INFLUENCE OF HORMONAL DISORDERS ON ENDOTHELIAL DYSFUNCTION IN PATIENTS WITH ARTERIAL HYPERTENSION AND COMORBIDE ENDOCRINOPATHIES

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Abstract

Purpose: to investigate the effect of hormonal changes on endothelial dysfunction (ED) in patients with a comorbid course of hypertension (H), type 2 diabetes mellitus (T2DM) and subclinical hypothyroidism (SHT). **Methods:** 183 patients with H stage II were divided into 3 groups: Group 1 (n=50) – with isolated H (comparison group); Group 2 (n=63) – with a combined course of H and T2DM; Group 3 (n=70) – with comorbidity of H, T2DM and SHT. Blood pressure levels, carbohydrate, lipid and thyroid metabolism, plasma insulin concentration, insulin resistance (IR) the HOMA-IR index, vascular endothelial growth factor (VEGF-A) plasma levels were investigated. **Results:** Dyslipidemia was more pronounced in group 2 than in group 1. The addition of SHT was accompanied by a tendency to increase all the atherogenic lipids. IR was observed in all patients groups and was significantly higher than in control group ($p<0.05$). Significant increase of VEGF-A levels in all patients groups in comparison with the control ($p<0.05$) was found. In group 2 VEGF-A was lower than in group 1, which is probably due to the protective effect of metformin. Analysis of the influence of thyroid dysfunction degree on ED revealed significant increase of VEGF-A levels in TSH>6.0 ?MU/ml subgroup (352.55±17.64 pg/ml vs 461.74±20.13 pg/ml ($p<0.05$)). **Conclusion:** Hormonal disorders contribute to aggravation of endothelial dysfunction in patients with hypertension and comorbid endocrinopathies – type 2 diabetes mellitus and subclinical hypothyroidism. Even minor decrease in thyroid function lead to the progression of endothelial dysfunction.

Key words: *hypertension, type 2 diabetes mellitus, subclinical hypothyroidism, endothelial dysfunction.*

Endothelial dysfunction (ED) is a complex of multi-stage balance disorders of opposing factors: relaxation and vasoconstriction, procoagulation and anticoagulation, factors of hyperproliferation and inhibition of endothelial growth, etc. Various triggers can lead to ED development, e.g. changes of blood flow velocity, increased pressure, hypoxia, hyperhomocysteinemia, increased processes of hyperperoxidation, hormonal imbalance, etc. [1]. The occurrence and progression of ED is the basis of many diseases development and formation of various vascular complications. The leading role of ED in development of arterial hypertension (H), atherosclerosis, diabetes mellitus (DM), chronic heart failure, and others has been proved [2]. It is important that ED develops already in the early stages of pathological processes and precede the clinical manifestations of the disease. Therefore, detection of ED in the early stages has a great diagnostic and prognostic significance.

Achievements of modern medicine have significantly expanded the capabilities of diagnosis, treatment and prevention of various diseases, however, the issues of effective treatment of the most common and socially significant diseases, the ability to influence the course of the disease, prognosis and the quality of life are still relevant. Treatment of patients with

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comorbid diseases such as H and the most common endocrinopathies – type 2 diabetes mellitus (T2DM) and hypothyroidism, including subclinical one (SHT), which often affect able-bodied people, is of particular importance and determines their great social significance.

The combined course of these diseases greatly increases the risk of cardiovascular complications (CVC) development. And if, in the combined course of H and T2DM, similar pathogenetic disorders develop, the adverse effect of which on CVC formation is realized, including through ED, then in cases of H and thyroid imbalance, many questions still remain unclear. It is known that the thyroid system, actively interacting with other neurohormonal factors, also influences the processes of vascular regulation.

It is believed that T2DM with hypothyroidism, including subclinical one, make a significant contribution to formation of cardiometabolic risk factors, which determine the course and prognosis of various cardiovascular diseases (CVD) and CVC development.

Until now the data on the impact of thyroid dysfunction, developing against a background of SHT, on the state of endothelium and ED formation are very diverse and remain unclear [3]. It is suggested that a decrease in endothelium-dependent vasodilation in patients with hypothyroidism may be a manifestation of free triiodothyronine deficiency. There is also evidence of vascular endothelial damage due to immune complexes in the presence of chronic autoimmune thyroiditis (AIT), which can enhance ED manifestations [4].

Numerous factors and conditions which effect ED development, such as age, hormonal changes, in particular postmenopause, dyslipidemia (DL), especially hypercholesterolemia and hypertriglyceridemia, T2DM, smoking, H have been established . The risk of ED development progressively increases depending on the presence of different risk factors combination.

One of the important and widely investigated during the recent years marker of ED is Vascular Endothelial Growth Factor-A (VEGF-A), which is considered to be one of the earliest blood serum marker of ED, the changes of which appear even ahead of active intravascular inflammation[5–7].

