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**Editor**
**Komarytskyy M.L.**
*Ph.D. in Economics, Associate Professor*

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**e-mail:** kyiv@sci-conf.com.ua

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**MEDICAL SCIENCES**

# ENDOTHELIAL DYSFUNCTION AS A FACTOR IN THE DEVELOPMENT OF RENAL DYSFUNCTION IN PATIENTS WITH HYPOTHYROIDISM

**Viun Tetiana**
Ph.D., Assistant of General Practice department
Family Medicine
**Hlushko Svitlana**
**Sloz Diana**
Students
Kharkiv National Medical University
Kharkiv, Ukraine

**Introduction.** The endothelium is an organ of internal secretion that controls the tone of blood vessels, protects them from the negative effects of circulating cells and substances, regulates the transfer of soluble substances to the cells of the vessel wall, and also controls immune, inflammatory and reparative processes, maintains the balance of local hemostasis processes. Today, the endothelium is considered another target organ. It is known that a violation of its function, known as endothelial dysfunction (ED), is an important component of the development of many diseases. Several studies have confirmed that hypothyroidism can lead to endothelial dysfunction.

The main goal of our work is to analyze the scientific literature with the aim of summarizing information about the current views of the influence of endothelial dysfunction on kidney function in patients with primary hypothyroidism.

**Materials and methods.** 188 patients with detected hypothyroidism who are registered with an endocrinologist took part in the study. The average age of the patients was 56 years, with a medical history of about 8 years. The control group also included 30 people who did not have any thyroid diseases.

The criteria for inclusion in the study provide for the presence of a previously confirmed diagnosis of hypothyroidism, provided that the level of TSH exceeds 4.0 mIU/l. A criterion is also the presence of reduced levels of free thyroxine (fT4) less than 10.3 pmol/l and free triiodothyronine (fT3) less than 2.3 pmol/l. In addition,

it is important that the patient gives voluntary consent to participate in the study.

Exclusion criteria from the study are such factors as cerebral circulation disorders, any form of coronary heart disease, arterial hypertension above the first degree, chronic diseases of the cardiovascular system in the anamnesis. Persons with chronic kidney and liver diseases, oncological diseases, autoimmune diseases, pregnancy, taking hypolipidemic drugs and mental diseases are also excluded.

A comprehensive laboratory-instrumental study of kidney function and assessment of endothelial function was performed at baseline, 3 and 6 months after treatment using a test with reactive hyperemia. The basis for the analysis was the assessment of endothelium-dependent vasodilatation (EDVD) of the brachial artery (BA). The reaction of BA to the phase of reactive hyperemia, which is manifested by dilation by more than 10% of the initial value, is considered normal. If the LVEF was less than 10% or vasoconstriction was observed, the patient was considered to have endothelial dysfunction. Similarly to the sample with reactive hyperemia, the endothelium-independent vasodilatation index was calculated - the relative change in the internal diameter of the PA after sublingual administration of nitromint. The level of vasculoendothelial growth factor (VEGF) in blood plasma was also determined.

All patients underwent a complete general clinical examination, including measurements of body mass index (BMI), thyroid hormone (TSH) and TSH levels at the beginning of the study and after 6 months of treatment. The presence of kidney damage was determined by the presence of violations of the permeability of the glomerular filter, which was manifested by the presence of albuminuria and indicators of the glomerular filtration rate (GFR) calculated according to the CKD-EPI formulas. To assess the impact of the autoimmune process in the thyroid gland, as well as BMI, patients were divided into four groups: the first consisted of 45 patients with hypothyroidism on the background of autoimmune thyroiditis (AIT) without obesity; the second - 46 patients with AIT with hypothyroidism and obesity; the third - 47 patients with manifest hypothyroidism without obesity; the fourth - 50 patients with manifest hypothyroidism with obesity. There were no significant differences between patients in the main and control groups in terms of age, gender,

and baseline therapy.

Changes in clinical signs of hypothyroidism, indicators of endothelial dysfunction during treatment with levothyroxine, enalapril and atorvastatin were studied. The method of variational statistical analysis was used for the analysis.

**Research results.** Endothelial function was assessed using the endothelium dependent vasodilatation (EDVD) index.

The revealed more pronounced ED in patient groups II and IV indicates the effect of obesity on endothelial dysfunction. In addition, in these groups, the increase in the diameter of the brachial artery after compression is half as much, and the EDVD is also smaller than in the control group, by 46.4 and 47.7%.

According to modern scientific data, VEGF induces the expression of one of the most powerful factors of ED - endothelin-I.

