The role of thyroid hormones in carotid arterial wall remodeling in women

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Introduction: Thyroid hormones affect the cardiovascular system, but the precise mechanisms of their effects on the development of atherosclerosis are not entirely clear. The relationship between subclinical hypothyroidism, dyslipidemia and carotid atherosclerosis has been widely investigated, but the findings were controversial. The aim of the present study was to determine whether female subjects with subclinical hypothyroidism (SHypo) have increased carotid intima-media thickness (IMT) compared with euthyroid subjects, as well as to examine the association of SHypo, carotid atherosclerosis and dyslipidemia.

Methods: This research included 100 women aged 30 to 70 years who were divided into two groups: the SHypo group including subjects with signs of subclinical hypothyroidism and the control group of euthyroid subjects. Carotid IMT thickness using B mode ultrasound was determined and its correlation with serum concentrations of fT4, TSH, CRP, and lipid profile including small dense LDL (sdLDL) was analysed.

Results: Subjects with SHypo had significantly increased carotid IMT (IMT ≥ 75th centile) in all three measured segments of the right ($p < 0.001$) and the left ($p = 0.001$) carotid artery compared to the control group, with a significantly more frequent appearance of plaque (25% vs. 9%; $p = 0.05$). Significant positive correlations were found between higher TSH and higher IMT values. Increased age, LDL cholesterol, and TSH predicted thickening of the carotid artery IMT.

Conclusions: It is important to screen people showing early, subclinical signs of thyroid gland dysfunction due to its impact on carotid atherosclerosis development.

Key words: Carotid intima-media thickness (IMT), cerebrovascular diseases, dyslipidemias, hypothyroidism, LDL cholesterol.

What is new? What is important?

Subjects with subclinical hypothyroidism have elevated carotid intima-media thickness (IMT). It is important to screen people showing early, subclinical signs of thyroid gland dysfunction to prevent development of atherosclerosis and its complications. Along with assessment of conventional risk factors, carotid IMT as a marker of atherosclerosis using B-mode ultrasound should be measured.

INTRODUCTION

Subclinical hypothyroidism (SHypo) is a condition characterized by mild to moderate thyroid dysfunction with normal thyroid hormones serum levels, but mildly elevated TSH (thyroid-stimulating hormone, thyrotropin). The prevalence of this condition is 4–8.5% in adulthood, and it increases with aging to be found in 20% of older women [1]. Although the link between SHypo and cardiovascular disease (CVD) is known, its relevance in the process of atherosclerosis development remains a topic of debate [2,3].

Carotid atherosclerotic disease begins gradually, first with the development of asymptomatic changes in the blood vessels, thereby initiating a series of adverse events that might end in a stroke

[4]. Subclinical changes are characterized by the appearance of thickening of the intimal and medial part of the carotid artery wall (intima-media thickness, IMT), a functional disorder of elasticity in the extracranial cerebral vessels and, lastly, formation of carotid plaques [5]. These initial, subclinical changes of the carotid vessels can be quantified by measuring IMT thickness using B-mode ultrasound [4,6,7].

So far in the literature, association between thyroid function, atherosclerosis and IMT was reported, but the exact mechanisms of the influence of thyroid hormones on the development of atherosclerosis have not yet been fully elucidated [2,3,8]. In their systematic review, Karagiannis *et al*. found that correlation between SHypo and increased IMT may be due to arterial hypertension, dyslipidemia and elevated TSH levels [9]. In a meta-analysis Gong *et al*. showed that SHypo was associated with endothelial dysfunction in which hypertension and dysli-pidemia play a crucial role [10].

The aim of this study was to determine whether female subjects with SHypo have increased carotid IMT compared with euthyroid subjects, as well as to examine the association of SHypo, carotid atherosclerosis and dyslipidemia.

MATERIAL AND METHODS

This is a retrospective study based on data collected between December 2014 and December 2015 at Zabok General Hospital and Hospital of Croatian Veterans. The study was approved by the Ethics Committee of Zabok General Hospital and Hospital of Croatian Veterans, as well as the Ethics Committee of the University of Zagreb School of Medicine, and conducted in accordance with the principles of Good Clinical Practice and Declaration of Helsinki. All subjects signed the informed consent form.