The multifactorial mechanisms of ED development in comorbid pathology are complex and not sufficiently investigated. The study of comorbid conditions, each of them is characterized by the presence of ED in the pathogenesis and factors, exacerbating this dysfunction, which can lead to changes in VEGF-A expression and, probably, will allow better understanding the common pathogenetic processes and development of more effective preventive and therapeutic measures, is of particular interest.

2. Purposes, subjects and methods:

2.1. Purpose was to investigate the effect of hormonal changes on endothelial dysfunction in patients with a comorbid course of hypertension, type 2 diabetes mellitus and subclinical hypothyroidism.

2.2. Subjects & Methods

The study involved 183 patients (of them 114 women) aged 40–75 (mean age 57.4±5.2 years) with stage II H. Depending on the comorbid pathology all patient were divided into 3 groups: Group 1 (n=50) – with isolated H (comparison group); Group 2 (n=63) – with a combined course of H and T2DM; Group 3 (n=70) – with comorbidity of H, T2DM and SHT, which developed as a result of autoimmune thyroiditis (AIT).

Non-inclusion criteria were symptomatic H, diabetes type 1 and other endocrine disorders, clinical signs of coronary heart disease or severe concomitant chronic diseases, pregnancy. Patients with diagnosed manifested hypothyroidism or with treated SHT, after surgical treatment of thyroid gland were not included. Administration of iodine preparations, glucocorticoids, amiodarone, lithium medicines, estrogens was also exclusion criteria. The control group consisted of 20 age- and sex-matched volunteer patients, and without cardiovascular diseases and endocrinopathies.

Against a background of dietary recommendations, all patients received basic antihypertensive therapy in individually selected doses in accordance with international and national Guidelines [8–10]. Antidiabetic therapy included Metformin in individually selected doses from 1000 to 2500 mg/day.

The survey program included a single list of laboratory and instrumental studies. Blood pressure levels were assessed by means of blood pressure obtained from three measurements at 2-minute intervals in a sitting position.

Assessment of carbohydrate metabolism included fasting glucose (analyzer "Humolizer", Germany); glycosylated hemoglobin level (HbA1c) with "Hummer" kits (USA); lipid metabolism assessment included: total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-cholesterol) in blood serum (by enzymatic colorimetric method with kits "Human", Germany); very low density lipoproteins

cholesterol (VLDL-cholesterol), low density lipoprotein cholesterol (LDL-cholesterol) by standard methods; plasma insulin concentration – by enzyme immunoassay (Insulin ELISA, DRG, Germany). To determine insulin resistance (IR) the HOMA-IR index was used according to the formula: (fasting glucose) x (fasting insulin)) mmol/ml/22.5). For verification of the diagnosis of SHT and AIT the concentration of thyroid stimulating hormone (TSH), free thyroxine (fT4) and antibodies to thyroid peroxidase (AT-TPO) in serum with enzyme immunoassay were measured using diagnostic kits reagents, "Granum" Ltd (Ukraine). Ultrasound examination of the thyroid gland was performed according to the standard procedure on the device "LOGIQ5".

The level of VEGF-A in blood plasma was studied by an immunoassay (ELISA) kit IBL International Gmbh (Germany) on a semi-automatic immunoassay microplate analyzer "ImmunoChem-2100", HighTechnology, Inc. (USA).

Statistical data were processed using SPSS 21.0 software. Qualitative data were presented as percentages; quantitative in the form of the mean and standard error (M±m). The Student criterion was used to estimate the differences between groups in the distribution close to normal. The differences were considered statistically significant at $p<0.05$.

The study was performed in compliance with the basic provisions of the World Medical Association (WMA), Helsinki Declaration on ethical principles for medical research involving human subjects (1964–2000) and MOH of Ukraine Order No. 690 dated September 23, 2009. The study was approved by the Bioethics Commission of Kharkiv National Medical University in accordance with the principles set forth in Helsinki Declaration. All the patients signed the inform consent.

Conflict of interests

The authors declare that they have no competing interests.

3. Results and discussion

To objectify the study all selected patients had controlled H, which made it possible to minimize the effect of blood pressure (BP) on the studied parameters. Thus, in all groups of examined patients BP levels differed non significantly ($p>0.05$, see Table).

DL was observed in all groups of examined patients: in patients of group 2, DL was more expressed than in patients of group 1. Addition of SHT in patients of group 3 was accompanied by a tendency to increase all the atherogenic lipids.The presence of more expressed DL in patients of group 3, obtained in our study, coincides with the results of HUNT study, which showed a direct relationship between TSH levels and blood lipids [11] and again confirm the existing data on the presence of atherogenic dyslipidemia on the background of incomplete compensation of thyroid metabolism, including with comorbid pathology, as a risk factor for the progression of atherosclerosis and, accordingly, the risk of its complications [12].

