RESEARCH STUDIES

Some peculiarities of lipid and hormonal metabolism and mechanical properties of the blood in menopausal women

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Abstract

Background: Many aspects of age-related correlation and causal relationship between the mechanical properties of red blood cells (RBCs) and parameters of lipid and hormonal metabolism in women are unclear till now.

Material and methods: 58 reproductive-aged (less than 45 years) and 32 menopausal (more than 45 years) women admitted to the Central Clinic of Tbilisi State Medical University, Georgia were investigated. In each group we studied blood estradiole, free nitric oxide (NO) content, density of inactive form of β_2-adrenergic receptors (β_2ARs) and mechanical property of RBCs membrane.

Results: In the blood of menopausal women NO content and deviation of volume (DV) of RBCs, reflecting their deformability, with lower density of inactivated β_2ARs on the surface of RBCs membranes was greater than the corresponding parameter in the reproductive-aged women. DV of RBCs rapidly decreased at low HDL (high-density lipoprotein) in reproductive-aged women and wasn't sensitive to HDL content in menopausal women.

Conclusions: Lack of blood estrogens content in menopausal women causes the development of dislipidemia, impairment of renewal of phospholipids in RBCs membranes, decreased activity of adrenergic structures and the subsequent decrease in the NO production. These factors contribute to reducing deformability of RBCs membrane and impairment of mechanical properties of the blood.

Key words: menopause, metabolism, red blood cells.

Introduction

In the period of clinical manifestation of cardiovascular diseases lesions in blood vessels are irreversible; identification of early diagnostical markers of cardiovascular diseases, types and quality of metabolic disorders causing their development is very actual for determination the key spots of pathogenesis of these diseases, planning preventive measures, elaboration a strategy that would be more focused on the prevention of irreversible pathological changes and complications associated with alterations of cardiovascular tissues.

There is a significant gender and age difference between reproductive-aged women and age-matched men and/or menopausal women in the frequency of induced by cardiovascular diseases mortality and disability [1], which is associated with differences in mechanical properties of their blood – an insufficient blood supply due to altered mechanical properties of blood, particularly RBCs. It is proposed that the remarkable dissimilarity in morbidity and mortality due to cardiovascular diseases in pre-menopausal women versus men and post-menopausal women could be related to the increased amount of "young" red blood cells (RBCs) caused by monthly bleeding in pre-menopausal women [2].

It was shown that the chemical composition of RBCs membranes affects their mechanical properties and alterations of lipid composition of membranes as well as serum lipids alterations would contribute to the atherosclerosis progression and can be considered as a new risk factor for atherosclerosis [3].

Several studies have confirmed a direct correlation between β_2-adrenergic receptors (β_2ARs) density in peripheral blood cells (lymphocytes, erythrocytes) and those in cardiovascular tissues. Therefore, β-adrenoceptors in peripheral blood RBCs might be an indirect index of cardiovascular tissues [4].

In many studies it was shown that activation of different intracellular signaling pathways, including the adenylilcyclase–cAMP (adenosine 3'-5'- cyclic monophosphate) and adrenergic regulation systems are related to the alterations of mechanical properties (aggregation and deformation) of RBCs. Exposure of RBCs to catecholamine (stimulation of membrane's β-adrenoreceptors, or adenilatcyclase) led to the change in their micro rheological properties, elevation of deformability and decreased aggregation [5]; β_2AR mediate increase in intra-erythrocyte c AMP synthesis with farther ATP release from erythrocytes, which join to purinergic receptors of endothelium resulting in the production of endothelial vasodilators (such as nitric oxide), stimulating vessel diameter and blood flow in the microcirculation [6].

The aim of our study was to establish the correlation and causal relationship between the mechanical properties of RBCs and parameters of lipid and hormonal metabolism of women in reproductive and menopausal ages.

Material and methods

58 reproductive-aged (less than 45 years) and 32 menopausal (more than 45 years) women with dislipidemia, arte-

rial hypertension, obesity, metabolic syndrome and other symptoms, who had been admitted to the Central Clinic of Tbilisi State Medical University, Georgia during 2009-2011, were investigated and compared with each other. A subject with cystic disease, ovariectomy, or using hormonreplacement therapy was excluded from this target group.