The study included women who were diagnosed with subclinical hypothyroidism (SHypo group), as well as those whose thyroid function was determined to be normal (control, euthyroid group). Along with thyroid hormones levels (fT4 - free thyroxine, TSH), lipid profile (total cholesterol, HDL, LDL, small dense LDL – sdLDL, triglyceride) and CRP (C - reactive protein) were determined during the first stage of our research where association of SHypo and dyslipidemia was examined [11]. In the present study, these variables were used for the analysis of their possible effects on carotid atherosclerosis measured by IMT.

Exclusion criteria were: fT4 values outside the reference range, TSH values >10mIU/L or <0.35 mIU/L, pregnancy, previously diagnosed thyroid disease or thyroid surgery, primary hyperlipidemia, ovarian dysfunction, ovariectomy, hysterectomy, diabetes mellitus, liver or kidney disease, chronic pancreatic inflammation, malignancy, previous heart attack, previous stroke, previous carotid artery surgery, use of medication for regulation of thyroid function or lipid metabolism, amiodarone use, and high fever or signs of inflammation.

Carotid artery ultrasound – IMT determination

Carotid artery examination was performed using Aloka SSD 4000 with a linear 10 MHz probe (UST -5524-7.5). The technique of carotid IMT evaluation was performed according to the standardized protocol [12] using B-mode in the three segments of carotid artery: CB – carotid bifurcation, CCA – common carotid artery, ICA – internal carotid artery.
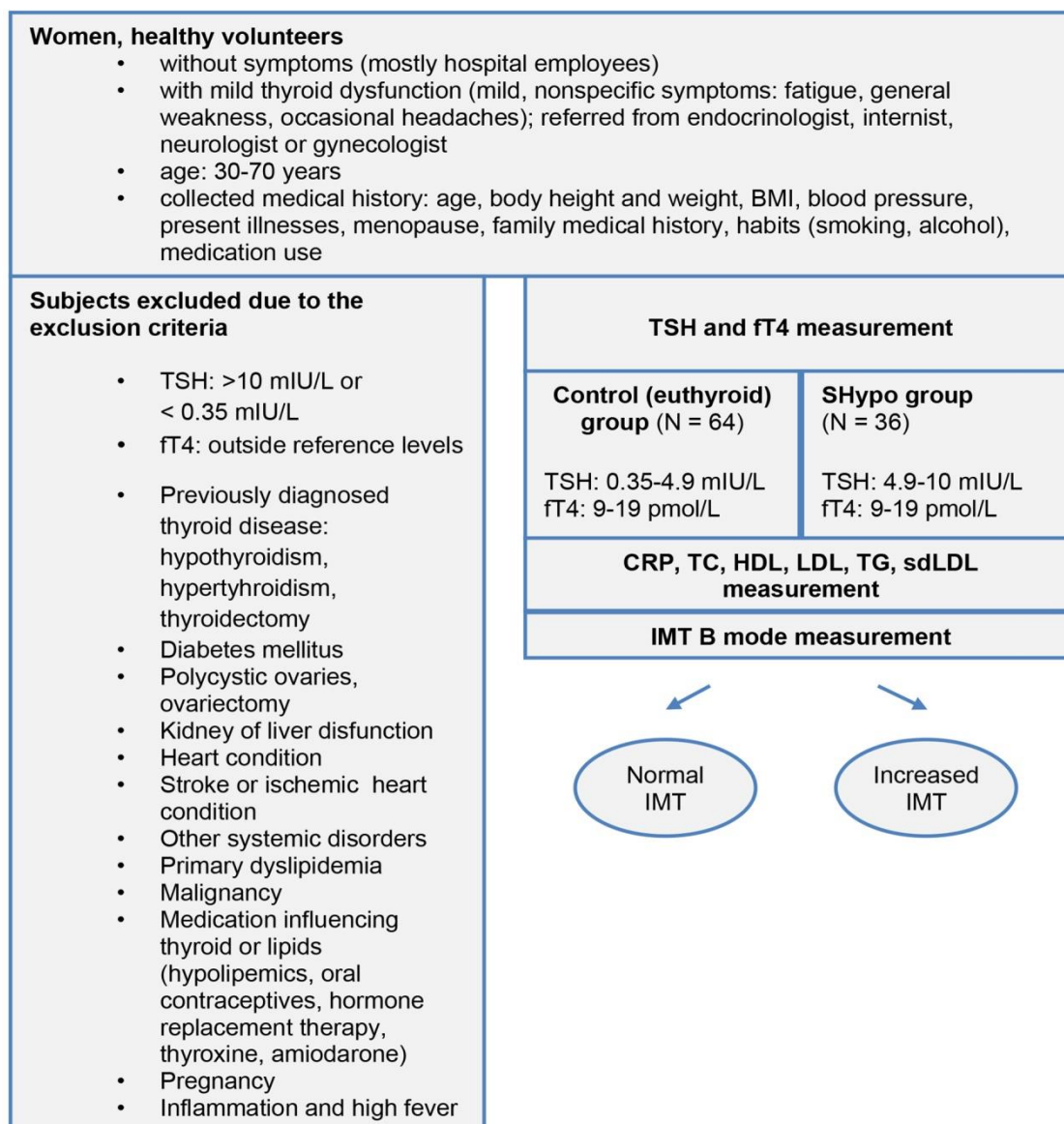
Sociodemographic and clinical features

