

Particularities of endothelial dysfunction in hypothyroid patients

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Abstract

Background: It is well known that hypothyroidism promotes the premature onset of subclinical atherosclerosis. This condition is defined by endothelial dysfunction (ED) and increased arterial stiffness (AS) and leads to augmentation of peripheral vascular resistance.

Aim: To assess the presence and severity of ED and to follow its evolution under therapy in three groups of hypothyroid patients, we used three different noninvasive methods: carotidian intima-media thickness (IMT), flow mediated vasodilatation (FMD), and AS.

Methods: The study group consisted of 56 young, hypothyroid women without associated cardiovascular pathology or risk factors for atherosclerosis. We selected our patients in order to have normal IMT (< 0.9 mm) and assessed the basal diameter of the brachial artery and the alterations of FMD and of AS parameters: pulse wave velocity (PWV) and augmentation index (AIx).

Results: We found, in all patients, a reduced basal diameter of brachial artery, pathological patterns of FMD, and increased values of PWV and AIx, compared to controls, in relation with the severity of thyroid dysfunction. We documented an improvement of ED after therapy with L-thyroxin.

Conclusions: ED, documented in hypothyroid patients by means of three noninvasively methods, was strongly related to the severity of thyroid disease. We detected, in all three subgroups, significant alterations of FMD and AS, even in the absence of structural changes, documented by a normal IMT. ED improved consistently after restoring the euthyroid state.

Key words: hypothyroidism, subclinical atherosclerosis, endothelial dysfunction, flow-mediated vasodilatation, arterial stiffness

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INTRODUCTION

Thyroid hormones, especially triiodothyronine (T_3), interact directly with the receptors of the smooth muscle cells from the arterial walls, exerting a relaxing effect mediated through nitric oxide (NO) pathways. This vasodilator process leads to the reduction of up to 50–70% of peripheral vascular resistance [1, 2]. In hypothyroidism, the absence or decreased release of T_3 induces endothelial dysfunction (ED), with reduced vasodilatation and increased arterial stiffness (AS) [3, 4]. ED is characterised primarily by impaired regulation of the vascular tone, as a result of reduced endothelial NO synthesis and availability [5]. These changes are associated with alterations of lipid metabolism and ultimately lead to the progression of atherosclerosis [2, 6]. Oxidative stress, vascular inflammation, impaired coagulation, thrombosis, hypertension, and atherosclerosis could all contribute to ED [6].

The infiltration of the arterial wall and of the surrounding tissues, found in myxoedema, can indirectly influence the basal vascular tone. In hypothyroidism, ED develops early and signals the onset of subclinical atherosclerosis [3, 5]. The pathophysiological pathways are well established in overt forms [6], but alterations of the endothelium dependent vasodilator response, resulting in reduced NO availability, were found even in subclinical hypothyroidism (SHt) [7, 8] where the levels of FT_3 and FT_4 are normal. This, in turn, supports the involvement of other factors, such as an increased level of thyroid stimulating hormone (TSH), as it is known that there are receptors for TSH in the endothelium and in the vascular smooth muscle cells of the entire cardiovascular system [9, 10]. Recent data sustains that a normal TSH level enhances vascular reactivity by increasing endothelium-mediated vasodilation [10].

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Several noninvasive methods have been developed for the evaluation of ED, and many of them are widely used. Some of them, such as carotid intima-media thickness (IMT), document early structural changes in the arterial wall, but others, such as AS, analyse the stiffening of small arteries as a consequence of vasoconstriction or/and structural changes [3, 4, 11, 12]. The measurement of flow-mediated vasodilatation (FMD) represents a simple approach to examine the dynamic vasodilator function in *in vivo* conditions. FMD induced by reactive hyperaemia, known as being endothelium dependent, can be detected noninvasively by means of vascular sonography, in the arteries of the arm [11, 12]. AS characterises the alterations of elasticity and compliance, as well as the process of stiffening of the arterial walls. The question remains: is ED, in hypothyroidism, reversible under substitution therapy with L-thyroxin [13–15]? More studies support the improvement of the vasodilator function and of AS after restoring the euthyroid state and the normal level of TSH, with a direct impact on cardiovascular risk reduction [16–18].

The aim of this study was to assess the presence and severity of ED in three groups of female patients with hypothyroidism of different severity, by means of three non-invasive methods: carotidian IMT, FMD, and AS. Furthermore, another aim was to assess the evolution of ED under substitution therapy with L-thyroxin.