In each group we investigated blood estradiole, nitric oxide (NO) content, and density of inactive form of β_2ARs and mechanical property of RBCs membrane. NO content and density of inactive form of β_2ARs on the membrane of RBCs were measured by Electron Paramagnetic Resonance (EPR) method. EPR spectres of blood were registered on rediospectrometre PE-1307 (Russia). Density of inactive form of β_2ARs was detected according to the intensity of EPR signal g = 2.01 [7]. Free nitric oxide was measured with spin-trap natrium diethildithiocarbamate (DETC) (Sigma). EPR spectres of NO-Fe^{2+}-$(DETC)_2$ complexes were measured at the temperature of liquid nitrogen at microwave power 20 mVt. Mechanical properties of RBCs were studied according to the derivate of their volume (DV) determined by spectrophotometric method. Lipid spectrum in peripheral blood from patients was investigated by enzyme-colorimetric method. Estrogens content in blood was measured by ELISA method.

Statistical analyses of the obtained results were performed by SPSS (version 10.0) program package. The result was obtained in the form of standard deviation of average values. The difference between groups was assessed by student t+criterion. In all cases statistical confidentiality was defined according to < 0.05 index.

The research complies with the norms of the Foundation of Bioethics. The local ethics committee approved the protocol, and informed consent was obtained from all participants.

Results and discussion

Our study showed that in the blood of menopausal women estradiole content is statistically significantly lower than in the reproductive-aged women (0.41 ± 0.024 versus 0.52 ± 0.034) (fig. 1), free Nitric Oxide was statistically significantly lower than in the reproductive age (1.89 ± 0.050 versus 2.26 ± 0.112) (fig. 2). At the same time, density of inactivated β2AR (corresponding to the intensity of the EPR signal g = 2.01 [7]) on the surface of RBCs membranes in menopausal women was greater than the corresponding parameter in women of reproductive age (1.6 ± 0.3 versus 0.8 ± 0.2) (fig.3). This result indicates the decreased activity of adrenergetic regulation during menopause. β-adrenoreceptors are involved in regulation of mechanical properties of RBCs, through the influence on the deformability of the membrane integral/skeleton proteins; β-adrenergic agonists may improve in the RBCs passage through microvasculature [8].

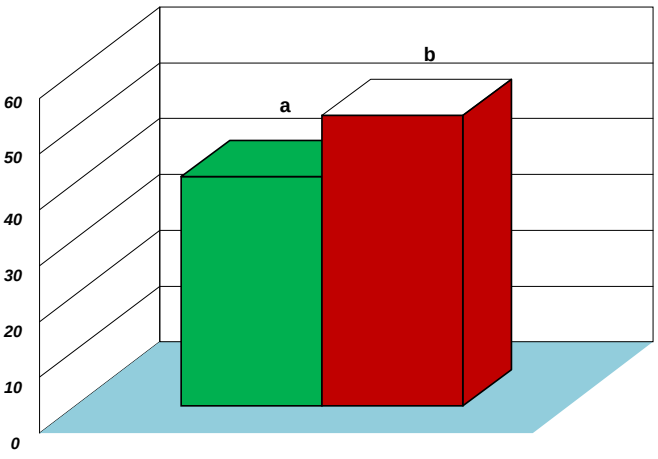

Fig. 1. Blood estradiole content in menopausal (a) and reproductive-aged (b) women.

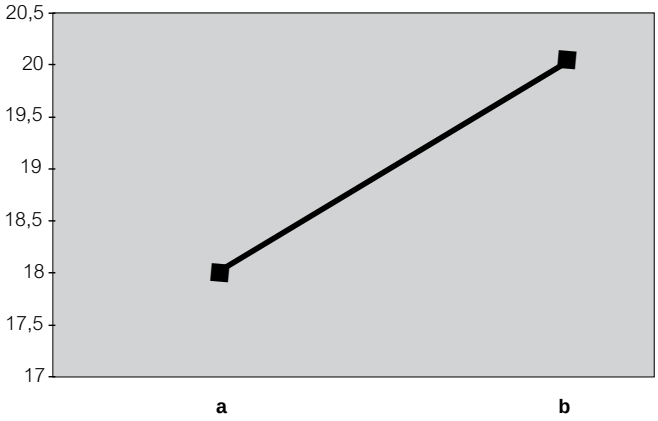

Fig. 2. Blood free nitric oxide content in menopausal (a) and reproductive-aged (b) women.

