, K. H. Koo, J Orthop Surg Res, **13(1)**, 36 (Feb 13, 2018) doi: 10.1186/s13018-018-0730-4
3. A. I. Bernakevich, S. A. Vasilyev, N. A. Yeskin, Thrombosis, hemostasis and rheology, **2**, 30-37 (2007)
4. R. Abbate, D. Prisco, C. Rostagno, M. Boddi, G. F. Gensini, Int J Clin Lab Res, **23(1),** 1-3 (1993) doi: 10.1007/BF02592271
5. D. Mari, G. Ogliari, D. Castaldi, G. Vitale, E. M. Bollini, D. Lio, Hemostasis and ageing Immun Ageing, **5**, 12 (Oct 23, 2008) doi: 10.1186/1742-4933-5-12
6. E. Pretorius, H. M. Oberholzer, W. J. Van Der Spuy, J. H. Meiring, J Thromb Thrombolysis, **29 (3)**, 271-5 (2010) doi: 10.1007/s11239-009-0433-0
7. B. Hemmeryckx, C. E. Van Hove, P. Fransen, J. Emmerechts, A. Kauskot, H. Bult, H. R. Lijnen, M. F. Hoylaerts, Arterioscler Thromb Vasc Biol, **31 (11)**, 2552-9 (2011) doi: 10.1161/ATVBAHA.111.229062
8. W. R. Wilkerson, D. C. Sane, Semin Thromb Hemost, **28 (6)**, 555-68 (2002) doi: 10.1055/s-2002-36700
9. Z. S. Barkagan, Clinical gerontology, **4**, 25-32 (2007)
10. M. J. Engbers, A. Van Hylckama Vlieg, F. R. Rosendaal, J Thromb Haemost, **8 (10),** 2105-12 (2010) doi: 10.1111/j.1538-7836.2010.03986.x
11. A. Di Panfilo, M. Cornette, Rev Med Liege, **59 (9)**, 497-503 (2004)
12. B. S. Oberweis, G. Cuff, A. Rosenberg, L. Pardo, M. A. Nardi, Y. Guo, E. Dweck, M. Marshall, D. Steiger, S. Stuchin, J. S. Berger, J Thromb Thrombolysis, **38 (4)**, 430-8 (2014) doi: 10.1007/s11239-014-1078-1.
13. O. E. Dahl, J Cardiothorac Vasc Anesth, **11 (3)**, 322-8 (1997) doi: 10.1016/s1053-0770(97)90102-6
14. B. I. Kuznik, Cell and molecular mechanisms of hemostasis system regulation in normal state and pathology, Chita: Express Publishing House, 832 (2010) ISBN 978-5- 9566-0253-9
15. S. Frøssing, B. Rønø, A. Hald, J. Rømer, L. R. Lund, Exp Dermatol, **19 (8)**, e234-40 (2010) doi: 10.1111/j.1600-0625.2009.01062.x
16. M. Kramer, M. Drexler, A. Herman, T. Kalimian, Y. Klassov, L. Abu Nasser, Use of Intraoperative Tranexamic Acid and Wound Complications in Spine Surgery: A Retrospective Cohort Study, Asian Spine J. (Mar 30, 2020) doi: 10.31616/asj.2019.0235
17. M. Kłak, N. Anäkkälä, W. Wang, S. Lange, I-M. Jonsson, A. Tarkowski, T. Jin, Scand J Infect Dis, **42 (5)**, 351-8 (2010) doi: 10.3109/00365540903510690.
18. G. Dolan, K. Neal, P. Cooper, P. Brown, F. E. Preston, Br. J. Haematol, **86 (4)**, 798-803 (1994) doi: 10.1111/j.1365-2141.1994.tb04832.x
19. A. V. Mazurov, Physiology and pathology of platelets, 480 (M.: Littera, 2011) ISBN 978-5-4235-0049-8
20. C. I. Jones Platelet function and ageing. Mamm Genome, **27 (7-8)**, 358-66 (2016) doi: 10.1007/s00335-016-9629-8
21. E. V. Reino, N. L. Kuznetsova, I. P. Antropova, Orthopedics genius, **3**, 74-76 (2012)
22. G. Biino, C. L. Balduini, L. Casula, P. Cavallo, S. Vaccargiu, D. Parracciani, D. Serra, L. Portas, F. Murgia, M. Pirastu, Haematologica, **96 (1)**, 96-101 (2011) doi: 10.3324/haematol.2010.029934

23. X. Troussard, S. Vol, E. Cornet, V. Bardet, J. P. Couaillac, C. Fossat, J. C. Luce, E. Maldonado, V. Siguret, J. Tichet, O. Lantieri, J. Corberand, J Clin Pathol, **67 (4)**, 341-4 (2014) doi: 10.1136/jclinpath-2013-201687
24. Y. Kim, Y. Park, Y. Joo, S. Y. Kim, J. Kim. Int J Lab Hematol, **41 (1)**, 102-108 (2019) doi: 10.1111/ijlh.12932
25. I. P. Antropova, B. G. Yushkov, Bulletin of Experimental Biology and Medicine, **153 (4),** 495-498 (2012)
26. S. Craven, L. Dewar, X. Yang, J. Ginsberg, F. Ofosu, Blood Coagul Fibrinolysis, **18 (3)**, 219-25 (2007) doi: 10.1097/01.mbc.0000264704.90039.5d
27. J. N. Harr, E. E. Moore, T. L. Chin, A. Ghasabyan, E. Gonzalez, M. V. Wohlauer, A. Banerjee, C. C. Silliman, A. J. Sauaia, Trauma Acute Care Surg, **74 (3)**, 756-62 (2013) doi: 10.1097/TA.0b013e3182826d7e
28. T. Misaki, I. Kitajima, T. Kabata, M. Tani, C. Kabata, T. Tsubokawa, H. Asakura, K. Tomita, J Orthop Sci, **13 (5)**, 419-24 (2008) doi: 10.1007/s00776-008-1266-y
29. M. K. Waśko, M. Burbul, K. Gawroński, A. Pepłoński, K. Kwiatkowski, Ortop Traumatol Rehabil, **20 (5)**, 401-408 (2018) doi: 10.5604/01.3001.0012.8276
30. M. Stegnar, T. V. Cuderman, M. Bozic, Clin Chem Lab Med, **45 (1)**, 40-6 (2007) doi: 10.1515/CCLM.2007.020
31. N. Li, S. He, M. Blombäck, P. Hjemdahl, Arterioscler Thromb Vasc Biol, **27 (2)**, 407-13 (2007) doi: 10.1161/01.ATV.0000253906.19648.ac
32. V. W. Van Hinsbergh, Semin Immunopathol, **34 (1)**, 93-106 (2012) doi: 10.1007/s00281-011-0285-5
33. B. Hemmeryckx, C. E. Van Hove, P. Fransen, J. Emmerechts, A. Kauskot, H. Bult, H. R. Lijnen, M. F. Hoylaerts, Arterioscler Thromb Vasc Biol, **31 (11)**, 2552-9 (2011) doi: 10.1161/ATVBAHA.111.229062
34. N. O. Zakharova, A. I. Lysenko, The successes of gerontology, **24 (2)**, 268-273 (2011)
35. A. J. Reininger, Haemophilia, **14 (5)**, 11-26 (2008) doi: 10.1111/j.1365-2516.2008.01848.x
36. S. Takano, S. Kimura, S. Ohdama, N. Aoki, Blood, **76 (10)**, 2024-9 (1990)