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Age Features of the Hemostatic System in People with Insulin Resistance and Prediabetic Carbohydrate Metabolism Disorders

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Abstract—The risk of thrombosis due to an increased level of coagulation factors, decreased concentration of physiological anticoagulants, and inhibition of fibrinolysis is increased In prediabetic disorders, in the pathogenesis of which insulin resistance (IR) plays a leading role. Similar age-related changes in the hemostatic system are observed. We investigated the characteristics of the hemostatic system in middle-aged and elderly people with IR in the absence and presence of impaired glucose tolerance (IGT). It has been shown that IR in middle-aged and elderly people is accompanied by an increased content of the plasminogen activator inhibitor type-1, which may lead to potential inhibition of fibrinolysis. Indications of significant prothrombotic changes associated with IR in the elderly include reduced clotting time of blood plasma in the APTT test and elevated levels of soluble fibrin and D-dimer. The intensity of these changes in the hemostatic system is enhanced in the presence of IGT. The results substantiate need for correction of hemostasis by reducing the IR.

Keywords: hemostasis, age features, prediabetic disorders

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INTRODUCTION

The incidence rate of pre-diabetic carbohydrate metabolism disorders in the world nowadays amounts to 350 million people and continues to grow steadily [14]. About 5% of people with prediabetes develop diabetes mellitus (DM) type 2 within a year, which significantly increases the level of cardiovascular risk. The maximum risk of progression to diabetes is observed under impaired glucose tolerance (IGT) [11].

Insulin resistance (IR) is considered a key mechanism in the development of prediabetic disorders and is characterized by a reduced sensitivity of peripheral tissues to insulin. At present, IR and hyperinsulinemia, overweight, decreased carbohydrate tolerance, and dyslipidemia are regarded as major factors of cardiovascular risks that commonly accompany the development and clinical course of a cardiovascular disease. Epidemiological studies have shown that IR occurs long before the emergence of DM type 2, ischemic heart disease, hypertensive disease (HD), and their complications, Alzheimer's disease, and neoplastic diseases, which are the main causes of increased disability and mortality [9, 16, 23]. Furthermore, since the incidence of IR also increases with age, the study of this problem in gerontological practice is relevant.

Pathological changes in the hemostatic system play an important role in the development of cardiovascular events in patients with IR. Hemostasis is provided by three cooperating functional structural units: walls of the blood vessels (endothelium), blood cells (mainly platelets), and plasma enzyme systems.

Both age and IR influence the hemostatic system. Age-related changes in the hemostatic system include increased blood coagulation and decreased activity of the fibrinolytic system, which contribute to hypercoagulable state of blood. Blood viscosity, aggregation, and adhesive activity of platelets increase in the elderly [3, 5]. In models of the effects of stress factors on the organism (adrenaline injection), blood viscosity increases and blood coagulation is intensified in patients older than 60 in contrast to younger people [3, 4]. With aging, the concentrations of factors VII and VIII and fibrinogen increase; each of them enhances the risk of venous thrombosis and cardiovascular events [21]. On the other hand, there is no sufficient increase in the concentration of protein C, protein S, and antithrombin III physiological anticoagulants in the blood of the elderly [19]. An age-related reduction in activity of the fibrinolytic system's condition is evidenced by the increased blood concentration of the plasminogen activator inhibitor type 1 (PAI-1)

[24]. Meanwhile, the content of D-dimer in the blood plasma increases with age in healthy subjects reflecting lysis of fibrin, the level of which rises due to increased blood coagulation [15].

IR has both a direct effect on the functional state of platelets and an indirect effect, i.e., through atherogenic dyslipidemia and endothelial dysfunction. The surfaces of platelets carry insulin receptors to regulate their function [22]. Platelet sensitivity to the inhibitory influence of insulin on aggregation is reduced in patients with type 2 diabetes; therefore, IR leads to easier activation of platelet aggregation. Dyslipidemia contributes significantly to the functional hyperactivity of platelets. The elevated total cholesterol, LDL, and VLDL levels lead to pathological intensification of thromboxane A_2 release with increasing platelet aggregation [5].

