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ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

Медицинские новости Грузии

საქართველოს სამედიცინო სიახლენი

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გამოიცემა თბილისის სახელმწიფო სამედიცინო უნივერსიტეტთან
თანამშრომლობითა და მისი პატრონაჟით

ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

ТБИЛИСИ - НЬЮ-ЙОРК

GMN: Georgian Medical News is peer-reviewed, published monthly journal committed to promoting the science and art of medicine and the betterment of public health, published by the GMN Editorial Board and The International Academy of Sciences, Education, Industry and Arts (U.S.A.) since 1994. **GMN** carries original scientific articles on medicine, biology and pharmacy, which are of experimental, theoretical and practical character; publishes original research, reviews, commentaries, editorials, essays, medical news, and correspondence in English and Russian.

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GMN: Медицинские новости Грузии - ежемесячный рецензируемый научный журнал, издаётся Редакционной коллегией и Международной академией наук, образования, искусств и естествознания (IASEIA) США с 1994 года на русском и английском языках в целях поддержки медицинской науки и улучшения здравоохранения. В журнале публикуются оригинальные научные статьи в области медицины, биологии и фармации, статьи обзорного характера, научные сообщения, новости медицины и здравоохранения.

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GMN: Georgian Medical News – საქართველოს სამედიცინო სიახლენი – არის ყოველთვიური სამეცნიერო სამედიცინო რეცენზირებადი ჟურნალი, გამოიცემა 1994 წლიდან, წარმოადგენს სარედაქციო კოლეგიისა და აშშ-ის მეცნიერების, განათლების, ინდუსტრიის, ხელოვნებისა და ბუნებისმეტყველების საერთაშორისო აკადემიის ერთობლივ გამოცემას. GMN-ში რუსულ და ინგლისურ ენებზე ქვეყნდება ექსპერიმენტული, თეორიული და პრაქტიკული ხასიათის ორიგინალური სამეცნიერო სტატიები მედიცინის, ბიოლოგიისა და ფარმაციის სფეროში, მიმოხილვითი ხასიათის სტატიები.

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При представлении в печать научных экспериментальных работ авторы должны указывать вид и количество экспериментальных животных, применявшиеся методы обезболивания и усыпления (в ходе острых опытов).

4. К статье должны быть приложены краткое (на полстраницы) резюме на английском, русском и грузинском языках (включающее следующие разделы: цель исследования, материал и методы, результаты и заключение) и список ключевых слов (key words).

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2. Size of the article, including index and resume in English, Russian and Georgian languages must be at least 10 pages and not exceed the limit of 20 pages of typed or computer-printed text.

3. Submitted material must include a coverage of a topical subject, research methods, results, and review.

Authors of the scientific-research works must indicate the number of experimental biological species drawn in, list the employed methods of anesthetization and soporific means used during acute tests.

4. Articles must have a short (half page) abstract in English, Russian and Georgian (including the following sections: aim of study, material and methods, results and conclusions) and a list of key words.

5. Tables must be presented in an original typed or computer-printed form, instead of a photocopied version. **Numbers, totals, percentile data on the tables must coincide with those in the texts of the articles.** Tables and graphs must be headed.

6. Photographs are required to be contrasted and must be submitted with doubles. Please number each photograph with a pencil on its back, indicate author's name, title of the article (short version), and mark out its top and bottom parts. Drawings must be accurate, drafts and diagrams drawn in Indian ink (or black ink). Photocopies of the X-ray photographs must be presented in a positive image in **tiff format**.

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7. Please indicate last names, first and middle initials of the native authors, present names and initials of the foreign authors in the transcription of the original language, enclose in parenthesis corresponding number under which the author is listed in the reference materials.

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ავტორთა საყურადღებოდ!

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2. სტატიის მოცულობა არ უნდა შეადგენდეს 10 გვერდზე ნაკლებს და 20 გვერდზე მეტს ლიტერატურის სიის და რეზიუმეების (ინგლისურ, რუსულ და ქართულ ენებზე) ჩათვლით.

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6. ფოტოსურათები უნდა იყოს კონტრასტული; სურათები, ნახაზები, დიაგრამები - დასათაურებული, დანომრილი და სათანადო ადგილას ჩასმული. რენტგენოგრამების ფოტოასლები წარმოადგინეთ პოზიტიური გამოსახულებით **tiff** ფორმატში. მიკროფოტოსურათების წარწერებში საჭიროა მიუთითოთ ოკულარის ან ობიექტივის საშუალებით გადიდების ხარისხი, ანათალების შეღებვის ან იმპრეგნაციის მეთოდი და აღნიშნოთ სურათის ზედა და ქვედა ნაწილები.

7. სამამულო ავტორების გვარები სტატიაში აღინიშნება ინიციალების თანდართვით, უცხოურისა – უცხოური ტრანსკრიპციით.

8. სტატიას თან უნდა ახლდეს ავტორის მიერ გამოყენებული სამამულო და უცხოური შრომების ბიბლიოგრაფიული სია (ბოლო 5-8 წლის სიღრმით). ანბანური წყობით წარმოდგენილ ბიბლიოგრაფიულ სიაში მიუთითეთ ჯერ სამამულო, შემდეგ უცხოელი ავტორები (გვარი, ინიციალები, სტატიის სათაური, ჟურნალის დასახელება, გამოცემის ადგილი, წელი, ჟურნალის №, პირველი და ბოლო გვერდები). მონოგრაფიის შემთხვევაში მიუთითეთ გამოცემის წელი, ადგილი და გვერდების საერთო რაოდენობა. ტექსტში კვადრატულ ფჩხილებში უნდა მიუთითოთ ავტორის შესაბამისი N ლიტერატურის სიის მიხედვით. მიზანშეწონილია, რომ ციტირებული წყაროების უმეტესი ნაწილი იყოს 5-6 წლის სიღრმის.