METHODS

Study population

Our study group consisted of 56 hypothyroid women, admitted in the Clinic of Endocrinology of the County Hospital Timișoara in the period June 2010 – June 2013. All patients had hypothyroidism of autoimmune aetiology, were all non-smokers or had ceased smoking for more than one year, and were premenopausal. Moreover, the women were between the ages of 32 and 49 years (mean age 42.71 ± 6.29 years), thus limiting the impact of age on our results. We excluded all patients with diabetes mellitus, moderate or severe hypertension, and cerebral, coronary, and peripheral artery disease. We included in the study only patients with IMT under 0.9 mm. It should be mentioned that, although normal, mean IMT was higher in patients than in controls. For practical reasons, considering the severity of thyroid disease, expressed by the level of TSH and free thyroxin (FT_4), we divided the patients into three subgroups: severe clinical thyroid insufficiency (STI) — 26 subjects with $TSH > 70 \mu U/mL$, $FT_4 < 6 \text{ pmol/mL}$; overt hypothyroidism (OHT) — 15 patients with $15 < TSH < 70 \mu U/mL$, $6 < FT_4 < 11.5 \text{ pmol/L}$; and SHt — 15 women ($4.2 < TSH < 15 \mu U/mL$, normal FT_4 and FT_3). We compared our results with a control group of 15 healthy, age-matched women (between the ages of 30 and 50 years, mean age 42.15 ± 7.8 years) with similar risk factors as our patients. All patients signed a written informed consent form, and the study was approved by the Ethics Committee of our hospital.

After an initial endocrinological evaluation (hormonal determinations: TSH, FT_4 , FT_3 and thyroid sonography) to establish the aetiology and severity of thyroid disease, the patients were examined by a cardiologist. The examination included a detailed history and physical examination, ECG, echocardiography, and assessment of subclinical atherosclerosis through three different noninvasive methods.

IMT assessment

We assessed IMT by using an Aloka CV Prosound SSD-4000SV echocardiograph with a linear transducer (10 MHz). We examined both common carotid arteries at the beginning of the dilatation of the carotid bulb. On a frozen optimal longitudinal image of the far wall, we traced the leading edges, corresponding to the transition zones between lumen-intima and media-adventitia, over a length of 1 cm, proximal to the reference point, at its thickest point, not including plaques. For each subject, IMT was calculated as the mean of five measurements.

FMD — method of assessment

We used the same equipment in order to assess the basal diameter of the right brachial artery and the vasodilatations induced as a response to reactive hyperaemia. The study was performed in the morning, in a dark, quiet, temperature-controlled room (25°C), with the subjects resting for at least 10 min in a supine position. Patients were advised to fast and to drink no coffee for at least 9 h prior the exam. We measured the blood pressure in the left arm with a sphygmomanometer. The subjects' right arms were comfortably immobilised in an extended position to allow consistent access to the brachial artery. The internal diameter of the brachial artery was assessed at the end of diastole, and the velocity of the arterial flow was measured using the pulse Doppler sample volume placed in the centre of the artery. A pneumatic arm cuff was inflated up to 30 mm Hg above the subject's systolic arterial pressure for 5 min. Then the cuff was deflated, the arterial flow was recorded, and the diameter was measured at 60 s after deflation. To avoid inter-observer variability, all measurements were performed by the same examiner. FMD index was calculated according to the following formula: $FMD \text{ index} = (\text{post occlusion diameter} - \text{baseline diameter}) \times 100 / \text{baseline diameter}$.

Arterial stiffness evaluation

The two parameters of AS: pulse wave velocity (PWV) and augmentation index (AIx), were assessed with a SphygmoCor device, software version 9. We determined the PWV at the level of the right carotid artery and then, of the right radial artery. For the AIx, we placed the tonometer over the radial artery and recorded 10 s of quality pulse waves, making two measurements for each subject. The obtained values were compared, by the system, to the population reference range values.