In the presence of IR, it was proven that the hemostasis plasma unit changes in the direction of increased thrombosis. Thus, P.A. Sakkinen and coauthors demonstrated that the levels of vitamin K-dependent coagulation factors (II, VII, IX, X) were elevated in subjects with IR [20]. One study found that the concentrations of protein S and protein C physiological anticoagulants increased in the blood under reduced sensitivity to insulin [8]. Both proteins are elevated in people with high activity of PAI-1 as a compensatory mechanism to counteract hypofibrinolysis at IR. The insulin resistance atherosclerosis study (IRAS) by A. Festa and coauthors revealed elevated levels of fibrinogen, factor VIII, and von Willebrand factor in presence of IR, especially in people with IGT and diabetes type 2 [13]. Hyperinsulinemia leads to increased synthesis of PAI-1 in hepatocytes, adipocytes, and vascular endothelium, which impairs fibrinolysis and elevates thrombus formation [12].

Despite the large amount of research concerning this issue, the age-related influence of IR on the formation of hemostatic disorders has not been studied well. First, it is not known whether IR enhances age-related changes in hemostasis. Second, it is not clear whether the priorities of medical tactics should be changed in people with IR at different ages. Because of the high risk of transformation from prediabetic disorders to type 2 diabetes, the study of age-related aspects of the hemostatic system state at IR, especially when it is combined with IGT, is urgent.

The purpose of this work is to give an age-related characterization of the hemostatic system changes in healthy subjects and in people with IR and IGT.

MATERIALS AND METHODS

The study was conducted at a clinic of the Chebotarev State Institute of Gerontology, National Academy of Medical Sciences of Ukraine, in accordance with Ukrainian law and the Declaration of Helsinki of Human Rights. A written informed consent to participate in the study was obtained from each patient. The study included subjects without chronic diseases of the cardiovascular system (patients with hypertension stage I were allowed to participate), central nervous system, respiratory system, without diseases of kidney, liver, blood system, connective tissue diseases, cancer, diabetes types 1 and 2 and other endocrine diseases, acute infectious diseases, varix dilatation, and chronic thrombophlebitis.

Anthropometric measurements included measurement of the body weight (kg), height (cm), and waist circumference (WC, cm). Blood pressure was measured with an Erkameter 3000 mercury sphygmomanometer (Germany) in the brachial artery in accordance with the recommendations of the Ukrainian Association of Cardiology [7].

The glucose level in the blood plasma was analyzed by multiplying the glucose level in the serum by a factor of 1.1. Glucose in the blood serum was analyzed by the glucose oxidase method with a BTS-330 semiautomated biochemical analyzer with a Bio LATEST Glucose kit (Lachema Diagnostica). To reveal hidden carbohydrate metabolism disorders, the surveyed individuals were subjected to a standard glucose tolerance test (GTT). IGT was diagnosed at blood glucose of 7.8–11.1 mmol/L at 120 min of GTT [18].

To assess the lipid metabolism state, the total cholesterol, HDL cholesterol, and triglyceride (TG) levels were measured in the serum by standard biochemical methods with a BM Autolab PM 4000/3 automated biochemical analyzer manufactured by Boehringer Mannheim. The LDL cholesterol level was calculated according to a standard formula.

Insulin level in blood plasma was determined by enzyme immunoassay with DRG Insulin ELISA kits (DRG Instruments GmbH, Germany). The sensitivity of tissues to insulin was assessed based on HOMA-IR (Homeostasis Model Assessment for Insulin Resistance) index calculation. The value of the HOMA-IR index greater than 2.77 arbitrary units was regarded as a marker of IR [17].