9. სტატიას თან უნდა ახლდეს: ა) დაწესებულების ან სამეცნიერო ხელმძღვანელის წარდგინება, დამოწმებული ხელმოწერითა და ბეჭდით; ბ) დარგის სპეციალისტის დამოწმებული რეცენზია, რომელშიც მითითებული იქნება საკითხის აქტუალობა, მასალის საკმაობა, მეთოდის სანდოობა, შედეგების სამეცნიერო-პრაქტიკული მნიშვნელობა.

10. სტატიის ბოლოს საჭიროა ყველა ავტორის ხელმოწერა, რომელთა რაოდენობა არ უნდა აღემატებოდეს 5-ს.

11. რედაქცია იტოვებს უფლებას შეასწოროს სტატია. ტექსტზე მუშაობა და შეჯერება ხდება საავტორო ორიგინალის მიხედვით.

12. დაუშვებელია რედაქციაში ისეთი სტატიის წარდგენა, რომელიც დასაბეჭდად წარდგენილი იყო სხვა რედაქციაში ან გამოქვეყნებული იყო სხვა გამოცემებში.

აღნიშნული წესების დარღვევის შემთხვევაში სტატიები არ განიხილება.

Содержание:

CORRELATION OF THYROID AUTOIMMUNITY WITH ATHEROSCLEROSIS EVALUATION IN HASHIMOTO'S THYROIDITIS

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According of clinical and scientific research result, the thyroid gland dysfunction (hypothyroidism) play significant role in development of dyslipidemia, atherosclerosis (At) and hence the coronary heart disease (CHD) pathogenesis.

Accumulating results of numerous cross-sectional epidemiological investigations indicate that among other important risk factors, the hypothyroidism and high serum TSH levels are more pronounced cause of endothelial dysfunction, histomorphological changes of large vessels' wall and impact on the mechanisms of cholesterol metabolism. McLeod 2013 [1], based on the large meta-analysis study [2], suggested a causal relationship between autoimmune thyroid disease and atherosclerosis [3-5].

By 2019 ESC/EAS Guideline [6], except of the traditional risk factors, such as the dyslipidemia - high level of Total cholesterol (TC), low density lipoprotein cholesterol (LDLC), triglycerides and low level of high density lipoprotein cholesterol (HDLC) - noted the high importance of carotid and femoral intima- media thickness (IMT) for presence of atherosclerosis in patients with CHD and subclinical hypothyroidism (SH) [7-12].

The study region – Georgia (South Caucasus) is iodine-deficient area with a high prevalence of iodine-deficiency-related disease, such as endemic goiter, thyroid nodules, Hashimoto thyroiditis (HT) - most common cause of primary hypothyroidism [1, 13-15]. Due to the substantial changes in lipid metabolism, these conditions increase high-risk morphological features of atherosclerosis [16, 17]. Against this background, hypercholesterolemia has a direct relationship and the impacts on the dynamics of histomorphological changes in the Hashimoto's thyroid parenchyma; there are significant debates regarding the aim on which the present study is mainly concentrated.

Recently, the relationship between subclinical hypothyroidism (SH) and cardiovascular diseases has been one of the most popular topics. There is still some controversy concerning the cardiovascular impact of SH and management protocols.

The aim of the present study is to investigate the putative association between Hashimoto thyroiditis parenchyma changes and At cardiovascular disease (CHD) clinical characteristics focusing on the causal connection between thyroid function indexes, the lipid profile with follicular epithelia's molecular biology details.

Material and methods. We investigated the patients in Georgian National Center of Internal Medicine and Tbilisi State University affiliated Hospitals (Departments of cardiology, surgery and pathology). Present study was reviewed and deemed exempt from written informed consent by the Ethics committee and Board of medical sciences at Tbilisi State University based on Helsinki-ethical principles declaration for medical research [18].

To reach the planed goal we investigated 52 patients (female), which had undergone total thyroidectomy, lobectomy. In the research basic groups (I and II) were included the patients (pts) with Hashimoto thyroiditis (HT) - 28 pts, and HT with atherosclerosis - 24 pts. For underling the significance of HT in atherosclerosis patients with atherosclerosis (without HT) - 27 pts were included in control (group III).

The diagnosis of atherosclerosis were established by 2019 ESC/EAS criteria - confirmed ACVD (CHD, carotid and femoral arteries atherosclerosis) by using ECG, echocardiography, stress testes, carotid and femoral arteries ultrasonography and in some cases coronarography. The diagnosis of HT were established by TSH, FT4, FT3, anti-TPO tests and confirmed in postoperative specimens histology.

The exclusion criteria were: the patients having III-IV functional class (by Canadian Cardiovascular Society grading of angina pectoris) and unstable angina pectoris, heart failure III-IV (by NYHA classification), arterial hypertension grade 1, 2, 3 (by ESC/ESH guideline, 2018) [19], diabetes mellitus, hepatic and renal failure.

For all studying patients the following analysis was provided: lipid profile, TSH, FT4, Anti TPO; carotid, femoral, thyroid gland ultrasonography.

Laboratory tests

Thyroid hormones and anti TPO

Subclinical hypothyroidism (SH) is characterized by normal serum free T_4 and free T_3 levels and increased serum TSH levels.

Patients involved in the study underwent TSH by the enzyme-linked immunosorbent assay (ELISA) methods name "SANDWICH"-96, well plate, source-serum, venous blood, plasma, IU/ml 0-35 IU/ml, free thyroxine testing, and antibody titer to thyroid peroxidase [20].

Thyroid markers reference range: TSH 0.3-4.2 mIU/L, FT4 0.9-1.7 ng/dL, Anti-TPO <9.0 IU/mL, Anti-Tg<4.0 IU/mL [21, 22].

