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DYSLIPIDAEMIA AND HYPERTENSION IN PATIENTS WITH SUBCLINICAL HYPOTHYROIDISM

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A b s t r a c t: *Objective*. The aim of this study was to assess whether subclinical hypothyroidism (SCH) is associated with dyslipidaemia and arterial hypertension.

Methods. At the Department of Endocrinology, Diabetes and Metabolic Disorders, Skopje, R. Macedonia, we examined 24 consecutive patients with SCH and 13 healthy controls in a period of 6 months. SCH was defined as an elevated thyrotropin (TSH) (> 4.2 mU/l) and normal free thyroxine (fT4) level (10.3–24.45 pmol/l). None of the patients had been previously treated with thyroxine. In all participants we determined blood pressure, body mass index (BMI), TSH, fT4, antibodies to thyroid peroxidise (TPOabs), total lipids (TL), total cholesterol (TH), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and triglycerides.

Results. Mean diastolic blood pressure increased in SCH patients vis-a-vis controls (85 vs. 74 mmHg; $p < 0.05$). Mean values of TL, TH, HDL-C, LDL-C, triglycerides, TC/HDL-C, and LDL-C/HDL-C were no different in patients with SCH compared with controls. Individual analysis revealed that the percentages of patients with SCH having arterial hypertension (29%), hypertriglyceridaemia (34.78%), elevated LDL-C (41.66%), elevated TC/HDL-C (21.7%), and LDL-C/HDL-C (21.74%) ratios were higher than the percentages in controls. No significant correlation between TSH and biochemical parameters was detected.

Conclusion. Our study revealed that SCH patients have a greater prevalence of dyslipidaemia and arterial hypertension, and, as well, a greater value of mean diastolic pressure vs. control patients.

Key words. Subclinical hypothyroidism; arterial hypertension; dyslipidaemia; atherosclerosis; risk factors.

Introduction

SCH, also called mild hypothyroidism, is a term used for a condition in which there are small elevations in the thyroid-stimulating hormone, yet normal circulating levels of thyroid hormones. This condition is more common in the elderly and is found twice as often in women as in men [1]. In general, the prevalence of this condition in women ranges from 4% at age 20 to 17% at age 65 and in men from 2% at age 20 to 7% at age 65 [2, 3].

Thyroid hormones have significant effects on the synthesis, mobilezation and metabolism of lipids [4].

Overt hypothyroidism is associated with significant increases in circulating concentrations of TH and LDL-C [5], but it is uncertain whether SCH is also associated with dyslipidaemia. Some case-control studies [6–9], but not others, have reported an association between SCH and dyslipidaemia in subjects with SCH compared with euthyroid controls. Two large cross-sectional studies [10, 11] reported increased serum TH, LDL-C, and triglycerides in subjects with SCH. By contrast several large cross-sectional studies found no significant difference in TH, LDL-C, and triglycerides between subjects with SCH and euthyroid subjects [12–17].

Whereas overt hypothyroid patients in the fifth and sixth decades of life have significantly higher diastolic blood pressure and arterial hypertension than age-matched controls, an association between arterial hypertension and SCH has not been reported [10, 18, 19].

Dyslipidaemia and arterial hypertension are risk factors for atherosclerosis. The idea that overt hypothyroidism promotes atherosclerosis has been generally accepted, but whether SCH is associated with increased risk of atherosclerosis, is still a matter of debate [20–22].

The study aimed to assess SCH effects on blood pressure and lipids.

Patients and methods

The study was conducted from 01.09. 2008 to 28.02. 2009, at the Department of Endocrinology, Diabetes and Metabolic Disorders in Skopje, R. Macedonia. We prospectively included 24 consecutive patients (22 female, 2 male) with newly diagnosed SCH, defined by normal FT4 (10.3–24.45 pmol/l)

and elevated TSH (> 4.2 mU/l) levels. Their mean age was 45.37 ± 16.31 years and mean BMI was 27.67 ± 5.69 kg/m^2.

