The frequency of metabolic syndrome in patients with the subclinical hypothyroidism

Učestalost metaboličkog sindroma kod bolesnika sa supkliničkom hipotireozom

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Abstract

Background/Aim. An increased cardiovascular risk of thyroid dysfunction is associated with the impairment of lipid and lipoprotein metabolism, endothelial dysfunction, metabolic, hormonal, hemodynamic changes and coagulation disorders. Subclinical hypothyroidism is characterized by supernormal thyroid-stimulating hormone (TSH) level along with normal values of thyroid hormones. The association of subclinical hypothyroidism with higher cardiovascular risk has not been fully clarified. The aim of the study was to determine the frequency of metabolic syndrome and the associated cardiovascular risk factors in patients with the subclinical hypothyroidism. **Method.** The study included 140 subjects aged from 18 to 65 years, out of which 105 subjects had subclinical hypothyroidism and 35 subjects were the euthyroid controls. The clinical trial program, completed in all subjects, included: detailed medical history and physical examination, waist circumference, and laboratory tests [fasting glycemia, lipid and lipoprotein status, free triiodothyronine (FT3) and free thyroxine (FT4) and TSH levels]. **Results.** Out of 105 patients with the subclinical hypothyroidism, mean age 44.15 ± 11.23 years, 77 (73.3%) patients had metabolic syndrome. In the control group consisting of 35 subjects, mean age 33.80 ± 10.60 years, only 3 (8.6%) subjects had metabolic syndrome. Mean values of the waist circumference, fasting glycemia, triglycerides, systolic and diastolic blood pressure were higher in subclinical hypothyroidism group in relation to the controls ($p < 0.0001$). Mean value of high-density lipoprotein (HDL) cholesterol was lower in subclinical hypothyroidism group as compared to the controls ($p < 0.002$). **Conclusion.** The frequency of metabolic syndrome was 9 times higher in subjects with the subclinical hypothyroidism in relation to subjects without any subclinical hypothyroidism.

Key words:
hypothyroidism; metabolic syndrome x; cardiovascular diseases; risk factors; risk assessment.

Apstrakt

Uvod/Cilj. Povećan kardiovaskularni rizik u disfunkciji štitaste žlezde u vezi je sa poremećajima metabolizma lipida i lipoproteina, endotelijalnom disfunkcijom, metaboličkim, hormonskim, hemodinamskim promenama i poremećajima koagulacije. Supklinička hipotireoza karakteriše se supranormalnim nivoom tireostimulišućeg hormona (TSH) uz normalne vrednosti tireoidnih hormona. Udruženost supkliničke hipotireoze sa povišenim rizikom od nastanka kardiovaskularnih bolesti još uvek nije u potpunosti razjašnjena. Cilj rada bio je određivanje učestalosti metaboličkog sindroma i pridruženih faktora rizika od nastanka kardiovaskularnih bolesti kod bolesnika sa supkliničkom hipotireozom. **Metode**. Istraživanjem je obuhvaćeno 140 ispitanika starosti 18–65 godina – 105 ispitanika sa supkliničkom hipotireozom i kontrolna grupa od 35 ispitanika bez nje. Kod svih ispitanika sproveden je program istraživanja koji je uključivao: detaljnu anamnezu i fizikalni pregled, merenje obima struka, laboratorijska ispitivanja [glikemija našte, lipidni i lipoproteinski status, slobodni trijodtrionin (fT3), slobodni tiroksin (fT4) i TSH]. **Rezultati**. Od 105 bolesnika sa subkliničkom hipotireozom, prosečne starosti 44,15 ± 11,23 godina, 77 (73.3%) bolesnika imala su metabolički sindrom. U kontrolnoj grupi od 35 ispitanika, prosečne starosti 33,80 ± 10,60 godina, samo 3 (8.6%) ispitanika imala su metabolički sindrom. Srednje vrednosti obima struka, našte glukoze u krvi, triglicerida, sistolnog i dijastolnog krvnog pritiska bile su više u grupi sa supkliničkom hipotireozom u odnosu na kontrolnu grupu ($p < 0.0001$). Srednja vrednost HDL-holesterola bila je niža u grupi sa supkliničkom hipotireozom u poređenju sa kontrolnom grupom ($p < 0.002$). **Zaključak**. Učestalost metaboličkog sindroma je oko 9 puta veća kod ispitanika sa supkliničkom hipotireozom u odnosu na eutireoidne ispitanike.

Ključne reči:
hipotireoidizam; metabolički sindrom x; kardiovaskularne bolesti; faktori rizika; rizik, procena.

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Introduction

Presently, atherosclerosis is the most significant factor of blood vessel diseases, causing the highest morbidity and mortality worldwide. The increased levels of a total cholesterol, low density lipoprotein (LDL) cholesterol and triglycerides as well as decreased values of high density lipoprotein (HDL) cholesterol have been also classified to risk factors of development of ischemic heart diseases.

Subclinical hypothyroidism (SH) attracts attention and the researchers expand the need for exploring the possible meaning of this condition.

