CLINICAL RESEARCH

Effect of Age on the Hemostatic Function in Patients with Degenerative Diseases of the Large Joints

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Abstract

Background: Aging is associated with an increased hypercoagulable state. Degenerative diseases of the large joints are also accompanied by increased coagulation activity. We investigated the effect of age on the hemostatic function in patients with osteoarthritis.

Material and Methods: The study included 192 patients with osteoarthritis admitted to the clinic for primary hip or knee arthroplasty. The patients were categorized into 5 age groups: the age group under 40 years, the 41-to-50-year age group, the 51-to-60-year age group, the 61-to-70-year age group, and the age group over 70 years. The general blood clotting tests, platelet number, fibrinogen, antithrombin, protein C, TAT, D-dimer, vonWillebrand factor (vWF), PAI-1, ß-thromboglobulin were determined.

Results: Among patients with osteoarthritis, the antithrombin III level significantly decreased by the age of 50; however, above the age of 60 there was a distinct decrease in platelet count, and over the age of 70 the activity of the extrinsic coagulation pathway and the plasminogen level dropped significantly. TAT and D-dimer levels were elevated in most of the patients.

Conclusion: The decrease in platelet count coupled with the activity of the extrinsic coagulation pathway in elderly osteoarthritic patients may increase blood loss during total arthroplasty; also, the drop in the anticoagulant and fibrinolytic potential may play a negative role in strengthening the prothrombotic state during the postoperative period.

Keywords: aging, hemostatic system, arthritis.

Introduction

Advanced age is associated with changes in the hemostatic system [1,2]. The activity of coagulation enzymes is increased [3], the endothelial dysfunction is intensified [4], in particular the synthesis of prostacyclins and the antiaggregatory activity of the vessel wall get reduced with age [5]. Aging is associated with the increased binding of fibrinogen to the platelet receptor $\alpha IIb\beta$ [6] and the intensified expression of platelet P-selectin [7].

The activation markers of coagulation and fibrinolysis are positively correlated with age [8,9]. However, the markers of hemostasis are known to increase in various pathological conditions; the increased activity of coagulation and fibrinolysis is especially observed in osteoarthritic patients before hip and knee arthroplasty [10,11]. Surgical interventions in Orthopedics are associated with the increased risk of thromboembolic complications [11]. In this context, a study of the effect of age on the functioning of the hemostatic system in patients with severe degenerative joint diseases generates great interest.

Material and Methods

The investigation of hemostasis was conducted in 192 osteoarthritic patients admitted to the clinic for primary hip or knee arthroplasty. The patients were categorized into 5 age groups: the age group under 40 years included 21 patients (12 men and 9 women), the 41-to-50-year age group included 50 patients (21 men and 29 women), the 51-to-60-year age group included 62 patients (27 men and 35 women), the 61-to-70-year age group included 46 patients (17 men and 29 women), and the age group

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over 70 years included 13 patients (8 men and 5 women).

Venous blood was collected into a test tube to which was added 3.8% sodium citrate solution in 9:1 ratio. The parameters of plasma hemostasis were investigated in platelet-poor plasma (PPP), which was obtained by centrifuging the blood for 15 min at 3000 rev/min. Platelet counts were recorded in the EDTA stabilized blood using the hematology analyzer Cell-Dyn-1700.

To evaluate the coagulation system, activated partial thromboplastin time (APTT), prothrombin time (PT), and fibrinogen concentration based on the Clauss clotting technique on the CA-50 coagulometer (Sysmex) were determined using commercial kits from "Diagnostica Stago" and "Dade Behring".

The thrombin formation activity was determined by the quantity of complexes "thrombin – antithrombin" (TAT) and their concentrations were examined employing the enzyme-linked immunosorbent assay (ELISA), using Enzygnost TAT kits ("Dade Behring").

D-dimer as a marker of fibrinolysis and fibrin formation was measured by the ELISA reagent Asserachrom D-dimer ("Diagnostica Stago"). The fibrinolysis system was also assessed by determining plasminogen, using the amidolytic technique with kits from "Technology Standard", and by determining the plasminogen activator inhibitor type 1 (PAI-1) using the ELISA method with kits from Technozym PAI -1 Actibind ELISA (Technoclone).

The physiological anticoagulant antithrombin III was studied using the amidolytic method with kits from "Technology Standard", while protein C, the other physiological anticoagulant, was determined by the ELISA method using Asserachrom Protein C (from Diagnostica Stago).

Platelet activation was detected by measuring the ß-thromboglobulin using the ELISA reagent Asserachrom ß-TG.

As a marker of endothelial damage, the vWF antigen level was investigated using the reagent TECHNOZYM®vWF:Ag ELISA (Technoclone).

Clotting tests and determination of antithrombin and plasminogen were carried out within 2 hours after blood sampling. For ELISA testing the samples were frozen and stored prior to the study at -20 º C.

The values of the parameters obtained were compared against the values of standard reference [12].

All the data was processed employing the variation statistical methods using the software Statistica for Windows 6.0. Analysis of the distribution of values obtained was performed using the Kolmogorov – Smirnov test. The Mann-Whitney test and Kruskal-Wallis test were used to compare the differences between groups. The mean (m) and standard deviation (SD) were calculated.

Results and Discussion

Data obtained from the blood sample studies and the plasma of the patients of different ages is listed in Table 1.

Contrary to the studies of Hemmeryckx et al. [4], who recorded increased platelet number with age in healthy subjects, we found a significant decrease in the platelet number in patients over 60 years of age. In the absence of any evidence of active consumption of platelets, the reduced platelet counts can be explained by the decrease of their generation in patients with osteoarthritis. However, we observed a tendency for increased platelet secretion of β-thromboglobulin in patients over 40 years of age, which is consistent with previously reported data [13].