Thirteen (12 female, 1 male) healthy, euthyroid subjects were included in the study as a control group. Their mean age was 47.85 ± 15.78 years and mean BMI was 27.04 ± 4.46 kg/m^2. No patients had a previous history of thyroid disease or took any medication related to thyroid disease or lipid metabolism. Patients with diabetes mellitus, liver or renal disease, chronic pancreatitis, primary hyperlipidaemia, ovulatory dysfunction and infertility were excluded from the study. All patients gave informed consent to participate in the study.

Participants had a physical examination and laboratory analyses. Outcome measures were TSH, fT4, TPOabs, fasting TL, TH, HDL-C, LDL-C, triglycerides, blood pressure, and BMI.

Blood samples were drawn at 08:00am after a 14-hour fast. The blood samples for lipoproteins were analysed using Cobas Integra 700, according to standard methods. TH and triglycerides were determined by full enzymatic methods (TH-CHOD-POD-PAP and triglycerides-GPO; Cobas Integra 700, Hoffmann-La Roche, Basel, Switzerland). HDL-C was measured by the polyanion precipitation method, while LDL-C was calculated using the Friedewald formula. LDL-C were fractioned using ultracentrifugation in cases of triglycerides exceeding 4mmol/l. Serum TSH and free T4 concentrations were measured using an Immulite 2000 chemiluminescent analyser (Siemens Medical Solutions Diagnostics, Los Angeles, CA, USA). The sensitivity of the assays were 0.004 μIU/ml and 0.3 ng/dl, respectively. TPOabs was determined by immunometric assay obtained from Diagnostic Products Corporation (Los Angeles, CA). Blood pressure was measured twice in a supine position. In a case of hypertension (> 145/90 mmHg) the measurement was repeated after five minutes. The participants were weighed wearing clothes but without shoes in the morning with an electronic scale. Height was measured to the nearest 1 cm with a stadiometer.

Statistical analysis

Statistical analysis was performed using the Statistics for Windows programme, version 5.0. Comparison of the groups was examined using Student's t test. To determine the relationship between TSH and blood pressure, TL, TH, HDL-C, LDL-C, and triglycerides, Spearman's non-parametric correlation test was used. Spearman rank correlation was also used to determine the relationship between blood pressure and lipid profiles in patients with SCH. P values < 0.05 were considered statistically significant.

Results

The results of the thyroid function tests and the personal characteristics of the two groups are shown in table 1. Eight females in the patients group and three females in the control group were in the post-menopausal period. Smoking habits were comparable in the groups. None of these females had hormone replacement therapy at the moment or in the previous couple of years.

Table 1 – Табела 1

Hormonal and personal characteristics of patients with SCH and normal controls
Хормонални и лични карактеристики на пациентите
со СКХ и контолната група

Variables	Subclinical hypothyroidism (n = 24)	Controls (n = 13)	df = 35 t-value	P-value
Sex M : F	2 : 22	1 : 12	0.07	0.94(NS)
Age (years)	45.37 ± 16.31	47.85 ± 15.78	0.45	0.66(NS)
BMI (kg/m^2)	27.67 ± 5.69	27.04 ± 4.46	0.51	0.61(NS)
fT4 pmol/l	14.24 ± 3.38	16,21 ± 2.04	1.91	0.06(NS)
TSH mU/L	8.86 ± 4.28	1,53 ± 0.8	6.13	< 0.0001

Results are mean ± SD; df – degree of freedom; NS – non significant
Резултатите се просек ± СД; Дф – степени на слобода; НС – нема сигнификантност

The groups were similar with respect to sex, age and BMI (NS in all cases). the patients had a statistically higher TSH levels than the control group ($p < 0.0001$). Positive tests to TPOabs (> 34 iU/ml) were detected in 66.6% of patients and in 7.6% of controls. Patients with SCH had statistically significant higher diastolic blood pressure than the euthyroid, control group (85.24 ± 14.44 vs. 74.17 ± 14.89 mmHg); ($p = 0.04$). Serum mean levels of TL (8.46 ± 2.15 g/l), triglycerides (1.45 ± 0.74 mmol/l), TH (5.32 ± 1.35 mmol/l), HDL -C (1.32 ± 0.29 mmol/l), and LDL -C (3.29 ± 1.2 mmol/l) were not significantly different from the values in the controls (7.78 ± 1.25 g/l, 1.45 ± 0.44, 5.47 ± 1.01, 1.33 ± 0.46, and 3.18 ± 1.02, respectively) (NS in all cases).