Thyroid disease categorization and thyroid function index - TSH and FT4 respectively:

Subclinical hypothyroidism > 4.2 mIU/L and0.9-1.7 ng/dL
Subclinical hyperthyroidism < 0.3 mIU/Land0.9-1.7 ng/dL
Overt hypothyroidism > 4.2 mIU/Land< 0.9 ng/dL
Overt hyperthyroidism < 0.3 mIU/L and> 1.7 ng/dL

Lipids profile:

Blood samples were taken after 13 hour fasting. Lipid spectrum was studied in blood serum using "Janway" spectrometry. The quantitative determination of total cholesterol (TC) was performed triglycerides (TG) were determined by the enzyme method, while the content of high density lipoprotein-cholesterol (HDLC): low density lipoprotein - cholesterol (LDLC) and very low density lipoprotein - cholesterol (VLDLC) were determined after the precipitation of low density lipoprotein -cholesterol using BIOLABO, France reactive. LDLC were calculated by Friedwald. The main criteria were: total cholesterol (TC)>160mg/dl, low density lipoprotein - cholesterol (LDLC)>100mg/dl, high density lipoprotein - cholesterol (HDLC) 150mg/dl.

Ultrasound diagnostically methods

Echocardiography

LV mass (LVM) calculations have been made using linear measurements derived from 2D targeted M-mode. LVM estimated by the ASE-recommended formula (from LV linear dimensions): LVM= 0.8 {1.04[(LVIDd + PWTd + SWTd) 3 - (LVIDd)3]}+ 0.6 gwhere PWTd and SWTd are posterior wall thickness at end diastole and septal wall thickness at end diasto-

le, respectively. LVIDd (LV internal diastolic dimension. The indexation of LVM (g/m2) determined in accordance with Height (m) and Body surface area (BSA) m2.

Carotid and femoral arteries ultrasonography

Carotid and femoral arteries intima-media thicknesses were investigated by high-resolution ultrasonography on sonoscope TOSHIBA-SSH 140-A by 5 MHz and 7, 5 MHz linear transducers. The degree of carotid stenosis was determined in transversal and longitudinal sections. The intima-media complexes and atherosclerotic plaques height was measured by the triplex scanning method**.** Carotid arteries intima-media thickness (IMT) was defined from bifurcation 20 mm proximally and 30 mm distally [23]. IMT normal value is <1 mm.

Ultrasonography of the thyroid gland

Ultrasonographic examinations were performed on a TOSHIBA SSH-140-A scanner with 5, 7, and 3.5 MHz transmissions. Examination of the thyroid gland used B to assess the thickness, width, length, and size of the thyroid gland using the appropriate formula (thickness × width × length × 0.479) to assess the structure, surface condition, diffuse and focal changes.

Histological examination

All patients provided written informed consents. This study protocol was approved by the ethics committee of medical sciences at Tbilisi State University based on Helsinki-ethical principles declaration for medical research [18]. The research database included postoperative surgical pathology material obtained from patients with thyroiditis who had undergone total thyroidectomy, lobectomy, and partial resection of the thyroid gland. The pathology material was received from Surgical Units of Tbilisi and West Georgia National Center of Interventional Medicine. Both retrospective data (for the years 2014) as well as prospective material (for the years 2918-2019) were analyzed. Basically, thyroidectomies in the I and II groups of patients were performed for the following reasons: a. patients with bilateral or multiple nodules or symptoms of neck or throat compression, or enlargement during follow-up and b. clinical and physical data indicated for removal.

The diagnosis of HT was based on the level in serum anti peroxidase level - 186 (63-438), TSH, FT4 range and histological findings.

For histological examination of thyroid operative materials, the sliced sections were stained with routine Hematoxylin and Eosin (H&E). Formalin-fixed paraffin embedded (FFPE) tissue sections were routinely processed and stained with hematoxylin and eosin. Immunohistochemical (IHC) staining was performed on FFPE tissue sections with antibodies against the following markers: 1. S100 Protein (clone RTU-S100p Polyclone Antibodies, Biogenex, USA), because Hürthle cells reaction is most remarkable in HT disorders; and 2. p63 (clone 7JUL, Leica, UK), which is a p53 gene family at 3q27-29 homologue nuclear transcription factor. Three of p63 isoforms encode proteins that transactivate on p53 activity and induct cell into apoptosis. The other three isoforms encode proteins, which have inhibitory effect on p53 activity [24]; in our cases, p63 is important to detect oxyphilic metaplasia of thyroid follicular epithelium. As positive control Palatine Tonsils lymphoid tissue specimens were used.

FFPE sections were fixed on poly-L-lysine-coated glass slides and prepared as follows: 1) deparaffinization, rehydration and incubation for 20 minutes in 3% H_2O_2; 2) Immersion in phosphate-buffered saline (PBS) for 20 min; 3) Antigen retrieval in the microwave (600 W) for 20 min, followed by cooling in citrate buffer (0.01 m, pH 6.0). Specimens were incubated with the primary antibodies for 1 hour at room temperature. After that was washed three times with PBS at room temperature. Hematoxylin is used for nuclei counterstaining. All procedures were carried out in compliance with antibodies manufacturers' protocols (Bio Genex, USA; Leica, UK).

Histology slides were reviewed by two pathologists (L. G., T. G.). We used the 2015 American Thyroid Association management guidelines [21, 22].

The statistical analysis was performed using Microsoft Excel 7.0, SPSS-20 version and Mann–Whitney U–test. M±SD (M-mean SD-standard deviation) was calculated. Student-t test was used for the analysis of the data obtained for the groups, Fisher's F criterion for comparing dispersions Differences were considered statistically significant when "p" value was less than 5% ($p < 0.05$). Correlation was tested according to the Pearson's correlation. Comparisons between groups and factors were made using Multivariable linear regression and analysis to evaluate independent risk factors (TSH, IMT, demographic variables (age and gender)) [3, 5, 7]. The coefficient of reliability was calculated by t-s statistics for two different averages and F-statistics. The results of the study were recorded in tables and diagrams.

Results and discussion. The confidence of our results is based on the following points:

1. The study groups do not differ by age, BMI or numbers of patients, which excludes influences in the comparison of Lipid spectrum, TSH and FT4 levels.

2. The clinical characters similarity of the study groups of HT+At (group II) and At (group III) permits to underline the TSH responsibility on the development of dyslipidemia (Fig. 1).