The following measurements were determined for all subjects: age, body height and weight, and body mass index (BMI) according to the formula: BMI = kg/m^2. Habits such as smoking and alcohol consumption were also noted. Hormonal status such as menopause and medication use were recorded. Family history for cardiovascular and cerebrovascular diseases was considered positive if the subject had at least one first relative with a stroke or heart attack.

Statistical analysis

Continuous data were presented using median with interquartile ranges and arithmetic means with standard deviations for comparison with available literature data. Differences in quantitative values were analyzed by Mann-Whitney U-test. Differences in categorical values were analyzed by Fisher's exact test. Spearman's rho correlation coefficients between TSH values and IMT were calculated. All *p* values less than 0.05 were considered statistically significant.

For this analysis we used IBM SPSS Statistics software, version 24.0.0.12.

Women, healthy volunteers
- without symptoms (mostly hospital employees)
- with mild thyroid dysfunction (mild, nonspecific symptoms: fatigue, general weakness, occasional headaches); referred from endocrinologist, internist, neurologist or gynecologist
- age: 30-70 years
- collected medical history: age, body height and weight, BMI, blood pressure, present illnesses, menopause, family medical history, habits (smoking, alcohol), medication use

Subjects excluded due to the exclusion criteria

- TSH: >10 mIU/L or < 0.35 mIU/L
- fT4: outside reference levels
- Previously diagnosed thyroid disease: hypothyroidism, hypertyhroidism, thyroidectomy
- Diabetes mellitus
- Polycystic ovaries, ovariectomy
- Kidney of liver disfunction
- Heart condition
- Stroke or ischemic heart condition
- Other systemic disorders
- Primary dyslipidemia
- Malignancy
- Medication influencing thyroid or lipids (hypolipemics, oral contraceptives, hormone replacement therapy, thyroxine, amiodarone)
- Pregnancy
- Inflammation and high fever

TSH and fT4 measurement

Control (euthyroid) group (N = 64)	**SHypo group** (N = 36)
TSH: 0.35-4.9 mIU/L fT4: 9-19 pmol/L	TSH: 4.9-10 mIU/L fT4: 9-19 pmol/L

CRP, TC, HDL, LDL, TG, sdLDL measurement

IMT B mode measurement

Normal IMT

Increased IMT

BH – body height; BW – body weight; BMI – body mass index; CRP – C-reactive protein; fT4 – free thyroxine; HDL – high-density lipoprotein; IMT – intima-media thickness; LDL– low-density lipoprotein; sdLDL – small dense low-density lipoprotein; TC – total cholesterol; TG – triglycerides; TSH – thyrotropin

Figure 1. The study flow chart.