Table 1. Results of endothelial dysfunction (ED) assessment in hypothyroid patients

Characteristics and results of ED assessment in 56 hypothyroid women	41 patients with OHT		SHT	Controls
	STI (n = 26)	OHT (n = 15)	(n = 15)	(n = 15)
Mean age [years]	42.6 ± 2.4	39.6 ± 5.7	36.7 ± 5.2	42.15 ± 6.8
TSH (0.34–4) [μIU/mL]	51.20 ± 13.7	31.15 ± 14.5	11.92 ± 2.7	2.78 ± 0.57
FT ₄ (7.5–21.1) [pmol/L]	4.85 ± 1.7	5.17 ± 3.1	6.52 ± 3.9	8.51 ± 3.14
FT ₃ (3.67–10.43) [pmol/L]	2.06 ± 1.08	3.12 ± 2.5	5.31 ± 1.7	8.31 ± 4.17
Total cholesterol [mg/dL]	268.4 ± 43.8	251.7 ± 38.3	231.5 ± 29.7	218.6 ± 27.8
Triglycerides [mg/dL]	201.5 ± 35.6	187.2 ± 22.9	156.7 ± 28.9	164.5 ± 12.7
Blood glucose [mg/dL]	97.6 ± 6.8	91.6 ± 8.7	92.7 ± 6.4	92.5 ± 10.7
Body mass index [kg/m ²]	28.4 ± 2.5	27.18 ± 2.7	26.24 ± 2.7	27.5 ± 6.71
Intima-media thickness [mm]	0.81 ± 0.08	0.78 ± 0.16	0.72 ± 0.14	0.62 ± 0.31
FV — brachial artery:				
Ø basal [mm]	3.21 ± 0.27	3.37 ± 0.33	3.51 ± 0.42	3.68 ± 0.54
Ø final [mm]	3.29 ± 0.35	3.46 ± 0.43	3.65 ± 0.38	3.94 ± 0.61
Ø final — Ø basal [mm]	0.08 ± 0.02	0.09 ± 0.01	0.14 ± 0.03	0.5 ± 0.07
FMD index [%]	2.4 ± 0.14	2.67 ± 0.32	3.98 ± 0.48	11.11 ± 0.52
Basal velocity of flow [m/s]	12.18 ± 2.5	20.51 ± 3.1	28.15 ± 3.7	31.15 ± 3.9
Final velocity of flow [m/s]	32.9 ± 1.7	36.1 ± 2.3	37.3 ± 3.1	39.8 ± 4.5
Pulse wave velocity [m/s]	8.73 ± 1.9	7.25 ± 1.05	6.98 ± 1.5	6.2 ± 1.41
Augmentation index [%]	30.57 ± 4.94	28.81 ± 2.7	27.6 ± 4.72	22.3 ± 4.72

STI — severe thyroid insufficiency; OHT — overt hypothyroidism; SHt — subclinical hypothyroidism; Ø — diameter; TSH — thyroid stimulating hormone; FV — flow velocity; FMD — flow mediated vasodilatation

In order to restore the euthyroid state and a normal level of TSH, all patients were treated with L-thyroxin: those with STI and OHT received an adequate dose and those with SHt received 25 μg/day. We repeated the evaluation of subclinical atherosclerosis at three and six months, when all subjects regained the euthyroid state.

Statistical methods

The obtained numerical values were reported as mean value ± standard deviation. We used the GraphPad Instat program in order to perform the statistical analysis and considered the p values under 0.05 as being statistically significant. We determined the correlations between our results and the TSH values by using the Spearman test for nonparametric data.

RESULTS

All 56 hypothyroid patients from the study group had no significant risk factors for atherosclerosis (except for dyslipidaemia) and no evidence of clinical atherosclerosis. The results regarding the laboratory results are presented in Table 1, in comparison with a control group of 15 age-matched healthy women. While 76% of the patients were overweight and 59% had hypercholesterolaemia, mean values of total cholesterol were increased in all three subgroups, the higher ones being detected in the patients with STI. Even the controls had borderline cholesterol values and were slightly overweight.

Regarding the markers of subclinical atherosclerosis, the patients were selected to have IMT < 0.9 mm. The controls had lower IMT values (0.62 ± 1.8 mm), and the statistical analysis highlighted a significant difference (p = 0.03) with the values determined in the STI group. It did not reveal a significant difference (p = 0.09) with the values measured in the patients with OHT and those with SHt.

By using vascular echography, we assessed the basal diameter (Øb) of the right brachial artery as a marker of the basal vascular tone. The mean values of Øb in all three subgroups were lower compared to those found in controls (3.58 ± 0.54 mm). The statistical analysis of these results revealed a significant difference between the Øb values determined in patients with STI (p = 0.02) compared to the controls, as well as a non-significant difference for those measured in subjects with OHT and SHt (p = 0.21 and p = 0.69, respectively) and the controls.