As a result of comprehensive clinical examination, 108 people were selected and assigned to groups: the first group included almost healthy people of middle (20 subjects) and elder (21 subjects) ages, nonobese (BMI of <30 kg/m^2), without carbohydrate metabolism disorders and with no laboratory-confirmed IR (HOMA-IR of ≤ 2.77 arbitrary units); the second group composed of middle-aged (29 people) and elderly (38 people) subjects manifesting IDF clinical criteria for diagnosing the metabolic syndrome (2005) and IR confirmed by laboratory tests (HOMA-IR of > 2.77 arbitrary units). Subjects with metabolic syndrome and confirmed IR formed two sub-groups—with IGT and without.

Venous blood was sampled according to the standard procedure into polyethylene test tubes with 3.8% sodium citrate in a ratio of 9 : 1 for assay of hemostasis system parameters. The blood viscosity was deter-

mined with an AKR-2 rotational viscometer (Russia) at a shear rate of 10–200 s^{-1}.

The hemostasis indicators (soluble fibrin, protein C, antithrombin III, plasminogen, and D-dimer) were determined in collaboration with the Palladin Institute of Biochemistry, National Academy of Sciences of Ukraine. The APTT test was performed as described in [2]. The concentrations of fibrinogen, soluble fibrin, and D-dimer were determined by the method of E. Lugovskoi et al. (2006) [6]. The activity of protein C was measured with protein C activator purified from the venom of Pallas' viper (*Agkistrodon halys halys*) by S2366 chromogenic substrate cleavage. *para*-Nitroaniline release was detected at 405 nm on a Thermo Multiskan EX spectrophotometer microplate [1]. The activities of antithrombin III and plasminogen were measured in accordance with the instructions of the Renam Company (Russia) [2]. The PAI-1 level was measured by immunoenzyme assay from citrate plasma with a standard kit manufactured by Technoclone (TECHNOZYM PAI-1 Antigen ELISA).

Since most indicators had distributions close to normal, the data were presented as $M \pm m$. Statistical analysis of the data was performed with the Statistica 6.0 software for Windows (StatSoft, United States). The difference probability between the groups was evaluated by Student's t-test. The differences were considered significant at $p < 0.05$. Pearson's correlation was performed (the results were considered significant at $p < 0.05$).

RESULTS AND DISCUSSION

Elderly people of group 1 were similar in anthropometric parameters, blood pressure, and carbohydrate metabolism on an empty stomach to the group of middle-age subjects (Table 1). The glucose level reduced insufficiently in elderly subjects without IR at 120 min of GTT in venous blood plasma, which can be attributed to insufficient compensatory increase in insulin levels or decreased sensitivity to insulin.

In IR development but with retained glucose tolerance, there was an increase in body weight, BMI, WC, and BP values in middle-aged and elderly people. This shows that IR was associated with the presence of both general and abdominal obesity in people of both ages. Moreover, in both groups of people with IR, the levels of insulin and glucose after 2 hours of GTT were significantly higher, reflecting decreased insulin sensitivity. The progression of carbohydrate metabolism disorders and the appearance of IGT in middle-aged subjects was accompanied by an increased tendency of general and visceral obesity manifestations, whereas in elderly they tended to reduce.

An age-related feature is the absence of hyperinsulinemia on an empty stomach in elderly people with IGT. However, 2 hours after the administration of glucose, s high level of insulin in combination with hyperglycemia in both age groups was observed, indicating decreased insulin sensitivity.

Age-related differences were absent in the analysis of lipid spectrum indicators of the blood serum of healthy people (Table 1). A significant increase in triglyceride levels occurred in people with IR, especially in middle-aged people. In addition, elderly people with IR showed a significant increase in LDL cholesterol levels. Meanwhile, the formation of IGT had no extra effect on indicators of lipid composition of the blood in both age groups.

Dyslipidemia is known to contribute to the dysfunction of blood cell membranes and to increase their adhesion and blood viscosity. As the results of the study show, blood viscosity elevated in the presence of IR only in middle-aged subjects (Table 1). Blood viscosity was observed to further increase under progression of IGT.