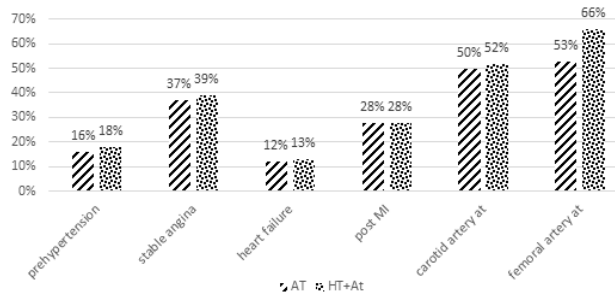

Fig. 1. Clinical characteristic of patients in group II (At+HT) and group III (At)

The clinical characters of the group III (AT) vs group II (AT+HT) are presented in Figure 1. By the analyses of the diagrams 1 and 2 there is no significant differences of group II vs group III patients clinical characteristics that describe the severity of At (Hypertension -16 % vs 18%; stable angina 37% vs 39%; HF 12% vs 13%; post- Myocardial Infarction (MI) 28% vs 28%; carotid artery At), except of femoral artery At - 53% vs 66%.

Analysis of the thyroid gland's functional tests - TSH and FT4, revealed statistically significant differences ($P<0.001$) between Anti-TPO negative group III (patients with At) (TSH:1.2±0.3mIU/L; FT4: 1.2±0.3 ng/dl) and Anti-TPO positive two groups: group I (patients with HT) (TSH:6.0±1.6mIU/L; FT4: 0.98±0.15 ng/dl) and group II (patients with HT+At) (TSH:5.80±1.7mIU/L). There was not thyroid gland's functional tests any differences between group I and II patients as we don't reveal statistical reliable differences of FT4 (P2-3 >0.2) level between group II patients (FT4: 1.1±0.2 ng/dl) and group III patients (FT4: 1.2±0.3 ng/dl) (Table 1).

Table 1. Summary of Baseline Characteristics for Patients With HT, HT+At and At

Groups		Age	BMI	TSH	FT4	TC	LDLC	HDLC	TG
HT (I)	M	62.8	27.4	6	0.98	246.2	172.1	49.3	123.9
	StD	1.2	1.2	1.6	0.15	25.5	23.3	6.1	26.2
HT+At(II)	M	64.6	27.6	5.8	1.1	276.6	204.1	41.3	155.8
	StD	3.8	1	1.7	0.2	11.7	14	6.5	23.6
AT (III)	M	*63.0*	*27.1*	*1.2*	*1.2*	*211.1*	*139.4*	*42.9*	*150.0*
	StD	*3.0*	*1.0*	*0.3*	*0.3*	*29.6*	*29.7*	*5.0*	*22.9*
				TSH	FT4	TC	LDLC	HDLC	TG
			p1-2	0.3	0.2	0.001	0.001	0.001	0.001
			p1-3	0.001	0.001	0.001	0.001	0.001	0.0002
			p2-3	0.001	0.2	0.001	0.001	0.001	0.001

HT- Hashimoto Thyroiditis; At-atherosclerosis; BMI (kg/m2)- Body mass index, TC (mg/dl) –Total Cholesterol; LDLC (mg/dl) –Low density Lipoprotein Cholesterol; HDLC (mg/dl) – High density Lipoprotein Cholesterol; Triglycerides (mg/dl); TSH – (mIU/L; FT4 (ng/dL);; Anti-TPO (IU/mL)

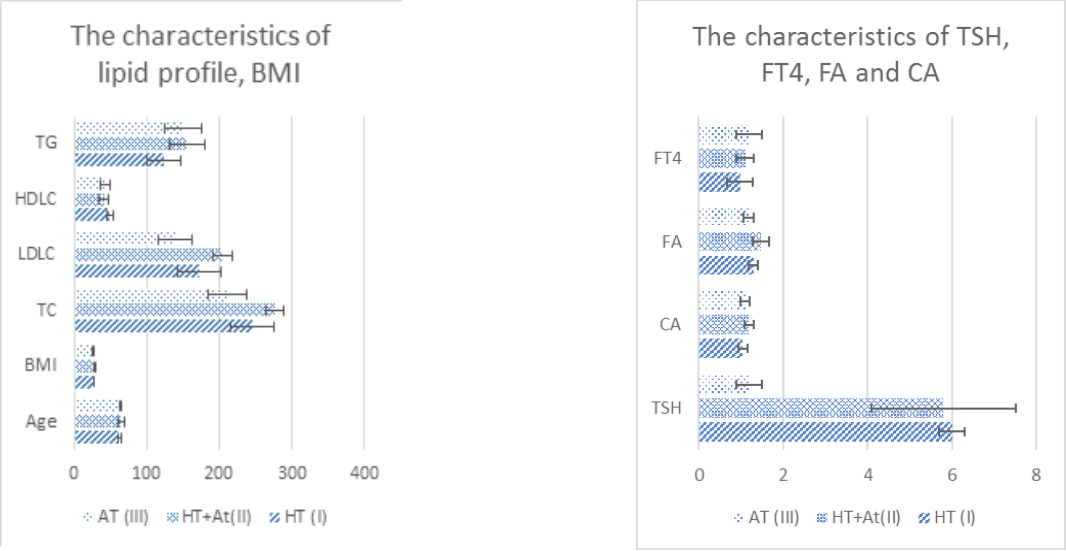

Fig. 2. The characteristics of lipid profile, BMI, TSH, FT4, FA and CA in the study groups

Table 2. CA and FA IMT in study groups

Atherosclerosis		HT(I)	HT+AT(II	At (III)		
CA (mm)	M	1.04	1.19	1.1	p1-2	0.001
	SD	0.09	0.1	0.11	p1-3	0.03
					p2-3	0.0004
FA (mm)	M	1.29	1.47	1.18	p1-2	0.001
	SD	0.13	0.2	0.12	p1-3	0.002
					p2-3	0.0001

Lipid spectre demonstrates more atherogenic changes in II group (HT+At) patients (TC 276,6±11.7.5 mg/dl; LDLC 204,1± 14.0mg/dl; TG 155.8±23.6mg/dl; HDL 41.3±6.5 mg/dl), than in patients with At, but without HT (group III) (TC 211.1±29.6 mg/dl; LDLC 139.4±29.7mg/dl; TG 123.9± 22.9 mg/dl; HDL 49.3± 6.1 mg/dl).