Analysis of age-related changes of the endothelium in patients with degenerative joint diseases revealed a tendency for the increased endothelial secretion of vWF. The level of this factor was also found to be increased in healthy elderly individuals [3].

The level of the factors of the extrinsic coagulation pathway remained at a stable level in patients under 70 years; however, over the age of 70 it gradually declined, resulting in a significant prolonged prothrombin time (PT) in Group 5. The factors of the internal coagulation pathway, conversely, showed a tendency to the increase after 40 years of age, as evidenced by the shortening of the APTT, consistent with the data obtained earlier [3,8].

The activity of the formation of TAT complexes increased relative to the reference value of the norm in the majority of patients studied and no significant differences was observed between the groups when compared with healthy individuals [8]. The concentration of the substrate for fibrin in osteoarthritic patients also exhibited no association with age, which distinguishes them from healthy elderly people [2,13].

The concentration of the natural anticoagulant protein C did not reduce with age. However, the antithrombin III level dropped greatly by the age of 50, thereafter remaining stable up to 70; however, in individuals above 70 years of age, a further drop in the antithrombin III level was seen. The data obtained showed age-related decrease in the potential of the natural anticoagulants in patients with degenerative joint diseases, whereas the healthy subjects revealed an increase in the anticoagulant levels which, according to Sagripanti et al., balances the increase in the coagulation potential [8].

The main pro-enzyme of the fibrinolytic system, plasminogen, remains stable up to 70 years of age; however, in patients above 70 years of age, a significant decline is observed that may limit the ability of the fibrinolytic system.

An increase in the concentration of D-dimer is described in healthy aging, which indicates the increased production and lysis of fibrin [8]. The elevated levels of the fibrin degradation products in relation to the reference standards were detected in most of the patients with osteoarthritis; however, the tendency for the D-dimer level to increase with age remained unchanged. The activity of PAI-1, the primary inhibitor of fibrinolysis, did not show any significant dependence on age.

Thus, degenerative diseases of the large joints in elderly patients are associated with a significant drop in the anticoagulant potential due to the decrease in the antithrombin III level and the significant reduction of the fibrinolytic potential due to the lower plasminogen levels. The presence of these changes against the backdrop of the increased thrombin activity and consequent fibrin formation may enhance the prothrombotic state during the postoperative period. However, the age-related lowering of the platelet count and the extrinsic coagulation pathway activity can increase the blood loss during total arthroplasty.

Acknowledgments

Table 1

Hemostasis parameters in osteoarthritic patients of different ages

Parameters	Age groups					Kruskal-Wallis test
	under 40 years	41-50 years	51-60 years	61-70 years	over 70 years	
	1	2	3	4	5	p
Age	35.5 ± 5.6	46.2 ± 2.7	56.3 ± 2.3	67.0 ± 2.5	72.8 ± 1.9	0.000
vWF, Units/mL	$1.00 \pm 0.37\ ^5$	1.15 ± 0.37	$1.13 \pm 0.28\ ^5$	1.22 ± 0.33	$1.39 \pm 0.19\ ^{1,2,3}$	0.106
Number of platelets $(x10^9/L)$	$273 \pm 76\ ^5$	$285 \pm 76\ ^{4,5}$	$264 \pm 53\ ^5$	$243 \pm 51\ ^2$	$228 \pm 58\ ^{1,2,3}$	0.014
Beta-TG/plat, IUx10 $^{-9}$/L	$60.6 \pm 19,5\ ^{2,5}$	$133.8 \pm 62.1\ ^1$	121.4 ± 79.0	118.0 ± 50.0	$113.4 \pm 26.3\ ^1$	0.207
APTT, sec	$32.5 \pm 3.5\ ^{2,4,5}$	$30.4 \pm 3.4\ ^1$	31.1 ± 3.7	$30.3 \pm 3.5\ ^1$	$30.6 \pm 3.9\ ^1$	0.193
PT, sec	$11.9 \pm 1.1\ ^5$	12.1 ± 1.3	$12.2 \pm 1.5\ ^5$	$12.3 \pm 1.3\ ^5$	$13.5 \pm 1.4\ ^{1,2,3,4}$	0.009
TAT (mcg/L)	4.8 ± 3.1	4.2 ± 2.1	3.3 ± 2.1	4.1 ± 3.4	4.1 ± 2.6	0.393
Fibrinogen, g/L	3.0 ± 0.9	2.9 ± 0.7	3.1 ± 0.9	3.1 ± 0.7	2.8 ± 0.4	0.722
Antitrombin III, %	$109.7 \pm 10.7\ ^{2,3,4,5}$	$101.6 \pm 13.7\ ^1$	$103.9 \pm 12.0\ ^{1,5}$	$100.6 \pm 13.4\ ^1$	$96.2 \pm 8.7\ ^{1,3}$	0.014
Protein C, %	94.7 ± 23.0	98.3 ± 17.7	98.2 ± 17.4	96.2 ± 15.8	91.7 ± 17.8	0.774
Plasminogen, %	$103.3 \pm 17.8\ ^5$	102.7 ± 18.6	$102.4 \pm 16.9\ ^5$	$96.4 \pm 14.3\ ^5$	$85.2 \pm 8.9\ ^{1,2,3,4}$	0.047
PAI-1, Units/mL	5.7 ± 6.1	4.3 ± 4.5	3.8 ± 4.0	4.4 ± 4.5	3.5 ± 5.8	0.409
D-D, ng/mL	$262 \pm 223\ ^5$	$232 \pm 217\ ^5$	$232 \pm 244\ ^5$	$305 \pm 316\ ^5$	$394 \pm 242\ ^{1,2,3,4}$	0.281

Note: *Mann–Whitney test,* ^{1,2,3,4}- *significant group differences (p<0.05).*

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