According to the results of the study, the level of VEGF significantly increases in the blood plasma of patients with manifest hypothyroidism, compared to controls. Thus, there was an increase in VEGF in the group with hypothyroidism on the background of AIT without obesity, 46.5 ± 1.4 pg/ml, and in patients with hypothyroidism on the background of AIT and obesity 48.1 ± 1.8 pg/ml. In patients with postoperative hypothyroidism, 43.0 ± 1.5 pg/ml — in patients without hypothyroidism and up to 45.8 ± 2.5 pg/ml in patients with postoperative hypothyroidism and obesity.

According to the data of correlation analysis, a direct correlation of medium strength was found between the level of VEGF and the level of TSH in the I group of patients, in the II group - a strong direct correlation, in the III group - a moderate direct correlation, and in the IV group - a significant direct correlation.

The relationship between the level of VEGF and the level of antibodies to thyroid peroxidase was found in groups I and II, and in groups III and IV this relationship is absent.

In addition, there is a direct moderate relationship between the levels of VEGF and total cholesterol in patients of groups I and III, significant in groups II and IV.

According to these data, the level of VEGF increases in patients with

hypothyroidism with and without obesity, but the highest indicators are registered in patients with hypothyroidism on the background of AIT.

For a more detailed description of the results of patient treatment, depending on the scheme, each group was divided into 2 subgroups. Subgroup A included basic treatment of LT4, subgroup B - complex treatment - LT4, atorvastatin 20 mg per day for 6 months and enalapril. Treatment included two stages. The first stage included dose titration of levothyroxine (LT4) and enalapril. Enalapril was prescribed to patients, with an initial dose of 2.5 mg/day, and it was increased until the maximum possible dose was reached, taking into account their hemodynamic parameters. The second stage of treatment included the addition of atorvastatin at a dose of 20 mg/day to individually selected doses of LT4 and enalapril.

In the patients of the first and second groups, compensation of hypothyroidism after 6 months led to a probable increase in EDVD. However, with complex treatment with atorvastatin and enalapril, the changes in EDVD were significantly better, already after 3 and 6 months. In the groups with postoperative hypothyroidism, the appointment of levothyroxine contributed to the tendency towards the increase of EDVD, but the changes were not probable even after 6 months. While in patients who received complex treatment, EDVD probably increased already after 3 months.

Analyzing the dynamics of the VEGF level in patients with basic and complex treatment, the following data were obtained: in group I (with AIT without obesity), in patients who received complex therapy with atorvastatin and enalapril, the VEGF level decreased from 46.5 ± 1.1 to 39, 9 ± 1.7 pg/ml, (on average by 14.2%), a slight decrease was found in group IA - from 46.4 ± 2.6 to 44.7 ± 3.8 pg/ml. In group II (with AIT and obesity), receiving basic treatment, the content of VEGF decreased improbably, and in patients with complex treatment from 47.7 ±1.7 to 37.4 ±2.2 pg/ml (by 21.7%) . In subgroup IIIA (manifest hypothyroidism without obesity, basic treatment) - a decrease in VEGF is unlikely, IIIB - an average decrease of 25.3%. In patients with manifest hypothyroidism with obesity who received basic treatment (subgroup IVA), VEGF decreased from 45.9 ± 1.8 to 39.9 ± 1.5 pg/ml (on average by

13%), in the subgroup with complex treatment (IVB) from 45.6±4.9 to 33.6±0.98 pg/ml, i.e. by 26.5% on average.

It can be concluded that the use of complex therapy with the addition of enalapril and atorvastatin reduces the formation of VEGF.

**Conclusion.** The obtained results indicate that people with uncompensated hypothyroidism have a violation of endothelium-dependent vasodilatation (ESVD). However, no violations in the mechanisms of endothelium-independent vasodilatation were detected.

The obtained correlations show the mutual influence of thyroid hypofunction, obesity and hypercholesterolemia on the development of endothelial dysfunction in people with primary hypothyroidism.

Endothelial dysfunction (ED) is an important factor in the development of atherosclerosis, complications associated with atherothrombosis, heart failure, as well as in the formation of clinical manifestations of some cardiovascular diseases. To study the effect of ED on kidney function, an analysis was conducted comparing one of the indicators of endothelial dysfunction - GFR. It was found that there is a reversible relationship between them, which was moderately expressed in groups I and II, and slight, but positive in groups III and IV. Therefore, it can be argued that ED has a negative effect on kidney function in patients with hypothyroidism.

The obtained results of treatment with the use of levothyroxine, enalapril (ACE inhibitor) and atorvastatin confirm the probable improvement of the endothelium in patients with hypothyroidism regardless of its origin and the presence of obesity. Thus, the combined use of levothyroxine, enalapril (an ACE inhibitor) and atorvastatin significantly inhibits the formation of VEGF and improves endothelial function.