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RESEARCH ARTICLE

Justification of Increasing the Blood Flow Velocity in the Arteries of the Thyroid Gland in Autoimmune Thyroiditis as a Reflection of Endothelial Changes Due to Inflammatory Status

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Abstract: ***Objective*:** The aim of the research was to determine the dependence of the blood flow velocity in the thyroid arteries in patients with autoimmune thyroiditis (AIT) on the presence of atherosclerotic carotid disease and the level of systemic blood pressure.

***Method*:** The research involved 20 patients with AIT in euthyroid state, 30 patients AIT in euthyroid state with stable coronary heart disease (CHD), 30 patients with stable CHD and 30 healthy individuals. Participants of the research were examined using ultrasound of carotid arteries and inferior thyroid arteries. Parameters of blood flow velocity were compared with the level of systemic blood pressure.

***Results*:** In AIT peak systolic velocity and resistance index in the inferior thyroid arteries were significantly higher than in healthy individuals and patients with CHD ($p<0.05$). In patients with CHD velocity parameters in carotid arteries were high, unlike in the healthy individuals and patients with AIT ($p<0.05$). In patients with AIT without CHD the atherosclerotic changes of carotid arteries were not found. Increased systemic blood pressure was noticed in all patients with CHD without significant differences between groups.

***Conclusion*:** The value of peak systolic velocity and resistance index of inferior thyroid arteries in autoimmune thyroiditis are noticed even with euthyroidism and do not depend on systemic blood pressure and atherosclerosis of carotid arteries. Increasing the thyroid arterial blood flow velocity parameters should be considered as sign of an active inflammatory period AIT, where advanced fibrosis is not present.

Keywords: Autoimmune thyroiditis, atherosclerosis, carotid arteries, thyroid arteries, systemic blood pressure, blood flow velocity.

1. INTRODUCTION

Endocrine diseases rank the 4th place in the world in the structure of all diseases, most of them are pathologies of the thyroid gland (TG) [1]. The prevalence of autoimmune thyroiditis (AIT) in Ukraine through the last decade has increased by 68 % [2]. The frequency of symptomatic forms of AIT is only 1 %. However, AIT is the most common cause of hypothyroidism (70-80 %), as chronic autoimmune inflammation leads to apoptosis of thyroid cells with subsequent fibrosis and loss of functional activity of the TG [3]. The abovementioned necessitates the early diagnosis of AIT aiming to take active prevention and treatment measures.

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In AIT, in most cases, enhancing thyroid blood flow through the blood component is being observed [4]. However, we have not found research works, which would study dependence of velocity parameters of arterial blood flow in the thyroid gland on the structural and functional status of the peripheral vasculature, particularly, the presence of atherosclerosis (ASVD) of the carotid arteries (CA) and blood pressure level (BP), which would provide an opportunity to expand understanding of the nature of thyroid blood flow changes in AIT and establish the diagnostic value of thyroid blood flow parameters as a marker of AIT.

The aim of our research is to identify the peculiarities of dependence of blood flow parameters in the arteries of the thyroid gland in patients with autoimmune thyroiditis on the structural and functional state of the carotid arteries and systemic blood pressure.

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2. MATERIALS AND METHODS

An observational study "case-control" has been conducted. The research involved 110 individuals: 20 patients with AIT in euthyroid state (13 women and 7 men aged 39±5.7), 30 patients (23 women and 7 men aged 54±6.2) with AIT in euthyroid state, who had an additional diagnosis of coronary heart disease (CHD), stable angina pectoris, FC II, Low-to-moderate risk grade 1 hypertension, 30 patients with stable CHD and Low-to-moderate risk grade 1 hypertension (17 men and 13 women aged 57±9.2), and 20 healthy individuals (16 women and 14 men aged 34±5.6), amounted to the control group.