As detailed in Table 1, the vasodilator function, characterised by FMD, was reduced in all hypothyroid patients. The dilator response was low in all subgroups, the difference between basal and final diameter (ΔØ) being less than 1 mm for the patients with STI and OHT and slightly higher for those with SHt. By analysing these results, reported to controls, we found a statistically significant difference (p < 0.0001) for all patients. Furthermore, we studied the possibility of any relation between FMD index and the severity of thyroid disease,

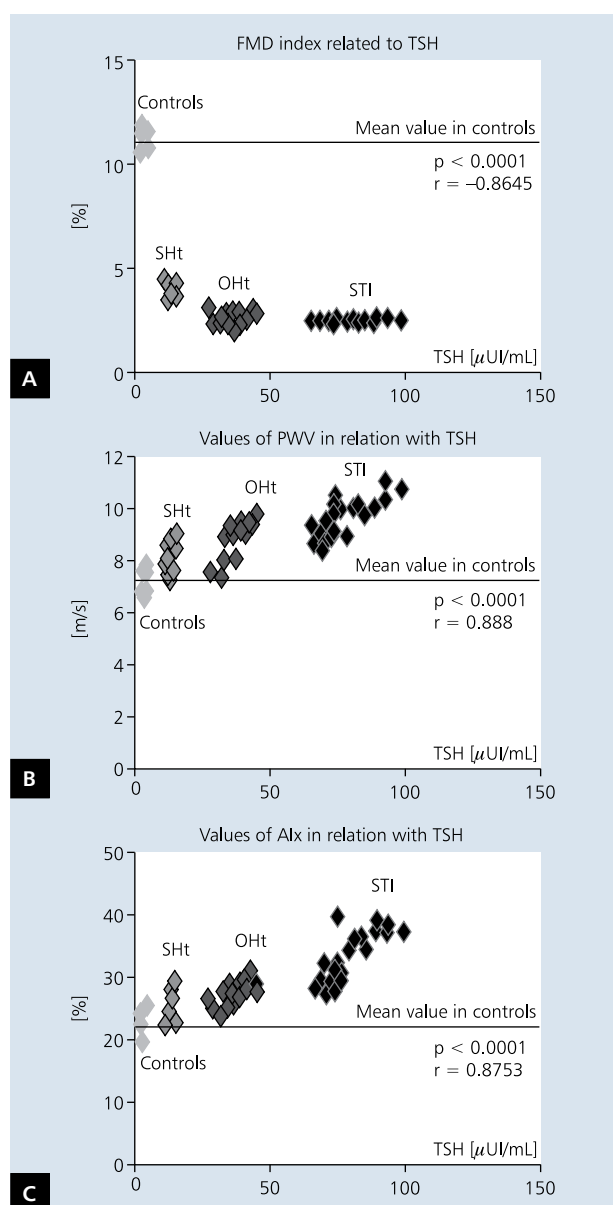


Figure 1. Correlations between flow mediated vasodilatation (FMD) index (A); pulse wave velocity (PWV) (B) and augmentation index (Alx) (C) and values of thyroid stimulating hormone (TSH); STI — severe thyroid insufficiency; OHT — overt hypothyroidism; SHT — subclinical hypothyroidism

expressed by the values of serum TSH. We found, by using the Spearman correlation, a negative, significant correlation ($r = -0.8645$, $p < 0.0001$) for all three categories of patients, as presented in Figure 1A.

Regarding the assessment of AS, all patients had values of PWV and Alx above the mean values found in controls (6.2 m/s and 21.3%, respectively) and the normal range described for non-smoking women in the same category of age (PWV < 7 m/s and Alx under 20%). Using the Spearman test, we found significant correlations between the levels of