The percentages of patients and controls with elevated blood pressure and abnormal lipid profiles are given in Table 2. The percentage of patients having borderline elevated triglycerides (≥ 2mmol/l), LDL-C (≥ 3.7 mmol/l), TH/HDL-C (> 5. 51) and LDL-C/HDL-C ratios (> 3.46) was significantly higher than in the controls ($p < 0.05$). Hypercholesterolaemia was detected in similar percentages in patients and controls.

Table 2 – Табела 2

Individual percentage analysis of lipid and blood pressure values of patients with SCH and normal controls
Индивидуални процентуални анализи на липидниот профил и крвниот притисок кај СКХ и контролната група

Variables	Subclinical hypothyroidism	Controls
Total lipids (≥ 10g/l)	36.84%	12.5%
Triglycerides (≥ 2mmol/l)	34.78%	7.7%
Total cholesterol (≥ 5.2mmol/l)	47.82%	46.15%
LDL-C (≥ 3.7mmol/l)	41.66%	25%
Total cholesterol/HDL-C (> 5.51)	21.74%	7.7%
LDL-C/HDL-C (> 3.46)	21.7%	0%
A. Hypertension ≥ 140/90mmHg	29%	15.3%

A significant positive correlation was observed between blood pressure and TH. Serum triglyceride levels were positively correlated with TH and negatively correlated with HDL-C (Table 3). In patients with SCH, no significant correlations were observed between TSH and TH, TL, triglycerides, LDL-C, HDL-C and blood pressure.

Table 3 – Табела 3

Spearman correlation coefficient between blood pressure and lipid profiles in patients with SCH
Коефициент на Спирманова ранг корелација помеѓу крвниот притисок и липидниот профил кај испитаниците со СКХ

Parameter	Systolic blood pressure		Diastolic blood pressure		Triglycerides	
	R	p	R	p	R	P
Total cholesterol	0.48	**0.01**	0.36	**0.04**	0.57	**0.003**
LDL-C	0.38	0.06	0.24	0.25	0.35	0.09
HDL-C	0.07	0.75	-0.01	0.97	-0.58	**0.003**
Triglycerides	0.29	0.16	0.38	0.06	1.00	0.01

Discussion

In the present study we have demonstrated non-significant differences between lipid profiles in patients with SCH and values observed in age-matched

euthyroid controls. However, a significant percentage of these patients had arterial hypertension, hypertrigliceridaemia, elevated LDL-C, elevated TH/HDL-C ratio, and elevated LDL-C/HDL-C ratio as compared with the control group.

Also, we have demonstrated that patients with SCH have significantly higher diastolic blood pressure than the control group. We found that approximately 29% of SCH patients had diastolic hypertension compared with 15.3% in the euthyroid, control group. Luboshitzky *et al*. [9] have shown that women with SCH have a mean diastolic blood pressure higher than control group. This corresponds with our findings. Several studies have reported impaired left ventricular diastolic and systolic myocardial functions in subclinical hypothyroidisms which reverted to normal during L-thyroxine replacement therapy [23–25]. Exposure of aortic endothelial and vascular smooth muscle cells to triiodothyronine (T3) resulted in cellular relaxation. Two binding sites specific for T3 were identified. When cells were exposed to T3, no effect on phosphorylation or nitric oxide production were observed, suggesting that T3 acted directly on the vascular smooth muscle cells to cause vascular relaxation [26]. These data provide our results with a greater physiologic impact and rationale for replacement therapy.