Shortly before, every patient signed the informed consent to participate in the research, according to the requirements of the Declaration of Helsinki of 1975. Ethical, moral and legal aspects of conducting the research were agreed with the Institutional Review Board of the Higher State Educational Establishment of Ukraine "Ukrainian Medical Stomatological Academy". Diagnosis of AIT was carried out due to the standards of European Thyroid Association 2013, diagnosis of CHD has been made by coronarography due to the recommendations of the European Society of Cardiology (ESC) 2013, FC of stable angina pectoris was confirmed by the data of ECG treadmill testing, diagnosis of arterial hypertension was carried out due to the recommendations of the European Society of Hypertension and of the ESC 2013 [5-7]. The criteria for inclusion into the research were men and women`s age of 25-70, euthyroidism, absence of destabilizing flow of CHD for at least two months, the patient's informed consent to participate in the research and his/her willingness to cooperate. Exclusion criteria were: the presence of grade 2 and 3 hypertension and high-risk grade 1 hypertension, class II heart failure, congenital and acquired heart disease, rheumatic diseases, anemia, DM and other endocrine diseases, chronic liver disease and kidney failure function, cancer.

Ultrasound of TG and CA was being performed on the ultrasound scanner "Fukuda UF 750-XT" (Japan) using multifrequency linear probe (6.0/7.5/9.0 MHz) in B-mode, color Doppler imaging (CDI) and pulsed-wave Doppler mode (PWD).

We determined the thickness of intima-media complex (IMC) of common carotid arteries (CCA), according to the consensus of the American Society of Echocardiography (2008). The measurement of IMC of CCA were being performed manually, sequentially in the right and left CCA, at a distance of 1 cm from the bifurcation in three projections with calculating the average value for each artery [8]. The criteria of ASVD of CA were considered to be the IMC thickening of 0.9 mm. In the presence of atherosclerotic plaques, their nature, size and hemodynamic significance (> 40 % of CA lumen) were being assessed due to the NASCET method: (D - d) / D = % of stenosis, where D is a diameter of the internal CA (ICA), d is a diameter of the residual lumen of atherosclerotic plaque in CCA [9]. In duplex Doppler mode (CDI+PWD) peak systolic velocity (PSV) in CCA was being measured.

Ultrasound of TG was being performed by the standard method [10]. In B-mode linear dimensions of thyroid lobes were being measured with volume calculation, ultrasound characteristics of thyroid tissues were being evaluated. With CDI vascularization of parenchyma was being assessed. In CDI+PWD peak systolic velocity of blood flow in the inferior thyroid arteries (ITA) was being measured and, through determining diastolic flow velocity (DFV), the resistance index (IR) (Pourcelot index) was being determined by the formula: IR = (PSV – DFV) / PSV [11]. According to the various researches, blood flow velocity in the superior and inferior thyroid arteries is not significantly different and has the same dynamics in case of the pathological processes [12]. Therefore, we measured the blood flow velocity and derived parameters in the right (r) and left (l) ITA only.

During the ultrasound of CA and TG, the registration of blood pressure - systolic (SBP) and diastolic (DBP) ones – was held with blood pressure gauge in order to determine its possible effect on the studied parameters of blood flow.

Statistical analysis of the results of the research was being carried out using KyPlot program (KyensLab Inc., Version 2.0 beta 15). The hypothesis of normal distribution was checked by Shapiro - Wilk test. Belonging to one set of samples was verified using Kruskal – Wallis rank test. When comparing data among the three and more independent groups, unpaired t-Student test with Bonferoni corrections and analysis of variance (ANOVA) was used. Data of statistical analysis was presented in the form of $X \pm \sigma$, where X was the average value, σ - standard deviation. Differences in data were considered to be accurate if the level of significance of p-value was <0.05.

3. RESEARCH RESULTS

Due to the results of ultrasound of TG, in patients with AIT in gray-scale B-mode the reduction or, conversely, the relative increase in TG by anteroposterior size was found, or the size and volume (V) of the gland stayed unchanged. 33 % of patients' thyroids had the shape of a "horseshoe" because of the isthmus thickening > 5 mm. Echogenicity of thyroid parenchyma in all patients was reduced, echostructure was characterized by diffuse heterogeneity due to small hypoechoic fuzzy areas of different size, sometimes confluent ones, more often - located closer to the front surface of the gland. A pronounced stromal component - numerous small linear, "punctiform" inclusions in the structure of the gland and thickening of the capsule - was detected. In CDI moderate diffuse hypervascularization with predominance of the arterial component was determined in 85 % of patients with AIT and in 86.7 % of patients with CHD combined with AIT. Hypervascularization was identified by CDI as the diffuse increase in the number of color signals in parenchyma of TG and enlargement of the diameter of the vessels in thyroid parenchyma to 3 mm and more [9]. In patients with CHD and in healthy individuals ultrasound evidence of thyroid pathology was not found.