TSH and anti-TPO are important in the development of atherosclerosis as indicated by correlation with atherogenic lipid levels (TC 246, 2±25.5 mg/dl; LDLC 211.1± 29.7mg/dl; TG 150.0 ± 22.9 mg/dl; HDL 42.9 ±5.0 mg/dl), increasing in patients with HT (group I). However, in II group (HT+At) LDLC 276.6± 11.7 mg/dl; TG 155.8 ± 23.6mg/dl; HDL 41.3 ±6.5 mg/dl demonstrate elevation of the same data according to a linear relationship between thyroid function index and lipid profile (Tab.1), respecting BMI and age factors.

The CA (carotid artery) intima-media complex thickening is more expressed in group II patients (1,19±0,1 mm) and statistically significantly differs (p2-3<0.0004) as from group II patients indices (1,1±0,11 mm) as from group I patients indices (1,04±0,09 mm). Also, the statistical reliable between group I and group III indices (p1-3<0.03) were observed (Fig. 2).

There were statistically reliable differences between group II patients FA (femoral artery) intima-media complex indicator (1,47±0,2 mm) with group III atherosclerotic patients without HT (1,18±0,12 mm) p2-3<0.0001 and group I patients with HT (1.29 ±0,13 mm) p1-3 <0.0001 as well between group I patients with group III patients (p<0,001) (Fig.2, Table 2).

These results are derived from linear regression data between serum TSH levels and key diagnostic parameters confirming atherosclerosis, where a linear correlation trend was observed between TSH, on the one hand, and FA and CA intima-media thickness, on the other. For intergroup comparison it's likely that the Pearson coefficient showed an active direct correlation with group II, namely, between TSH, LDLC and CA wall thickness ratios. Thus, the latter is one of the most reliable criteria for comparison between groups (Fig. 3).

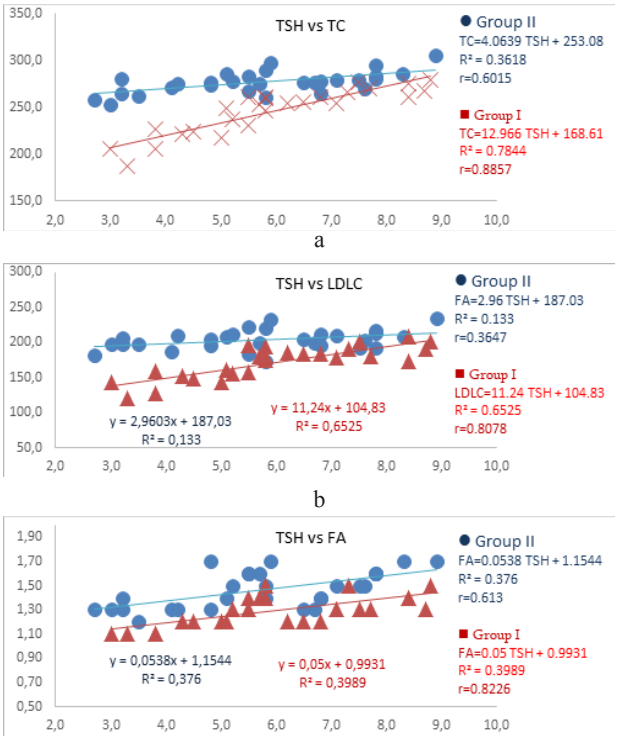

Fig. 3. Pearson correlation (r) between: a - TSH and TC in patients with HT and HT+At (group I and II); b - TSH and LDLC in patients with HT and HT+At (group I and II); c - TSH and FA in patients with HT and HT+At (group I and group II)

We can conclude that TSH, as the main thyroid function regulator, may be determined as principal risk-factor, which independently affects the thyroid morphology as well as carotid and femoral arteries IMT.

Baseline characteristics and Histology of Thyroid parenchyma

In generally, the histopathological diagnosis of HT was based on the presence of diffuse, chronic, inflammatory cells infiltrate, mainly composed of T-lymphocytes and plasma cells and macrophage, organized in germinal centers, also fibrotic areas presents, which did not extend beyond the capsule. The infiltrate had to occur in a normal region of the thyroid gland, as well as the presence of atrophic follicles with numerous Hürthle cells and enlarged thyroid cells, characterized by abundant cytoplasm, which was eosinophilic.

Group I (HT) - results of histopathological research of Hashimoto's thyroiditis causing subclinical hypothyroidism is associated with activity of parallel immunohistochemical reactions, indicating that the thyroid parenchyma is non-homogeneous in terms of parenchyma cell components, as well as molecular biological features. Hashimoto's thyroiditis leading histopathological process is the extensive lymphocytic infiltration of thyroid parenchyma (Fig. 4a), which is accompanied by hypertrophy/hyperplasia of lymphoid follicules and germinal centers, with the abundance of plasma cells and macrophages. In the thyroid parenchyma necrosis areas were not detected.

The high nuclear expression of the protein S100 in HT parenchyma indicates on the dysplasia of the thyroid parenchyma and disorganization of the architecture. Expression of high-intensity S100 protein is associated with Hashimoto's infiltrative foci in the domain between follicles (Fig. 4b).