RESULTS

This study included 100 subjects who were divided into two groups: the SHypo group (N = 36) and the control (euthyroid) group (N = 64). The mean age of all subjects was 49.46 ±10.30 years, in the SHypo group 50.85 ±10.74 years, and in the control (euthyroid) group 48.67 ±10.05 years (Table 1). Considering that there were no significant differences between the studied groups in age ($p = 0.21$) and body mass index ($p = 0.07$), it can be stated that the tested groups were uniform in both age and body mass index. The groups also did not significantly differ in alcohol consumption ($p = 0.06$), smoking ($p = 0.10$), menopause status ($p = 0.15$) and medication use (Table 2). Arterial hypertension was present in 42% of the SHypo and 30% of the euthyroid subjects ($p = 0.27$), whereas positive family history was significantly more common ($p = 0.02$) in the SHypo group

Table 1

The comparison of the quantitative clinical and laboratory variables in the SHypo and control group: Mann-Whitney U-test.
Variables were expressed as arithmetic means with standard deviations

	SHypo	Control	*p* value
Age (years)	50.86 ±10.74	48.67 ±10.05	0.205
Body weight (kg)	73.5 ±11.84	68.30 ±10.64	**0.030**
Body height (cm)	165.19 ±5.33	164.20 ±5.47	0.333
BMI (kg/m^2)	26.99 ±4.47	25.35 ±3.90	0.073
Cholesterol (mmol/L)	6.15 ±1.27	5.68 ±0.93	0.070
Tryglicerides (mmol/L)	1.37 ±0.62	1.22 ±0.58	0.251
HDL (mmol/L)	1.50 ±0.26	1.57 ±0.34	0.291
LDL (mmol/L)	3.80 ±0.97	3.45 ±0.91	0.094
sdLDL (mmol/L)	1.00 ±0.48	0.80 ±0.31	**0.047**
LDL/HDL index	2.60 ±0.80	2.31 ±0.81	0.112
Cholesterol/HDL index	4.18 ±0.99	3.76 ±0.93	**0.049**
CRP (mg/L)	2.21 ±1.94	2.15 ±2.95	0.321
TSH (mlU/L)	6.12 ±1.20	2.07 ±1.29	**<0.001**
fT4 (pmol/L)	12.31 ±1.07	13.32 ±1.47	**0.001**

BH – body height; BW – body weight; BMI – body mass index; CRP – C-reactive protein; fT4 – free tyroxine; HDL – high-density lipoprotein; LDL – low-density lipoprotein; sdLDL – small dense LDL; TSH – thyrotropin

Table 2

The comparison of the qualitative variables collected through medical history in the SHypo and control group: Fisher's exact test.
Variables were axpressed as percentages

	SHypo	Control	*p* value
Alcohol consumption	1.6%	11.1%	0.055
Smoking	13.9%	14.1%	0.999
Menopause	61.1%	45.3%	0.149
Arterial hypertension	41.7%	29.7%	0.273

Positive family history	58.2%	34.3%	**0.023**
ACE inhibitors	13.9%	14.1%	0.999
Ca channel blockers	16.7%	6.3%	0.161
Beta-blockers	27.8%	14.1%	0.114
Angiotensine II antagonists	11.1%	3.1%	0.184
Diuretics	16.7%	6.3%	0.161
Analgetics	25.0%	25.0%	1.000
PPI	11.1%	3.1%	0.184
Supplements	25.0	12.5	0.164
Triptans	2.8%	1.6%	0.999
Sedatives	0.0%	7.8%	0.156
ASA	11.1%	1.6%	0.055
Antidepressants	2.8%	3.1%	0.999
Other medications	2.8%	12.5%	0.151