In 41.7 % of patients with CHD and in 53.3 % of patients with CHD in combination with AIT atherosclerotic plaques - small heterogeneous or echogenic, mostly smooth, less frequently - irregular, but with no signs of ulceration - were detected in CCA and ICA. Hemodynamically, significant stenosis of CCA, due to the NASCET method (> 40 %), was not found.

Table 1. Parameters of blood flow in the inferior thyroid arteries (ITA), common carotid arteries (CCA), intima-media complex (IMC) of CCA values and blood pressure levels in patients of research groups

Group / Parameter, X ± σ	Group of healthy individuals, n=20	Group CHD, n=30	Group AIT (euthyroidism), n=20	Group CHD+AIT, n=30
V r. lobe, TG, cm^3	4.95±1.51	5.42±1.57	5.99±1.58	5.29±1.52
V l. lobe, TG, cm^3	4.35±1.00	4.31±1.02	5.19±1.35	4.65±1.94
PSV ITA r., m/s	0.17±0.02	0.17±0.03	0.28±0.03*▪	0.27±0.04*▪
PSV ITA l., m/s	0.15±0.03	0.17±0.03	0.26±0.03*▪	0.25±0.04*▪
IR ITA r., RVU	0.54±0.04	0.55±0.05	0.66±0.04*▪	0.66±0.04*▪
IR ITA l., RVU	0.53±0.05	0.54±0.05	0.64±0.04*▪	0.63±0.03*▪
PSV CCA r., m/s	0.83±0.12	1.01±0.18*▫	0.84±0.12▪	1.04±0.15*▫
PSV CCA l., m/s	0.83±0.08	0.98±0.21*▫	0.81±0.15▪	1.05±0.18*▫
IMC CA r., mm	0.62±0.08	0.96±0.13*▫	0.59±0.06▪	0.94±0.09*▫
IMC CA l., mm	0.65±0.09	0.96±0.06*▫	0.59±0.05▪	0.95±0.03*▫
SBP, mm Hg	120.43±11.29	143.16±11.21*▫	123.57±10.08▪	144.29±8.52*▫
DBP, mm Hg	77.40±6.65	89.47±4.68*▫	78.93±5.25▪	87.14±6.7*▫

Note: * - Significant difference compared with the data of healthy individuals ($p<0.05$),
▪ - Significant difference compared with the data of patients with CHD ($p<0.05$),
▫ - Significant difference compared with the data of patients with AIT ($p<0.05$).

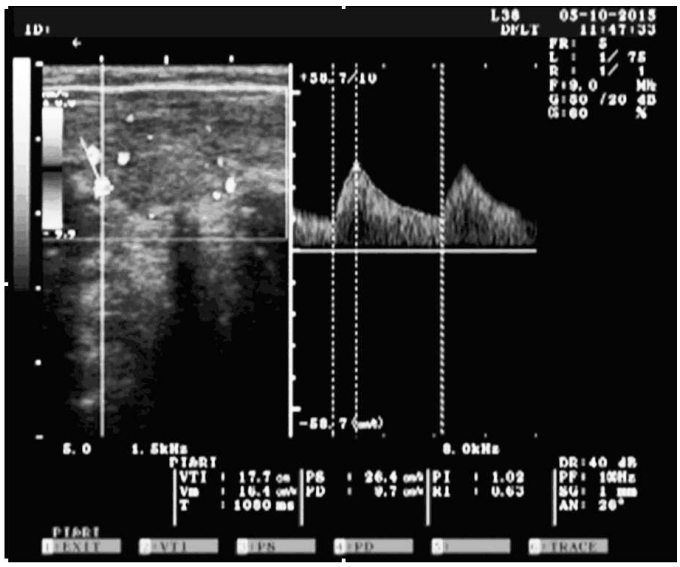

Fig. (1). Blood flow in the right inferior thyroid artery in the patient with AIT CDI+PWD.