With regard to indicators of coagulation hemostasis, elevated levels of fibrinogen in middle-aged and elderly people with IR were shown as compared to healthy subjects. The concentration of fibrin grew only in elderly subjects with IR and IGT. The clotting time of blood plasma in the APTT assay was reduced in elderly people with IR in contrast to patients without IR in the same age group (Table 2), which indirectly indicates the tendency of blood coagulation system activation.

Indicators of physiological anticoagulant activity in all groups were within normal limits, although there were some differences. The activity of antithrombin III in the elderly without IR was higher than in the same group of middle-aged people (Table 2). Along with this, the variation of activity of another physiological anticoagulant, protein C, was detected in all groups within the normal range. Protein C activity was lower in the surveyed middle-aged people with IR than in subjects without IR. However, the protein C concentration in the elderly did not differ from that in patients with and without IR. These findings contradict slightly the results of S. Agewall and coauthors, which state that IR is accompanied by increased protein C activity [8]. These differences can be explained by that the patients surveyed by S. Agewall were clinically healthy people, but IR patients with hypertension stage I, when the activity of the anticoagulant system is reduced, were allowed to participate in our study.

Analysis of the content of fibrinolysis components revealed that plasminogen levels tended to increase in the blood plasma of middle-aged people with IR. However, we found that the level of fibrinogen in elderly patients with IR did not rise when subsequently compared with a group of the same age without IR. In the presence of IR, there was a statistically significant elevation of PAI-1 in plasma in middle-aged subjects, which can lead to reduced fibrinolytic capacity (Table 2). Perhaps, the absence of PAI-1 rise in elderly patients with IR is associated with the fact that this group manifested abdominal obesity to a lesser extent [19].