Measured by B mode ultrasound, the subjects with SHypo had significantly higher values of IMT (IMT ≥ 75th centile) in all three measured segments of the right ($p < 0.001$) and left ($p = 0.001$) carotid artery relative to the control (euthyroid) group (Figure 2), with a significantly more frequent appearance of plaque than in the control group (25% vs. 9%; $p = 0.05$).
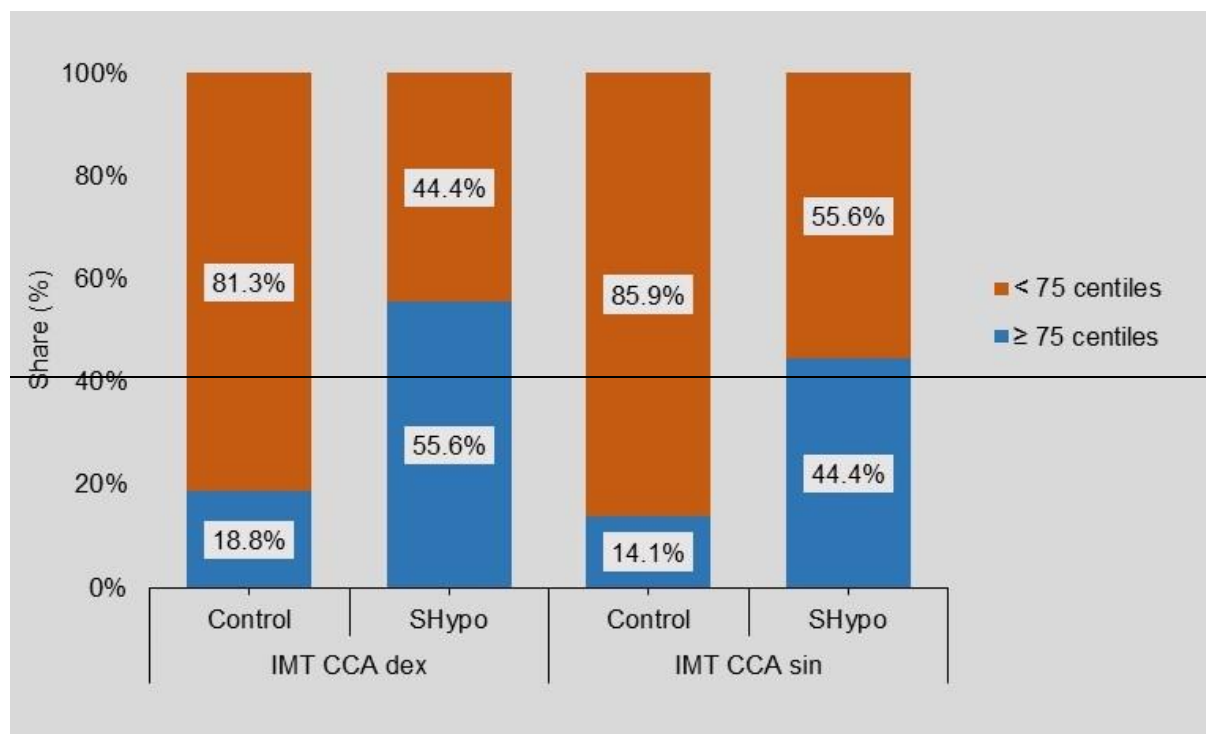
CCA – common cartiod artery, IMT – intima media thickness, SHypo – subclinical hypothyroidism.

Figure 2. Differences in IMT values of the right and left CCA in respect to TSH > 4.9 mlU/L
Greater proportions of the SHypo subjects had significantly increased IMT of the right ($p < 0.001$) and the left CCA ($p = 0.001$).

Spearman's correlation coefficients between TSH and IMT values for all three segments in the total sample and within each age group are shown in Table 3. Significant medium-strong positive correlations of TSH with all examined IMT values were recorded in the total sample indicating that higher TSH values are associated with higher IMT values.