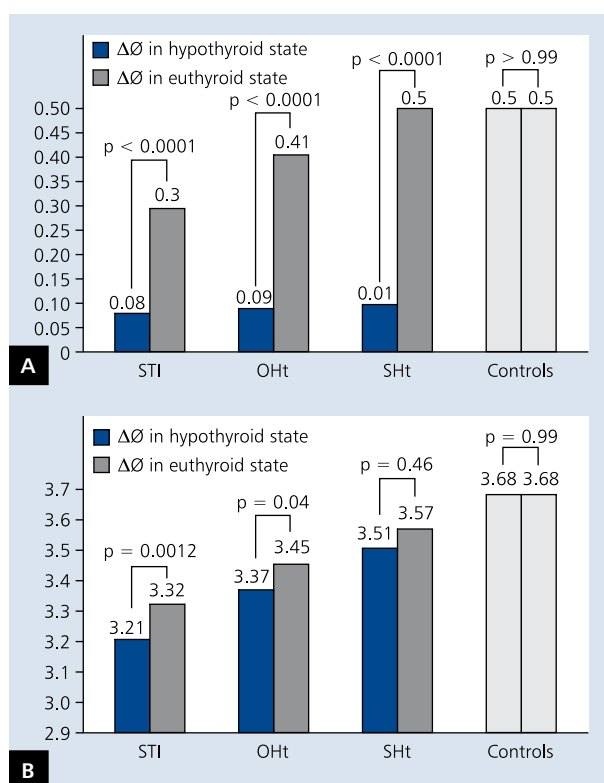


Figure 2. Comparison between vasodilator response ($\Delta\emptyset$) (A) and $\emptyset$ basal (B) in hypothyroid and euthyroid status at the level of brachial artery; normal response in controls; A. Difference between $\emptyset$ final and $\emptyset$ basal ($\Delta\emptyset$) in all three subgroups of patients in hypo- and euthyroid state compared to controls; B. Improvement of $\emptyset$ basal ($\Delta\emptyset$) in all three subgroups of patients in hypo- and euthyroid state compared to controls; STI — severe thyroid insufficiency; OHT — overt hypothyroidism; SHT — subclinical hypothyroidism

TSH and the rigidity of the arterial wall, expressed by PWV ($r = 0.888$, $p < 0.0001$) and Alx ($r = 0.8753$, $p < 0.0001$) (Fig. 1B, C).

All patients received substitution therapy with L-thyroxin in an adequate dose and were followed until the achievement of the euthyroid state. We repeated our investigations at three and six months and found an improvement of the vasodilator function (Figs. 2A, B, 3), but also an increase of the basal diameter (Fig. 2B). Analysing the difference between the initial value of the arterial diameter and the value determined in euthyroidism ($\Delta\emptyset$), the statistical analysis revealed a significant difference in the patients with STI ($p = 0.0012$) and with OHT ($p = 0.04$), and a non-significant difference in those with SHT ($p = 0.46$).

Regarding the initial FMD index and the one determined after six months of therapy, we detected a statistically significant difference ($p < 0.0001$) for all three subgroups (Fig. 3).

The monitoring of AS evolution, at three and six months, following therapy with L-thyroxin, until euthyroidism was