Results of serum lipid concentrations in SCH revealed conflicting data. TH and HDL-C were elevated in several reports, but were not different from those in the controls in most studies [7, 27]. Lower serum HDL-C levels were reported in few studies and were not different from the euthyroid controls in most other studies [7, 28]. Since LDL-C is atherogenic while HDL-C is protective, elevated TH/HDL and LDL/HDL ratios have been used as indexes of increased risk for atherosclerosis. In our study we found that the percentages of patients with atherogenic lipid profiles (TH/HDL-C and LDL-C/HDL-C) were higher than in the controls.

Maas *et al*. [29] have demonstrated the effect of LDL-C on increased atherogenesis in SCH. SCH-related mechanisms, including lipid alteration, have not been exactly established. The cause of these alterations may be increased cholesterol synthesis and decreased activity of hepatic and lipoprotein lipases in thyroid failure [30]. Additionally, decreased cholesterol excretion, a reduced number of LDL receptors on the liver cell surface and decreased plasma LDL receptors are possible mechanisms leading to lipid abnormalities in hypothyroidism [31].

There is a growing body of evidence indicating that elevated triglyceride levels are an independent risk factor for atherosclerosis [32]. Hypertriglyceridaemic patients often develop a lipoprotein profile characterized by elevated triglycerides and LDL-C and low HDL-C [33, 34]. It is estimated that the aggregated risk associated with triglycerides greater than 2.28nmol/L and a TH/HDL-C ratio greater than 5.0 contributes 25% of the cardiovascular events [35].

Although TSH has been suggested as the major factor in the relationship between lipid abnormalities and SCH, we did not observe any correlations between lipid profiles and blood pressure on the one hand and TSH levels in patients with SCH on the other [20]. The only explanation is probably the small sample of participants.

Conclusion

Our study revealed that SCH patients do have a greater prevalence of dyslipidaemia and arterial hypertension, and, as well, a greater value of mean diastolic pressure vs. control patients. This may increase the risk of accelerated atherosclerosis and premature artery disease in some patients that should be investigated in larger longitudinal studies.

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Резиме

ДИСЛИПИДЕМИЈА И ХИПЕРТЕНЗИЈА КАЈ БОЛНИ СО СУБКЛИНИЧКИ ХИПОТИРОИДИЗАМ

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Цел: Да откриеме дали субклиничкиот хипотироидизам е асоциран со дислипидемија и хипертензија.

Материјали и методи: Спроведовме проспективна, контролирана студија на Клиниката за ендокринологија – Скопје, во период од 6 месеци. Во студијата учествуваа 24 консекутивни лица со СКХ и 13 здрави, еутироидни лица, како контролна група. СКХ беше дефиниран како зголемено ниво на тиреостимулирачки хормон (TSH) (> 4,2 mU/l) и нормално ниво на слободен тироксин (fT4) (10,3–

24,45 pmol/l). Ниту еден од учесниците, претходно не беше лекуван со тироксин. На сите учесници им се измери крвен притисок, BMI (индекс на телесна маса), TSH, fT4, антитела против тироидната пероксидаза, вкупни липиди, вкупен холестерол, HDL, LDL холестерол и триглицериди.

Резултати: Просечниот дијастолен крвен притисок беше зголемен кај пациентите со субклинички хипотироизам наспроти контолната група (85 наспроти 74 mmHg; $p < 0,05$). Просечните вредности на вкупните липиди, триглицериди, вкупен холестерол, HDL холестерол и LDL холестерол не се разликуваат кај пациентите со СКХ во споредба со контролната група. Индивидуалните анализи откриja дека процентот на пациентите со СКХ кои имаат хипертензија (29%), хипертриглицеридемија (34,78%), зголемен LDL холестерол (41,66%), вкупен холестерол/HDL (21,74%) и LDL/HDL однос (21,7%) се повисоки во однос на истиот процент кај контролната група. Не беше утврдена сигнификантна корелација помеѓу TSH и испитуваните параметри.

Заклучок: Нашата студија откри дека пациентите со СХ имаат поголема преваленца на дислипидемија и хипертензија, како и повисок просечен дијастолен крвен притисок во споредба со контролната група.

Клучни зборови: субклинички хипотироидизам, дислипидемија, хипертензија, атеросклероза, ризик фактори.

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