Table 3

Spearman's correlation coefficients between TSH values and IMT in three segments of left and right carotid artery with regards to age of the subjects

		All subjects	< 40 years	41–50 years	51–60 years	≥ 61 years
IMT CCA dex (mm)	Correlation coefficient	0.447	0.553	0.461	0.443	0.641
	p value	**<0.001**	**0.009**	**0.023**	**0.006**	**0.004**
	Number of subjects	100	21	24	37	18
IMT CB dex (mm)	Correlation coefficient	0.416	0.436	0.400	0.531	0.236
	p value	**<0.001**	**0.048**	0.053	**0.001**	0.397
	Number of subjects	94**	21	24	34	15
IMT ICA dex (mm)	Correlation coefficient	0.327	0.460	0.452	0.332	0.355
	p value	**0.001**	**0.036**	**0.026**	0.059	0.149
	Number of subjects	96**	21	24	33	18
IMT CCA sin (mm)	Correlation coefficient	0.432	0.674	0.491	0.508	0.421
	p value	**<0.001**	**0.001**	**0.015**	**0.001**	0.082
	Number of subjects	100	21	24	37	18
IMT CB sin (mm)	Correlation coefficient	0.361	0.344	0.470	0.450	0.362
	p value	**<0.001**	0.127	**0.024**	**0.007**	0.224
	Number of subjects	92**	21	23	35	13
IMT ICA sin (mm)	Correlation coefficient	0.396	0.398	0.373	0.491	0.219
	p value	**<0.001**	0.074	0.080	**0.003**	0.414
	Number of subjects	94**	21	23	34	16

CB – carotid bifurcation; CCA – common carotid artery; ICA – internal carotid artery; IMT – intima-media thickness

**In some subjects IMT could not be measured in all carotid segments due to the presence of plaque.

The prediction of the average IMT values of the right and left CCA by univariate and multivariate regression analysis in shown in Table 4. At the univariate analysis level, 18 predictor variables (age, cholesterol, triglycerides, LDL, sdLDL, LDL/HDL index, cholesterol/HDL index, TSH, CRP, BMI, alcohol consumption, arterial hypertension, menopause, ACE inhibitors, Ca channel blockers, beta blockers, diuretics, ASA) were found to be significant. The strongest correlation coefficient with the CCA IMT was found for age (r = 0.710; *p* <0.001). All significant variables correlated positively with CCA IMT values (mean values of both CCAs), which means that an increase in these values was associated with an increase in CCA IMTs. Since this analysis showed an association at the univariate level, a multivariate regression model was developed further on: the CCA IMT value was used as the dependent variable, and all those that were statistically significant at the univariate level were used as predictor variables in the regression model. Since LDL was used to calculate the LDL/HDL index, only the LDL value was used to avoid redundancy in the multivariate model. The multivariate regression model explained 70.5% of the variance of the dependent variable (IMT of ACC) and was statistically significant (*p* <0.001).

The model thus distinguishes significant influences of three predictor variables that are positively associated with elevated CCA IMT values: LDL (beta = 1.37; $p = 0.018$), age (beta = 0.444; $p = 0.001$), and TSH (beta = 0.336; $p < 0.001$), with all other variables held constant.

Table 4

Univariate and multivariate regression model of prediction of increased CCA IMT

IMT ACC prediction	Univariate analysis		Multivariate linear regresssion[††]	
	Correlation coefficient	*p*	Standardized beta coefficient	*p*
Age (years)	0.710	**<0.001**	0.444	**0.001**
Cholesterol (mmol/L)	0.435	**<0.001**	-0.704	0.069
Tryglicerides (mmol/L)	0.268	**0.007**	-0.002	0.983
HDL (mmol/L)	0.029	0.778		
LDL (mmol/L)	0.436	**<0.001**	1.370	**0.018**
sdLDL (mmol/L)	0.345	**<0.001**	-0.187	0.203
LDL/HDL indeks	0.318	**0.001**		
Cholesterol/HDL indeks	0.336	**0.001**	1.158	0.058
TSH (mlU/L)	0.460	**<0.001**	0.336	**<0.001**
fT4(pmol/L)	-0.037	0.713		
CRP (mg/L)	0.327	**0.001**	0.122	0.079
BMI (kg/m2)	0.371	**<0.001**	0.082	0.293
Alcohol	0.255	**0.010**	0.000	0.996
Smoking	-0.055	0.584		
Positive family history	0.087	0.388		
Arterial hypertension	0.393	**<0.001**	-0.231	0.063
Menopause	0.623	**<0.001**	0.029	0.800
ACE inhibitors	0.296	**0.003**	0.138	0.155
Ca channel blockers	0.227	**0.023**	0.104	0.215
Beta-blockers	0.228	**0.023**	0.135	0.135
Angiotensine II antagonists	0.159	0.114		
Diuretics	0.344	**<0.001**	0.105	0.192
ASA	0.287	**0.004**	0.071	0.364