Table 1. Comparative characterization of people groups 1 and 2 of different ages

Indicator	Middle age			Elderly age		
	the first group—healthy subjects without IR, $n = 20$	the second group—patients with IR		the first group—healthy subjects without IR, $n = 21$	the second group—patients with IR	
		without IGT, $n = 19$	with IGT, $n = 10$		without IGT, $n = 20$	with IGT, $n = 18$
Age, years	47.8 ± 1.8	48.4 ± 1.5	54.5 ± 1.3**	69.8 ± 1.3*	66.0 ± 1.0	67.4 ± 1.4
Body mass, kg	68.3 ± 3.8	99.3 ± 5.0*	97.8 ± 6.1*	69.3 ± 2.3	87.0 ± 3.7***	82.5 ± 3.0***
Height, cm	170 ± 3	172 ± 2	169 ± 2	165 ± 2	164 ± 2	165 ± 3
Body mass index, kg/m^2	23.6 ± 0.9	33.6 ± 1.3*	34.13 ± 1.7*	25.4 ± 0.7	32.3 ± 1.0***	30.3 ± 1.1***
Waist circumference, cm	78.8 ± 3.3	101.8 ± 3.1*	104.1 ± 3.9*	81.8 ± 2.2	100.0 ± 3.1***	96.8 ± 2.4***
SBP, mm Hg	114.5 ± 3.2	138.0 ± 2.5*	140.4 ± 4.5*	120.5 ± 3.2	137.9 ± 3.4***	134.2 ± 3.4***
DBP, mm Hg	74.1 ± 2.5	89.7 ± 2.0*	89.4 ± 2.2*	74.5 ± 1.9	85.8 ± 2.0***	85.0 ± 2.2***
Glucose concentration on an empty stomach, mmol/L	5.1 ± 0.2	5.7 ± 0.2*	6.4 ± 0.3*, **	5.1 ± 0.2	5.5 ± 0.1***	6.3 ± 0.2***, ****
Glucose concentration at 120 min of GTT, mmol/L	5.1 ± 0.2	5.6 ± 0.2*	8.9 ± 0.3*, **	6.2 ± 0.4*	6.0 ± 0.3	8.9 ± 0.2***, ****
Insulin concentration of an empty stomach, μmol/L	5.9 ± 0.9	14.2 ± 1.1*	15.0 ± 2.2*	5.9 ± 0.7	12.7 ± 1.0***	10.8 ± 0.9***
Insulin concentration at 120 min of GTT, μmol/L	16.3 ± 4.2	25.8 ± 3.2*	42.0 ± 7.7*, **	21.2 ± 6.0	35.2 ± 5.8***	56.1 ± 7.2***, ****
HOMA-IR, arbitrary units	1.1 ± 0.2	3.5 ± 0.3*	4.2 ± 0.7*	1.4 ± 0.2	3.1 ± 0.2***	3.0 ± 0.2***
Total cholesterol, mmol/L	5.7 ± 0.3	6.0 ± 0.3	6.3 ± 0.4	5.4 ± 0.3	6.4 ± 0.3***	5.9 ± 0.2
LDL, mmol/L	3.9 ± 0.3	3.7 ± 0.3	4.0 ± 0.4	3.4 ± 0.2	4.3 ± 0.3***	3.8 ± 0.2
HDL, mmol/L	1.3 ± 0.1	1.2 ± 0.06	1.4 ± 0.1	1.4 ± 0.05	1.3 ± 0.07	1.3 ± 0.06
Triglycerides, mmol/L	1.2 ± 0.1	2.3 ± 0.3*	2.2 ± 0.4*	1.4 ± 0.1	1.9 ± 0.2***	1.9 ± 0.2***
Blood viscosity (sP) at a share rate, s^{-1} of						
200	3.54 ± 0.11	3.85 ± 0.09*	4.0 ± 0.14*	3.83 ± 0.15	3.81 ± 0.09	3.87 ± 0.09
100	3.70 ± 0.12	4.03 ± 0.09*	4.19 ± 0.13*	3.97 ± 0.15	3.95 ± 0.09	4.04 ± 0.09
50	3.94 ± 0.12	4.25 ± 0.1	4.48 ± 0.14*	4.19 ± 0.15	4.17 ± 0.10	4.27 ± 0.10
20	4.19 ± 0.13	4.48 ± 0.1	4.71 ± 0.13*	4.46 ± 0.17	4.45 ± 0.11	4.55 ± 0.12
10	4.35 ± 0.13	4.63 ± 0.1	4.89 ± 0.13*	4.64 ± 0.18	4.64 ± 0.11	4.76 ± 0.14

Here and in Table 2: * $p < 0.05$ compared to middle-aged people of group 1; ** $p < 0.05$ compared to middle-aged subjects group 2 with IR and without IGT; *** $p < 0.05$ compared to elderly people group 1 without IR; **** $p < 0.05$ compared to elderly patients group 2 with IR without IGT

Table 2. Indicators of the hemostasis system in people of different ages groups 1 and 2

Indicator	Middle age			Elderly age		
	the first group—healthy subjects without IR, $n = 20$	the second group—patients with IR		the first group—healthy subjects without IR, $n = 21$	the second group—patients with IR	
		without IGT, $n = 19$	with IGT, $n = 10$		without IGT, $n = 20$	with IGT, $n = 18$
Coagulation system						
Fibrinogen, mg/mL	3.0 ± 0.3	3.1 ± 0.2	3.7 ± 0.3*, **	3.1 ± 0.2	3.3 ± 0.2	3.4 ± 0.2
Fibrin, μg/mL	3.0 ± 0.6	2.9 ± 0.5	2.7 ± 0.6	3.2 ± 0.7	3.4 ± 0.6	4.5 ± 0.9****
APTT, s	33.2 ± 2.3	33.8 ± 1.6	30.7 ± 1.4	34.9 ± 1.4	32.3 ± 1.4	28.8 ± 1.3***, ****
Physiological anticoagulants						
Antithrombin III, %	85.0 ± 4.3	88.4 ± 4.7	104.8 ± 8.9**	98.3 ± 6.7*	99.3 ± 8.2	105.7 ± 6.5
Protein C, %	108.9 ± 5.7	88.1 ± 4.2*	102.6 ± 4.9**	90.0 ± 3.8*	99.2 ± 3.6	97.6 ± 3.6
Fibrinolysis system						
Plasminogen, %	80.8 ± 5.5	99.5 ± 6.6*	96.8 ± 3.4*	95.7 ± 3.9*	88.9 ± 5.5	89.7 ± 5.0
D-dimer, μg/mL	55.9 ± 15.8	74.2 ± 27.1	94.8 ± 30.4	117.6 ± 19.8*	178.5 ± 30.3*	197.1 ± 47.8***
PAI-1, ng/mL	61.0 ± 9.3	78.3 ± 8.1*	87.4 ± 13.3*	60.9 ± 10.0	61.6 ± 8.4	73.0 ± 8.9