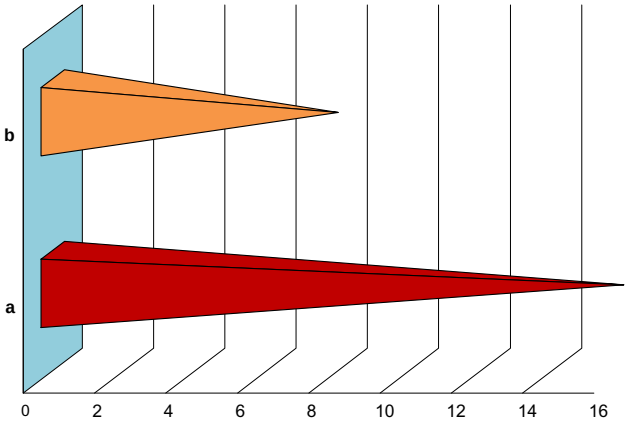

Fig. 3. Density of inactivated β_2AR on the surface of erythrocyte membranes in menopausal (a) and reproductive-aged (b) women.

The fluidity of blood, 45% volume of which is occupied by RBCs, strongly depends on its behavior in flow, which is a key factor of proper tissue perfusion [9]. The mechanical property (deformability) of RBCs depends on many parameters [10]. Parameter DV reflects the spherulation quality of RBCs in patient's blood. Due to the high deformability of the RBCs they easily change their form and are translocated in the thin capillaries. Senescent RBCs' membrane is characterized by low deformability, which causes high spherulation quality of this population. So, according to the numerical value of DV of RBCs we can detect their spherulation quality and therefore distribution according to the chronological age. In our study

it was revealed, that in menopausal women DV of RBCs is lower than in reproductive-aged women; that indicates the dominance of young RBCs in blood of this age group patients. In menopausal women dominate senescent RBCs, which are revealed by their high spherulation quality.

Maintenance of normal RBCs deformability also depends critically on the metabolic state of the cell – its metabolic energy. In order to find feedback between parameters of lipid metabolisms and physical properties of the RBCs membrane, we carried out a correlation analysis between blood HDL content and RBCs spherulation parameter (DV). It should be noted that HDL content in blood from women of menopause-aged group was statistically significantly lower, than in blood of women from reproductive-aged group (menopausal women – 3.01± 0.24 versus reproductive-aged women – 5.40 ± 0.32). Our research revealed the existence of dependence between the spherulation quality of RBCs and parameters of lipid metabolism – HDL content. Our data show that spherulation degree (or volume) of RBCs is rapidly decreased at low HDL in women of reproductive age and is not sensitive to HDL content in women of menopause age. This indicates the existence of estrogen-related dependence between those two parameters. The difference in incorporation of fatty acids in RBCs membrane phospholipids in reproductive-aged and menopausal women is defined by other authors as well [11]; estrogen-dependent acylation of phospholipids occurs predominantly in PE of senescent cells, increases as a function of cell age.

Conclusions

1. As it seems from the results of our study, lack of blood estrogens content in menopausal women is one of the major causes of the development of dislipidemia, impairment of renewal of phospholipids in RBCs membranes, decreased activity of adrenergic structures and the subsequent decrease of the β_2-AR-stimulated NO production.

2. These factors contribute to reducing deformability of RBCs membrane and impairment of mechanical properties of the blood.

3. These results do not give us the opportunity to get a complete picture of the development of cardiovascular diseases in menopausal women, but provide important novel information regarding the particularly physiological mechanisms underlying β-adrenergic regulation of vascular tone in menopausal women.

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