[††] In this multivariate linear regression model, included were only those variables that were found significant in a univariate analysis with the level $p < 0.05$; $r^2 = 70.5\%$, $p < 0.001$.

ACE inhibitors – inhibitors of angiotensin converting enzyme; ASA – acetylsalicylic acid; BMI – body mass index; CRP – C-reactive protein; fT4 – free thyroxine; HDL – high-density lipoprotein; LDL – low-density lipoprotein; sdLDL – small dense low-density lipoprotein; TSH – thyrotropin.

DISCUSSION

This study analyzed the effects of SHypo and dyslipidemia in women on changes in the walls of carotid artery, with the assumption that SHypo increased the risk of cardiovascular and cerebrovascular disease due to the effect of thyroid dysfunction on cardiovascular risk factors such as dyslipidemia, increased tendency for LDL oxidation and abnormal endothelial reactivity. The main results of this study showed that women with SHypo develop early signs of subclinical carotid atherosclerosis in the form of carotid wall thickening (IMT), with a more frequent occurrence of plaque than in the control (euthyroid) group.

Clinical traits

Given that arterial hypertension is known to have an impact on the rise of IMT, uniformity among the groups in this study is gaining in importance. In this study, 34% of all subjects had arterial hypertension, with no significant difference between the study groups. So far, the results from different studies were non coherent. Meta-analysis from eight observational studies, reported by Gao et al., concluded that SHypo was associated with elevated systolic but not diastolic pressure [13]. On the other hand, the results of a study conducted by Luboshitzky and Herer showed that in the SHypo group there were higher values of both systolic (p <0.01) and diastolic (p <0.001) pressure compared to the control group [14]. Lastly, in the study by Velkoska Nakova et al., mean systolic and diastolic pressures were higher in the SHypo group, with no statistically significant difference compared to the control (euthyroid) group [15].

In this study, consuming drugs that could affect the lipid and hormonal status of the thyroid gland was the exclusion criterion. Subject's personal drug report revealed that they mostly used analgesics (25%) and various supplements such as vitamins and minerals (17%), with no differences between the study groups.

The results of this study showed that the subjects with SHypo had significantly higher values of IMT (IMT ≥ 75th centile) in both carotid arteries compared to the control euthyroid subjects (Figure 2), with a significantly more frequent appearance of plaques (25% vs. 9%). Velkoska Nakova et al. reported similar results in a study in which average ACC (arteria carotis communis) IMT values in the SHypo group were significantly

higher than in the control group (0.61±0.1 mm vs. 0.56±0.1 mm; p = 0.034), with a higher incidence of plaque occurrence in the SHypo group (10.1% vs. 3.3%) [15]. The results of the study conducted in Brazil also showed higher values of IMT in a group of subjects with SHypo [16]. In a meta-analysis in which Gao et al. analyzed eight observational studies, with 3602 patients, an increase in carotid IMT by 0.056 mm (95% CI 0.020, 0.092, p = 0.002) was observed in the SHypo group compared to the euthyroid group [13]. Aziz et al. published a meta-analysis investigating the association between IMT and SHypo, and the results of levothyroxine substitution treatment. Carotid IMT was found to be significantly higher in the SHypo group (N = 280) compared with the control euthyroid group (N = 263) at baseline, and levothyroxine therapy in the SHypo subjects significantly reduced the thickness of carotid IMT and improved the subject lipid profile while modifying cardiovascular risk factors [17]. Moreover, the two studies conducted in China an inverse association between TSH and carotid IMT values, in which subjects with SHypo and lower TSH had higher carotid IMT values [18,19].