D-dimer levels increased with age even in healthy people without IR. In the presence of IR, an additional increase in the D-dimer level was observed in both age groups, which is consistent with the results of other authors [15].

In the next step, we analyzed indicators of the hemostatic system in people of different ages with IR in the absence or presence of IGT. In middle-aged persons with IGT, the fibrinogen level was greater than that in the examined individuals without IGT; however, in the presence of IGT, there was a compensatory increase in the activities of protein C and antithrombin III anticoagulants. At the elderly age, the level of natural anticoagulants did not increase in people with IGT. Hyperfibrination developed and higher levels of D-dimer were shown in elderly people with IR and IGT as compared to middle-aged people with IR and IGT. Decreased APTT was noticeable in both age groups of people with IR and IGT, which indicates an increased tendency of thrombosis. A more significant reduction of this indicator was observed in elderly people (Table 2).

Our data on the age-related differences in the coagulation/anticoagulation system, as well as changes in this system upon IR, on the whole agree with data of previous studies. Thus, the most frequent changes in both aging and in the presence of IR (age-related changes were not studied in the reference papers) is the increase in the concentration of fibrinogen, while other routine clinical indicators of coagulation/anticoagulation assessed at rest were within the normal range [10].

As the correlation analysis data show, PAI-1 ($r = 0.32$, $p < 0.05$) is the most sensitive indicator of the hemostatic system; it is associated with IR in middle age. APTT ($r = 0.38$, $p < 0.05$) is the indicator of this at the elderly age. The positive correlation of IR with PAI-1 in middle age can be attributed to the fact that visceral fat tissue is one of the main sites of the synthesis of the plasminogen activator inhibitor and that visceral obesity was greater in the middle-aged people group with IR.

APTT is a comprehensive indicator, and its reduction indicates an imbalance in the hemostatic system towards thrombosis. The mechanisms of hemostasis are likely better compensated in middle-age subjects with IR; therefore, APTT has no evident changes in these people. In elderly age, APTT is reduced in the presence of IR, confirming the progression of prothrombotic changes.

CONCLUSIONS

In healthy people age-related signs of dyslipidemia appear due to increased triglyceride levels, which is one of the reasons for increased blood viscosity. Insulin resistance contributed to blood viscosity to a greater extent in the examined middle-aged individuals, which may be associated with more severe hypertriglyceridemia.

An increasing D-dimer level is a feature of age-related changes of the hemostatic system in healthy elderly people. In healthy elderly people, decreased activity of protein C natural anticoagulant is one of the causes of an increased tendency of thrombosis.

PAI-1 levels increased in the plasma in both age groups of patients with insulin resistance, which can lead to a reduction of the capacity of fibrinolysis system. However, in the middle-aged people with insulin resistance, this reduction can be compensated for by an elevated plasminogen content.

Greater prothrombotic changes under insulin resistance in elderly subjects are evidenced by reduced clotting time of blood plasma in the APTT test and elevated levels of soluble fibrin and D-dimer.

The results substantiate a new approach to the correction of hemostasis disorders that consists in the reduction of insulin resistance and normalization of the glucose metabolism.

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