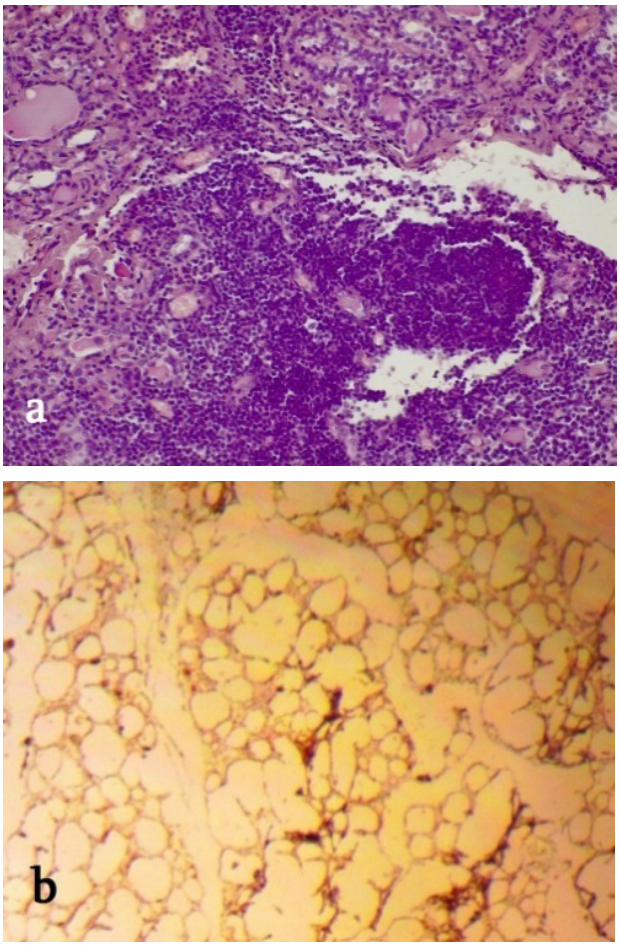

Fig. 4. HT. a. H&E. Atrophic follicles in the thyroid parenchyma, invasive lymphoid follicles with large germination center, X200. b. S100-protein expression is manifested in the domain between follicles in abundant Hürthle cells. Immunoperoxidase reaction, X160

Group II (HT+atherosclerosis) - In the material of the given group marked the typical histological features of Hashimoto's thyroiditis include moderate lymphoplasmacytic infiltration, follicular destruction following with variable degrees of fibrosis (Fig. 5a).

It is significant, that HT with atherosclerosis association characterised by independent line of Hürthle cells and their

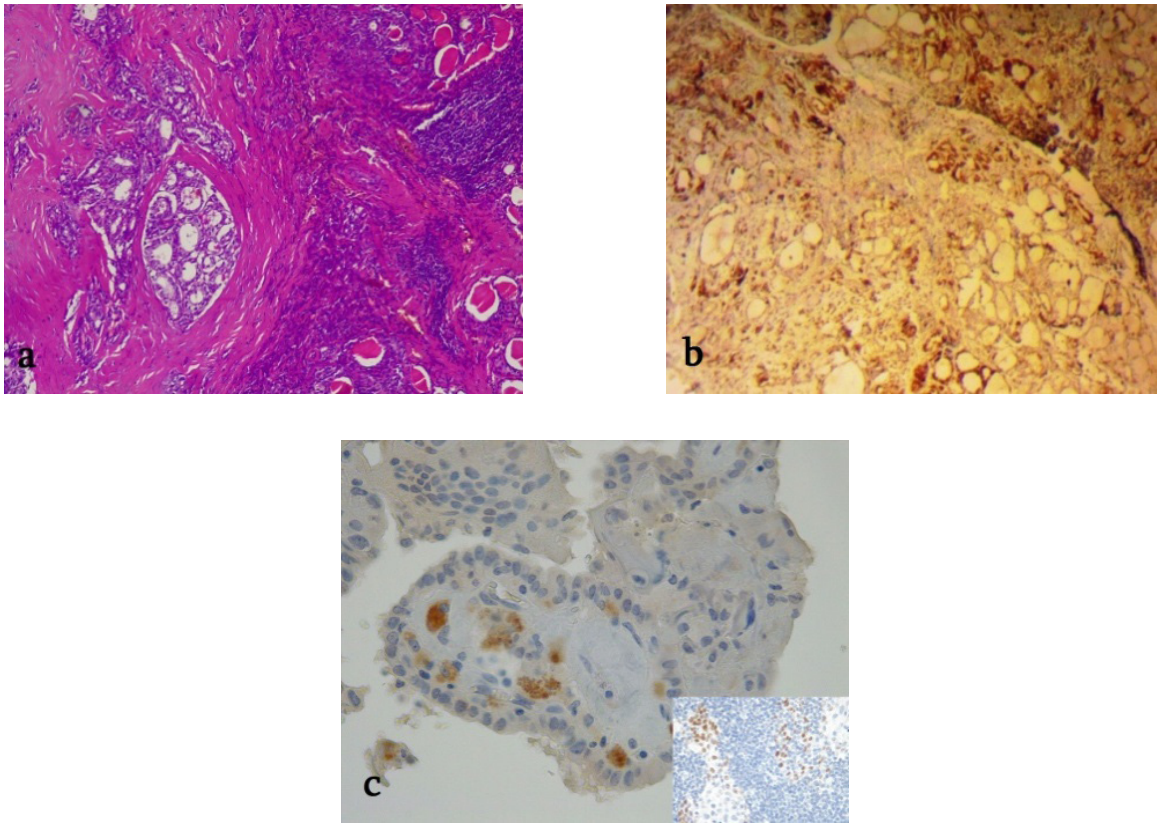

Fig. 5. HT. a. H&E, X100. b. Association of Hürthle cells adenoma and Hashimoto's Thyroiditis. Intense expression of S100 protein on the periphery of the adenoma and in the adenoma capsule, X160. c. Follicular epithelial squamous metaplasia with intense nuclear positive p63 immunostaining, X400; (in rectangle area – control reaction with lymphoid tissue from Palatine Tonsils, X200); Immunoperoxidase reaction

adenoma like hyperplasia, reducing follicular parenchyma, which decrease secretary activity, in fact, hypothyreosis reinforce (Fig. 5b).

In group II (HT+atherosclerosis), new morphological fact develops in some areas of thyroid parenchyma as oxyphilic metaplasia of follicular cells indicating on the severe molecular biological transformation of thyroid parenchyma due to higher low-density lipoprotein cholesterol concentration than in group I (Fig. 5c). Patient from this group also displayed greater CIMT than controls (Fig. 3a, b).