IR developed in all patients groups and was significantly higher than control group (HOMA-IR in groups 1, 2 and 3, respectively: 4.12±0.48; 8.24±1.29; 6.27±1.38; control – 2.23±0.36 ($p<0.05$)), significant differences between the examined patients with the control group and at the same time minimal differences between the plasma insulin levels in different groups (respectively in groups 1, 2 and 3 (μIU/ml): 15.28± 2.11 ; 18.54±2.17; 18.12±2.14; control -9.8±1.16 ($p<0.05$)) was found.

The obtained data on the presence of IR require clarification. The occurrence of IR with T2DM is an expected sign, but lower level of IR in patients with a comorbid course of H, T2DM and SHT is not completely clear. Xu C. et al. [13] have re-analyzed the data of a mature database (NHANES, 1999 ~ 2002) and found that both fasting plasma glucose levels and the proportion of hyperglycemic subjects among SHT patients were higher than that found in euthyroid controls. These authors confirmed increased HOMA-IR index in the SHT state in their study.

Contrariwise, the presence of significantly lower values of the HOMA-IR index in group 3 may be explained by the favorable effect of metformin, which was accepted by all participants in the study with diabetes. In recent years, there has been a number of studies indicating the positive effect of Metformin not only on carbohydrate metabolism but also on the thyroid gland [14], which may have a greater positive effect on the degree of IR than in the case of impaired carbohydrate metabolism alone at T2DM, but these data are quite contradictory and need further studying [15].

At the same time, the decreased dynamics of HOMA-IR in patients of group 3 can be explained by bi-directional effect of thyroid hormones: on the one hand, they have a counter-insular effect, and on the other hand, they can improve the transport and utilization of glucose in the periphery, i.e. have a synergistic effect with insulin, which probably explains such changes in IR.

ED was assessed by changing the VEGF-A levels and a significant increase in all groups of patients was found in comparison with the controls (respectively, control, groups 1, 2 and 3 (pg/ml): 270.11±18.34 pg/ml; 379.24±19.17 pg/ml; 327.10±26.25 pg/ml; 480.19±29.12 pg/ml; ($p < 0.05$)). In group 2, VEGF-A was lower than in group 1, which is probably due to the protective effect of Metformin which was an inclusion criteria for T2DM patients, on the functional state of endothelium [16, 17]. The maximum level of VEGF-A was observed in patients of group 3. The explanation for this may be a combination of adverse effects on the endothelium of several factors: the effect of thyroid hormones directly on ED, as well as the damaging effect of the immune complexes formed against a background of AIT.

To detail the effect of thyroid disorders on ED, the patients of the 3 groups were additionally divided into 2 subgroups depending on the level of TSH: 3^a subgroup (n=36) with a slight increase in TSH (≤ 6.0 μMU/ml) and 3b subgroup (n=34) with a significant increase in TSH (from 6.1 to 10 μMU/ml).

An additional analysis of the effect of the thyroid status on ED revealed significant differences in the level of VEGF-A in 3^a and 3b subgroups (respectively 3^a and 3b subgroups, pg/ml: 352.55±17.64 pg/ml vs 461.74±20.13 pg/ml ($p < 0.05$)), which confirms the negative effect of thyroid disorders on ED even at the stage of SHT despite the presence of factors contributing to its improvement (in our study, taking metformin). It is important to note that aggravation of ED occurred even with a slight increase in TSH.

Moreover, similar data were already obtained in another study conducted earlier, where a complex of carotid intima-media was studied as a marker of ED, in particular, its thickness in patients with the same pathology [18], and, the pathogenetic mechanisms of carbohydrate metabolism disorders, their relationship with ED were clarified [19].

Conclusions:

1. Hormonal disorders contribute to aggravation of endothelial dysfunction in patients with hypertension and comorbid endocrinopathies – type 2 diabetes mellitus and subclinical hypothyroidism.

2. The degree of negative impact of type 2 diabetes mellitus and subclinical hypothyroidism on endothelial dysfunction in patients with hypertension has certain differences. Endothelial dysfunction is more expressed with a combination of hypertension, type 2 diabetes and subclinical hypothyroidism.

3. Even minor changes in thyroid status contribute to the progression of endothelial dysfunction in patients with comorbid pathology.

4. Metformin may have a protective effect on endothelial dysfunction in patients with comorbid pathology.

5. Early detection of endothelial dysfunction and timely treatment of patients with a combination of hypertension and endocrinopathies – type 2 diabetes mellitus and subclinical hypothyroidism will not only reduce the risk of cardiovascular complications, but also change the course of the disease and improve the quality of the patient's life.

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