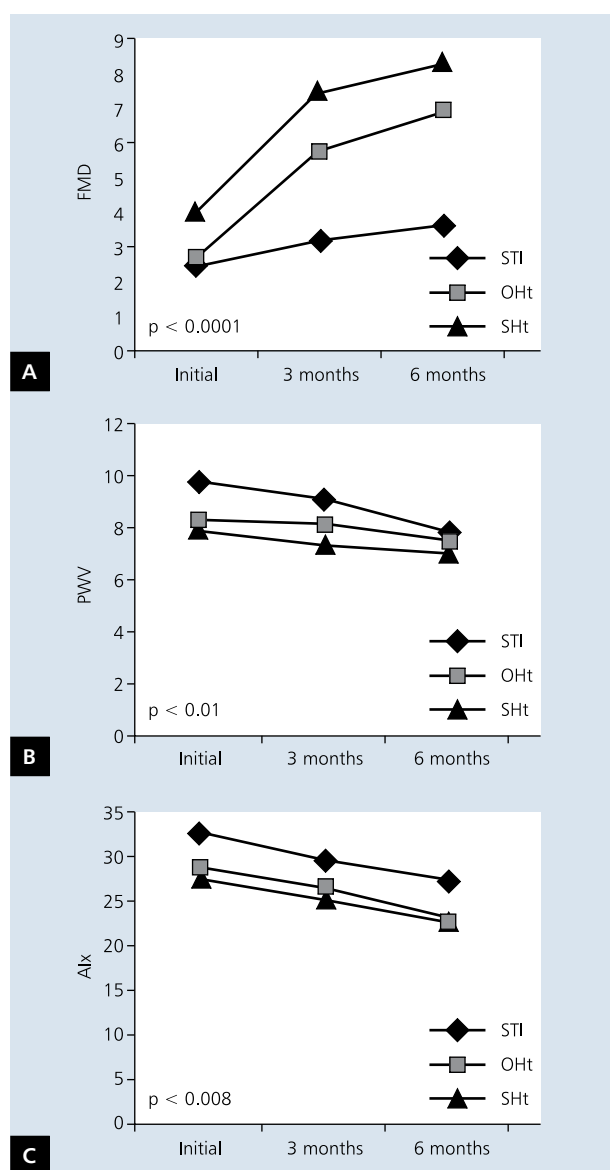


Figure 3. Evolution of flow-mediated vasodilatation (FMD) index (A), pulse wave velocity (PWV) (B), and augmentation index (Alx) (C) under therapy with L-thyroxine; STI — severe thyroid insufficiency; OHt — overt hypothyroidism; SHt — subclinical hypothyroidism

achieved, revealed a progressive reduction of PWV and of Alx in the majority of patients (Fig. 3). We registered normal values of PWV (≤ 7 m/s) only in three patients with SHt. The statistical analysis of PWV evolution revealed a significant regression between the initial value and the one registered at six months, only in patients with STI ($p = 0.01$), but not in those with overt and SHt ($p = 0.59$ and $p = 0.60$, respectively). By analysing the evolution of Alx, we observed a significant regression ($p = 0.008$) for the patients with STI and a non-significant one ($p = 0.06$ and 0.1 , respectively) for those with overt and subclinical disease. A complete

normalisation of Alx was found only in five (33.33%) patients with subclinical disease.

DISCUSSION

We studied the alterations of ED noninvasively, by means of three different independent methods (IMT, FMD, and AS), in a group of women with hypothyroidism of various degrees of severity. Our patients had no evidence of clinical atherosclerosis and were compared with healthy age-matched controls. Because IMT over 0.9 mm is considered a structural marker for subclinical atherosclerosis, we selected our patients in order to have IMT less than 0.9 mm, a criterion also used in other papers [19]. Although normal, the IMT values determined in our patients with STI were significantly higher ($p = 0.03$) than in controls, but not quite significantly higher for those with OHt and with SHt. The assessment of FMD revealed, in all our patients, a reduced basal diameter of the brachial artery, thus reflecting an increased arterial tone in basal conditions. The values were significantly lower in patients with STI, but not in those with OHt or with SHt, compared to the controls. FMD was diminished in all hypothyroid patients, the vasodilator response being depressed. By analysing these results, we found significant statistical differences ($p < 0.0001$), reported to controls. We highlighted, in all our patients, including those with SHt, a negative significant correlation ($r = -0.8645$, $p < 0.0001$) between the FMD index and the values of TSH. All our hypothyroid patients had increased AS, expressed by higher values of PWV and Alx compared to the controls and to the normal range described in the literature [20]. We found significant correlations between the rigidity of arterial wall, characterised by these parameters, and the levels of serum TSH ($r = 0.888$ for PWV and $r = 0.8753$ for Alx, $p < 0.0001$).

Many researchers tried to highlight in their papers the relation between hypothyroidism, ED, and the alterations of FMD, independent from other risk factors for atherosclerosis, but most of them referred to subclinical forms [7–12]. In their study, Cikim et al. [12] were among the first to compare patients with SHt, with euthyroid, risk and age-matched subjects and demonstrated a significant reduction of FMD, sustaining the hypothesis that endothelial function deteriorates before any morphological changes in hypothyroidism. Similar results were described later, in other studies [9, 13], all referring only to patients with SHt. There is little to no data about the concomitant assessment of ED, by use of many methods. Halcox et al. [19] and recently Kilic et al. [10] highlighted the abnormalities of FMD in patients with SHt and normal IMT, as a marker for structural changes in the arterial wall, but there is little data about the fluctuations of the basal diameter of the brachial artery as a marker for increased basal arterial tone.

The alterations of PWV and Alx were analysed by many authors, but most of them debate, in their studies, the changes of those parameters only in SHt [3, 4, 7, 8]. Our results

regarding AS were similar with the ones described in the literature [4, 9], but we highlighted the fluctuations of those parameters also in patients with overt thyroid hypofunction. In hypothyroidism, the assessment of AS markers is very important because data from various studies demonstrated that augmented PWV or/and Alx are associated with high risk for coronary artery disease, stroke, and cardiovascular mortality in the population [3, 14, 21].