Atherosclerosis and CVD events reduction is very important goal of modern medical society. That is why, beside of the traditional risk factors (dyslipidemia, obesity, hypertension, etc.), scientists attention is focused on the research of the new factors, such as metabolic risk factors and hypothyroidism among them. Taking account the numerous studies about immunological pathogenesis of atherosclerosis [25,26] the importance of Hashimoto thyroiditis influence on CVD events is evident. By 2019 ESC/EAS Guideline [6], next to coronarography, Doppler ultrasound method of carotid and femoral arteries atherosclerotic changes is accepted for confirmation of ACVD.

Based on the above considerations, we examined patients who were operated on due to Hashimoto thyroiditis indications: group I patients HT without atherosclerosis clinical manifestation and group II patients with HT+Atherosclerosis and group III – Atherosclerosis as in control version.

To pick out the importance of atherosclerosis risk factors (dyslipidemia) in the development of atherosclerosis we compared this data with markers of atherosclerosis using carotid and femoral arteries Doppler ultrasonography. This comparison allows immunological factors (anti-TPO) pathologic mechanism influence in patients with HT with atherosclerosis risk-factors. Data of HT+At group's patients vs group's III Atherosclerosis patients accentuate immunological factor (anti-TPO) action on the dyslipidemia that can promote further severity of the atherosclerosis. This point of view is supported by the results of immunohistochemical study of the p63 protein: It was during the combination of atherosclerosis and Hashimoto that foci of p63 expression of squamous epithelial dysplasia were detected (Fig. 5C).

The major risk factors of atherosclerosis – TC, LDLC, TG high and HDLC low levels relation with anti TPO, TSH and FT4 revealed lipid parameters statistically high level in the group II patients but despite high levels of atherogenic lipids, the same status was statistically low in group III (patients with atherosclerosis but without HT) in comparison with group II as well as in group I patients. This fact confirms hypothyreoidism with anti TPO importance in processing of atherosclerosis and HT as atherogenic risk factors significance the correlation under anti-TPO between TSH and TC. LDLC in the I (r =0.89**, 0.81**) and II groups' patients confirmed the immunological status influences in the development of atherosclerosis.

Thus the influence of thyroid hormones on CVD is in conclusive [27]. FT4 levels in middle-aged person are positively associated with At, independently caused cardiovascular risk factors [4,28-31]. In turn, At adversely affected on the lipid cholesterol

and carbohydrates rates metabolism, accelerating hypothyroidism with follicular epithelial meta- and dysplasia manifested in our study by: 1. Hurtle cells activity – adenomatous transformation, 2. follicular cell, oxyphilic metaplasia and focal dysplasia (p63 positivity) [14,17,32]. It's important that in euthyroid individual there was no significant difference between compared date [24, 33].

We suppose, that thyroid hormone plays an important role in the pathogeneses of atherosclerosis and cardiovascular complication through multifunctional physiological effects – such intranuclear genomic and extranuclear nongenomic influences: [26, 34] 1. thyroid hormone acts on the vascular smooth muscles cells, modified endothelial function developing systemic vascular resistance [2,4,33,35,36] and diastolic blood pressure instability [21,33]; 2. Thyroid hormone also reduced LDL and decrease LDL receptor activity [26, 37, 38].

It's well known, that the dyslipidemia and the diastolic hypertension predispose the hypothyroidism in HT and At combination group to accelerate carotid artery IMT. Respectively, our results are in good agreement with this opinion [37, 38].

In the current study we found that free T4 is associated with the severity of atherosclerosis clinical characteristics, but we also found, that TSH and anti-TPO antibody levels are directly and closely linked to the cardiovascular complications (Myocardial infarctions and hypertension).

Furthermore, as discussed above, biomarkers S100 and p63 data results demonstrate negative feedback effects of hypercholesterolemia on the high morphological risk features in Hashimoto parenchyma, which may partially explain the significant trend and pathobiological link of Hashimoto Thyroiditis association with Papillary thyroid carcinoma [13,14,24,25].

Doppler ultrasonography investigation data, revealing CA and FA atherosclerosis and TSH influence, show the presence: 1. FA is most important location for developments of IM complex thickening in HT (group I) and HT+At (group II) confirmed by presence of reliable differences ($p<0.001$) between II and III groups as between the I and III groups patients. 2. CA thickening characterised all three groups' patients, but more expressed in the group II patients. 3. TSH levels clarify the atherogenic quality by presence of correlation between TSH and FA atherosclerosis ($r=0.62$*) as between TSH and CA atherosclerosis ($r=0.6$* in the group I patients). Anti atherogenic HDLC level, statistically reliable, is highest in the group I patients in comparison to II and III groups' patients that can explain absence of clinical manifestation of atherosclerosis despite of the thickening of CA and FA.

Conclusion. Comparative analysis of key phenomena of HT and Atherosclerosis features show that free T4 is associated with the severity of atherosclerosis clinical characteristics, that TSH and anti-TPO antibody levels are directly and closely linked to the cardiovascular complications (Myocardial infarctions and hypertension). Dyslipidemia and the diastolic hypertension accelerate the hypothyroidism in HT and At combination group to predispose carotid artery IMT. Biomarkers S100 and p63 data results demonstrate negative feedback effects of hypercholesterolemia on the high morphological risk features in Hashimoto parenchyma, which may be partially explain the significant trend and pathobiological link of Hashimoto Thyroiditis with Papillary thyroid carcinoma.

Data, presented in the study, will serve as a reference for further investigation.