There were only a few studies analysing association of SHypo and IMT specifically in female subjects. In the study conducted by Saif et al., which included 40 female patients with overt hypothyroidism, 30 female patients with SHypo and 40 female partients with normal thyroid functions, the results have shown that carotid IMT is significantly higher (p <0.001) in patients with overt and SHypo than in subject of the control group [20]. On the other hand, Dias Cabral et al. did not find any significant change in mean carotid IMT after 12 months of L-thyroxine tratment, in study which included 32 female with mild SHypo [21].

Predictors of subclinical carotid changes

The results obtained by univariate regression analysis in this study showed that age, cholesterol, triglycerides, LDL, sdLDL, LDL/HDL index, TSH, CRP, BMI, alcohol consumption, arterial hypertension, and menopause correlated positively with mean IMT values in both CCAs (common carotid arteries).

Multivariate regression analysis showed that LDL, age, and TSH were positively associated with elevated CCA IMT values and thus predicted thickening of the carotid artery IMT (Table 4). In the study by Velkoska Nakova et al., TSH, triglycerides, and diastolic arterial pressure were

found to be independent predictors of average IMT, while fT4 proved to be an independent predictor of maximum IMT [15]. Takamura *et al*. found, by multivariate linear regression analysis adjusted for age and gender, in a study involving 1,772 subjects, that fT4 significantly correlated with carotid IMT thickness (beta = -0.13, p = 0.043), and TSH with HDL (beta = −0.001, p <0.001), HbA1c (beta = 0.04, p = 0.021), and carotid IMT (beta = 0.29, p = 0.001). They showed that the thickness of carotid wall (IMT) was independently associated with thyroid function of the reference range, and that there was an increase in cardiovascular risk in individuals with low normal thyroid function [22].

Based on the results of this and other studies, it can be concluded that increased age, LDL cholesterol, and TSH values are important predictors of subclinical atherosclerotic changes development in carotid artery.

Limitations of the study

Lastly, it should be noted that the limitations of this study are a small sample size, and a retrospective design. A longitudinal study including higher number of subjects of both genders may help clarify the underlying mechanisms of SHypo and IMT association.

Another limitation of this study is that we did not measure quantitative variables such as the vital signs, blood work (glycemia, creatinine, estimated GFR, sodium, potassium, transaminases, complete blood count).

CONCLUSION

This study confirmed the hypothesis that female subjects with SHypo develop early subclinical changes on the walls of common carotid artery detected as elevated IMT in comparison to the female control euthyroid group.

Based on these results, it can be concluded that screening and monitoring of patients showing early subclinical signs of thyroid dysfunction shoud take part in prevention of carotid atherosclerosis advancement and its complications.

Introducere. Hormonii tiroidieni pot afecta sistemul cardiovascular, dar mecanismul în dezvoltarea aterosclerozei nu este bine definit. Relaţia dintre hipotiroidismul subclinic, dislipidemie şi ateromatoza carotidiană a fost investigată însă rezultatele sunt încă controversate. Scopul studiului a fost de a evalua asocierea dintre hipotiroidismul subclinic (SHypo) şi indicele carotidian intimă-medie (IMT) la femei. Totodată au fost căutate asocierile dintre SHypo, ateroscleroză carotidiană şi dislipidemie.

Metode. Au fost incluse 100 de paciente cu vârste între 30 şi 70 de ani, împărţite în două grupuri SHypo şi eutiroidiene. A fost evaluat IMT alături de profilul lipidic (small dense LDL) şi cel al hormonilor tiroidieni.

Rezultate. Pacientele cu Shypo aveau IMT mai mare în toate cele trei segmente comparativ cu pacientele eutiroidiene. Placa de aterom a fost mai frecventă la pacientele SHypo comparativ cu pacientele eutiroidiene (25% vs 9% p=0.05). Au fost decelate asocieri pozitive între nivelurile TSH şi IMT. IMT a fost prezis de vârstă, LDL colesterol şi nivelurile TSH.

Concluzii. Acest studiu subliniază importanţa screeningului precoce al disfuncţiei tiroidiene şi asocierea riscului cardiovascular.

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