Although controversial, data about the evolution of ED exist, and most authors support the improvement of FMD and/or of AS under substitution therapy with L-thyroxin [13–17, 22]. The inconsistent results regarding the evolution of IMT, FMD, and AS presented in some studies can be explained in several ways, including the inherent limitations of the techniques, small study populations, and differences regarding the severity of hypothyroidism between the subgroups of patients. Our patients were treated with L-thyroxin and followed until euthyroidism was restored. ED, estimated by means of basal arterial diameter, FMD, and AS, was significantly modified after substitution therapy, in all hypothyroid patients, if compared to baseline. The most substantial improvement was registered for FMD index, and we highlighted significant differences ($p < 0.0001$) for all patients after six months of therapy. If we refer to the basal arterial diameter, the difference between the initial value and the one determined after six months was significant for the patients with STI and OHT, but not significant for those with SHt. Regarding the evolution of AS, the regression of PWV and Alx values after six months was significant for patients with STI ($p = 0.01$) but not for those with overt and subclinical forms.

All three non-invasive investigations used to explore ED in our study group of hypothyroid patients, without any structural signs of subclinical atherosclerosis, revealed that therapy with L-thyroxin was associated with significant improvement of ED. In hypothyroid patients, FMD index, as well as the assessment of basal arterial diameter, were more sensitive for monitoring the evolution of ED, compared to AS or IMT, which probably reflect more advanced changes and need a longer follow up to document a significant regression.

CONCLUSIONS

In this study we have documented that in patients with different severity of hypothyroidism, ED, assessed noninvasively, by means of three independent methods, was strongly related to the severity of thyroid disease, estimated by the levels of TSH. We detected significant alterations of FMD and AS, even in the absence of structural changes of the arterial wall, documented by a normal IMT of the carotid artery. It should be mentioned that all patients, even those with subclinical disease, had an increased basal arterial tone compared to the controls. ED improved consistently in all patients after restoring the euthyroid state.

Conflict of interest: none declared

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Dysfunkcja śródbłónka u chorych z niedoczynnością przytarczyc

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Streszczenie

Wstęp: Powszechnie wiadomo, że niedoczynność tarczycy przyczynia się do przedwczesnego rozwoju bezobjawowej miażdżycy. To zaburzenie, definiowane jako dysfunkcja śródbłónka (ED) i zwiększenie sztywności tętnic (AS), prowadzi do wzrostu obwodowego oporu naczyniowego.

Cel: Badanie przeprowadzono w celu oceny obecności i nasilenia ED oraz obserwowania jego ewolucji w trakcie leczenia w trzech grupach chorych z niedoczynnością tarczycy. Zastosowano trzy różne nieinwazyjne metody: pomiary grubości kompleksu błony środkowej i wewnętrznej tętnicy szyjnej (IMT), zależnego od przepływu rozszerzenia naczyń (FMD) oraz AS.

Metody: Badana grupa obejmowała 56 młodych kobiet z niedoczynnością tarczycy, u których nie występowały powiązane choroby sercowo-naczyniowe ani czynniki ryzyka miażdżycy. Wybrano pacjentki z prawidłowymi wartościami IMT ($< 0,9$ mm) i oceniono wyjściową średnicę tętnicy ramiennej, zmiany FMD i parametry AS: szybkość fali tętna (PWV) oraz wskaźnik wzmocnienia (Alx).

Wyniki: U wszystkich chorych stwierdzono obniżoną średnicę wyjściową tętnicy ramiennej, patologiczne FMD i zwiększone wartości PWV oraz Alx w porównaniu z osobami z grupy kontrolnej. Te zmiany wiązały się z nasileniem dysfunkcji tarczycy. Wykazano poprawę w zakresie czynności śródbłónka po leczeniu L-tyroksyną.

Wnioski: Dysfunkcja śródbłónka, potwierdzona u chorych z niedoczynnością tarczycy za pomocą trzech nieinwazyjnych metod badania, była silnie związana ze stopniem ciężkości choroby tarczycy. We wszystkich trzech podgrupach stwierdzono istotne zmiany FMD i AS, nawet w przypadku niewystępowania zmian strukturalnych (prawidłowy wynik pomiaru IMT). Po przywróceniu stanu eutyreozы następowała wyraźna poprawa czynności śródbłónka.

Słowa kluczowe: niedoczynność tarczycy, bezobjawowa miażdżycy, dysfunkcja śródbłónka, zależne od przepływu rozszerzenie naczyń, sztywność tętnic

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