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SUMMARY

CORRELATION OF THYROID AUTOIMMUNITY WITH ATHEROSCLEROSIS EVALUATION IN HASHIMOTO'S THYROIDITIS

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The relationship between subclinical hypothyroidism (SH) and Atherosclerotic (At) cardiovascular diseases (CVD) has been one of the most popular topics but causal connection between Hashimoto thyroiditis (HT), lipid profile and follicular

epithelial molecular biology is controversial. We investigated 3 groups of patients (group I – HT, group II - HT+At, group III - At). All laboratory tests for thyroid function and lipid profile detection were used according to international guideline recommendations, coronary and femoral arteries intima-media thickness (IMT) were tested by high-resolution ultrasonography, thyroid gland histology and immunohistochemistry carried out by p63 and S100 protein expression control. The statistical analysis was performed using Microsoft Excel 7.0, SPSS-20 version, Mann–Whitney U–test and Pearson's correlation. Comparisons between groups and factors were made using Multiple Linear Regression model. With the results obtained, dyslipidemia and the diastolic hypertension accelerate the hypothyroidism in HT+At group to predispose carotid and femoral arteries IMT. TSH and anti-TPO antibody levels are directly linked to the cardiovascular complications. Biomarkers S100 and p63 data show negative feedback effects of hypercholesterolemia on the high morphological risk features in Hashimoto parenchyma, which may partially explain the significant trend and pathobiological link of HT with Papillary thyroid carcinoma.

Keywords: Hashimoto Thyroiditis; Atherosclerosis; Thyroid; p63, S100 immunohistochemistry; Carotid, Femoral IMT.

РЕЗЮМЕ

КОРРЕЛЯЦИЯ МЕЖДУ АУТОИММУННЫМ ТИРОИДИТОМ И РАЗВИТИЕМ АТЕРОСКЛЕРОЗА ПРИ ТИРОИДИТЕ ХАШИМОТО

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Изучение взаимосвязи между субклиническим гипотиреозом и атеросклерозом сердечно-сосудистой системы (At) представляется актуальным, однако причинно-следственная корреляция между тироидитом Хашимото (HT), липидным профилем и молекулярной биологией фолликулярного эпителия щитовидной железы по сей день остается малоизученной.

Исследованы 3 группы пациентов: I группа – HT, II группа – HT+At, III группа – At. Использованы лабораторные тесты с целью определения функции щитовидной железы и липидного профиля, согласно указаниям международных гайдлайнов. Толщину интимы-медии сонных и бедренных артерий (IMT) оценивали высокоразрешенной ультрасонографией. Материал исследовали гистологическими и иммуногистохимическими методами: H&E, S100 протеин и p63.

Статистический анализ проводили по версии Microsoft Excel 7.0, SPSS 20, Mann-Whitney. Использовали U-тест и коэффициент корреляции Пирсона. Сравнительный межгрупповой анализ проводили методом линейной регрессии.

Согласно полученным результатам, дислипидемия и диастолическая гипертензия способствуют прогрессии гипотиреоза в группе HT+At; уровень TSH и anti-TPO антител находится в прямой зависимости от осложнений сердечно-сосудистых заболеваний. S100 и p63 биомаркеры указывают на обратный отрицательный эффект гиперхолестеринемии, на показатели высокого морфологического риска в паренхиме Хашимото, что частично объясняет тенденцию HT и патобиологическую связь с папиллярной карциномой.

რეზიუმე

ფარისებრი ჯირკვლის აუტოიმუნურობის კორელაცია ათეროსკლეროზის განვითარებასთან ჰაშიმოტოს თიროიდიტის დროს

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[1]ი, ჯავახიშვილის სახ. თბილისის სახელმწიფო უნივერსიტეტი, ალექსანდრე ნათიშვილის მორფოლოგიის ინსტიტუტი; [2]თბილისის სახელმწიფო სამედიცინო უნივერსიტეტი

სუბკლინიკური ჰიპოთირეოზისა და გულ-სისხლძარღვთა ათეროსკლეროზული (At) დაავადებების ურთიერთკავშირი ერთ-ერთი აქტუალური თემაა, მაგრამ სადავოა ჰაშიმოტოს თირეოიდიტს (HT), ლიპიდურ პროფილსა და ფოლიკულური ეპითელიუმის მოლეკულურ ბიოლოგიას შორის მიზეზობრივი კავშირი. გამოკვლეულია პაციენტების 3 ჯგუფი (I ჯგუფი - HT, II ჯგუფი - HT+At,III ჯგუფი - At). ფარისებრი ჯირკვლის ფუნქციისა და ლიპიდური პროფილის განსაზღვრისთვის გამოყენებული იყო ლაბორატორიული ტესტები საერთაშორისო გაიდლაინების მითითებების შესაბამისად, კორონარული და ბარძაყის არტერიების ინტიმა-მედიის სისქე (IMT) შემოწმდა მაღალი რეზოლუციის ულტრასონოგრაფიით, მასალა შესწავლილია კლასიკური ჰისტოლოგიური და იმუნოჰისტოქიმიური კვლევის მეთოდებით: H&E, S100 ცილა და p63-ის იმუნური პროფილის გათვალისწინებით. სტატისტიკური ანალიზი ჩატარდა Microsoft Excel 7.0, SPSS-20 ვერსიის, Mann-Whitney U-ტესტისა და პირსონის კორელაციის გამოყენებით. ჯგუფებსა და ფაქტორებს შორის შედარება განხორციელდა ხაზოვანი რეგრესიის მოდელის გამოყენებით. მიღებული შედეგების მიხედვით, დისლიპიდემია და დიასტოლური ჰიპერტენზია აჩქარებს ჰიპოთირეოზის განვითარებას HT+At ჯგუფში. TSH და anti-TPO ანტისხეულების დონე პირდაპირკავშირშია გულ-სისხლძარღვთა დაავადებების გართულებასთან. S100 და p63 ბიომარკერების მონაცემები აჩვენებს ჰიპერქოლესტერინემიის უარყოფით გავლენას ჰაშიმოტოს პარენქიმაში მაღალი მორფოლოგიური რისკის მახასიათებლებზე, რითაც ნაწილობრივ შეიძლება აიხსნას ჰაშიმოტოს მნიშვნელოვანი ტენდენცია და პათობიოლოგიური კავშირი ფარისებრი ჯირკვლის პაპილურ კარცინომასთან.