The results of measurements carried out in the research of TG and CA are given in Table **1**. According to our data, in patients with AIT, as well as in patients with AIT combined with CHD, PSV in ITA and IR of ITA were significantly higher than in healthy individuals ($p<0.05$). In patients with CHD values of these parameters were not significantly different from those in healthy individuals (Table **1**, Fig. **1**).

In patients with CHD and CHD in combination with AIT increased PSV in CCA and thickened CCA IMC was found, unlike in healthy individuals ($p<0.05$). As shown in Table 1, in patients with AIT no changes of parameters characterizing the state of CCA were revealed, but the blood flow rates in ITA were increased and not significantly different from those of patients with AIT combined with CHD ($p>0.05$). Increased systemic blood pressure was noticed only in patients with CHD and CHD in combination with AIT without reliable differences between groups.

3. DISCUSSION OF THE RESEARCH

Assessment of arterial blood flow in the thyroid was being carried out with determining PSV in CCA, CCA IMC along with evaluation of stenosis and systemic BP to detect the possible effect of various factors on thyroid blood flow. Analysis of the data received showed no causal association

of changes in thyroid arterial blood flow and the state of CA and systemic BP. Due to AIT, the characteristics of blood flow did not depend either on the presence or absence of CHD and atherosclerosis of CCA.

These data indicate that increased blood flow velocity parameters (PSV and IR), determined in ITA, are directly associated with pathological processes in the thyroid tissues.

One of the first researchers, who used ultrasound assessment of the thyroid blood flow velocity characteristics for verification of pathologies, was Bogazzi F. (1996). He found out the fact of increasing the blood flow velocity in thyroid arteries with subclinical hypothyroidism and hyperthyroidism and determined their limits [13].

He and subsequent researchers found that in diffuse toxic goiter blood flow velocity in the thyroid arteries increased tenfold, which could be an important differential and diagnostic sign of that disease and hypertrophic form of AIT, along with the defining the level of appropriate antibodies [14].

From then, the method of ultrasound evaluation of the thyroid blood flow velocity characteristics was used by certain number of scientists, and they confirmed its diagnostic value in AIT, Graves' disease and other thyropathies. Though, blood flow parameters were compared only with hormonal thyroid status [14]. However, either hyperthyroidism or subclinical and, in most cases, clinical hypothyroidism are accompanied with an increase in thyroid blood flow velocity parameters, calling into question the conclusion about their dependence on particularly hormone activity of the thyroid [15].

According to a number of researches, under conditions of fibrosis and significant thyroid hypoplasia, thyroid blood flow velocity and significant inhibition of its function decrease [11, 14]. These structural changes, mainly, are consequence of prolonged aggressive course of AIT. Although, probably, fibrosis does not cause compression or stenosis of the thyroid arteries, as blood flow velocity does not increase, but, on the contrary, it is reduced, and the activity of local inflammatory reactions in this stage of the disease is suppressed.

The patients with AIT and AIT in combination with CHD studied had euthyroidism, but the velocity indicators in ITA increased. In our opinion, the reason for it might be swelling and increased density of thyroid tissue under conditions of immune inflammation, or local vasculitis in the presence of autoaggression and Th1-cytotoxicity.

In our previous researches, patients either with AIT or with AIT in combination with CHD, along with increased levels of proinflammatory cytokines, have revealed an increase in the number of circulating microparticles $CD32^{+}CD40^{+}$ in the blood flow, which characterize the inflammatory activation of endothelium [16, 17]. We believe it is an immunoinflammatory component that determines the velocity increase in thyroid arteries in terms of AIT. Therefore, it makes sense to study the relationships of thyroid activation with the severity of inflammation in conditions of diffuse toxic goiter and other thyroid pathologies to develop effective therapeutic strategies in perspective.

CONCLUSION

Thus, in AIT PSV increase in ITA on average reaches 48-65 %, IR increase - 16-20 %. The thyroid arterial blood flow velocity parameters increase, regardless of the structural and functional status of the peripheral vasculature, non-stenosis ASVD CCA on the level of systemic BP in particular. Increasing the thyroid arterial blood flow velocity parameters should be considered as sign of an active in- flammatory period AIT, where advanced fibrosis is not pre- sent.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

HUMAN AND ANIMAL RIGHTS

No Animals/Humans were used for studies that are base of this research.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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Declared none.

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