SH is defined by finding the increased serum thyroid-stimulating hormone (TSH) concentration with concurrently normal thyroid hormone values [1]. The concept of SH appeared in 1980s when the sensitive tests for measurement of serum TSH were introduced. Classical population study from district of Whickham, England, found the prevalence of 75 and 28 per 1,000 women and 1,000 men, respectively [2]. Similar findings were reported in other studies [3]. According to the National Health and Nutrition Examination Survey (NHANES III) data, the frequency of SH in USA population was 4.3% [4]. On the other hand, some formerly published series of subjects established even higher SH frequency. Roterdam study revealed the frequency of 10.8% in older women [5], and Fremantle Diabetes Study, Fremantle, Western Australia, demonstrated the frequency of 8.6% in women with type 2 diabetes mellitus [6]. For example, a recent study using Korean population-based cohorts reported the SH prevalence of 11.3% [7].

The question whether the subclinical thyroid dysfunction may lead to fatal effects to cardiovascular system together with the increased risk of mortality still remains open.

The factors causing higher risk of cardiovascular diseases (CVD) in SH have not been fully clarified, but this association has been partially related to higher blood pressure, atherogenic lipid and lipoprotein status, proinflammatory condition, endothelial dysfunction and blood hypercoagulability [8–16].

The authors presume that benefit from l-thyroxine treatment of these patients will reflect in reduction of CD related mortality [13, 14, 17–19].

Metabolic syndrome (MetS) is a group of metabolic disorders which increases the risk of type 2 diabetes mellitus (T2DM) and CVD. MetS may be defined in different ways, but the central obesity, dyslipidemia, impaired glucose tolerance and hypertension represent its main characteristics [20–22]. The frequency of MetS in developed and developing countries is significant. It is estimated that about 20–25% of adult population is affected by MetS worldwide. The estimate is that MetS affects more than 34% of the USA population [23]. In Iran, 30% of men and 55% of women meet diagnostic criteria of MetS [24].

Coexistence of these disorders is more frequent than expected [25] and their associated occurrence is far more hazardous for developing CVD than the summation of their individual effects [22], which is not generally accepted viewpoint [26].

The association of SH with the increased cardiovascular risk has not been completely elucidated.

In this study, baseline hypothesis was that SH could have effect on MetS frequency. For this reason, we investigated the patients with and without SH as well as the resulting development of MetS.

The basic aim of the study was determination of frequency of MetS and associated cardiovascular risk factors in patients with the SH.

Methods

This clinical, non interventional cross-sectional study was approved by the Ethics Board of Medical Center in Novi Pazar and conducted in compliance with the Declaration of Helsinki. The study included 140 subjects aged 18-65 years, out of which 105 had SH and 35 were the euthyroid controls.

Before any study procedure, a patient was informed on study design and upon reading the informed consent, he/she signed it. History data were obtained by means of structured history questionnaire. Physical examination of each patient was performed. Anthropometric measurements of patients were taken in fasting state (not taking food 12 to 14 h prior testing). Biological samples were collected: 1 test-tube with citrate for erythrocyte sedimentation rate (ESR), 1 test-tube containing ethylenediamine tetracetic acid (EDTA) (5 mL) for complete blood count, 2 test tubes for serum separation (10 mL each) for biochemical analyses (glycemia, HDL, LDL) and immunometric analyses [free thyroxine (FT4), free triiodothyroxine (FT3), TSH].

The study included patients who met all inclusion and had none of exclusion criteria.

Inclusion criteria were: patients aged from 18 to 65 years and signed informed consent.

Exclusion criteria were: patients with diagnosed diabetes mellitus, evidence on acute infection in the last 2 weeks, positive biohumoral inflammatory syndrome and [accelerated ESR and leukocytosis with higher C-reactive protein (CRP) and fibrinogen level], use of medicaments that may interfere with studied parameters (glucocorticoids, iodine preparations, amiodarone, diuretics, lithium, cytostatics, antidepressants, estrogens, androgens), chronic diseases that may have effect on studied parameters (systemic autoimmune diseases, malignant diseases, chronic renal failure, liver insufficiency, acute coronary syndrome and stroke within the last 6 months), recent use of radioactive iodine, thyroid surgery and external neck radiation, pregnancy and breast feeding.

The initial study phase involved the collection of history data and thorough physical examination. Blood pressure was measured on both hands by indirect method over brachial artery in a patient assuming sitting position after 15 min of rest, using the mercury sphygmomanometer and listening to phases I and IV of Korotkoff sounds. The following measurement was done after 10 min on patient's hand showing the highest values. Mean values obtained from two measured systolic and diastolic pressure values were used. Waist circumference was measured with a patient

assuming standing position at the midline between costal arch and anterior superior iliac spine. Body mass index (BMI) was calculated as a quotient of body mass (kg) and body height (m^2) (Quetelet index). Blood samples collected after 12 hr fasting were used for the following measurements: fasting glycemia (adjustment method to dry chemistry principle), cholesterol, triglycerides, LDL, dHDL (colorimetric method based on end-point principle). TSH and FT4 were determined by immunochemical method – chemiluminescent procedure including chemiluminescent substrate. The method was automated (IMMULITE® DPC).

Reference values for: TSH were 0.27–4.20 mU/mL and FT4: 10–22 pmol/L, variation coefficient fT4: 6.20%, TSH: 5.50%. FT3 hormone was measured by enzyme-linked fluorescence assay (ELFA) using miniature VIDAS immunochemical analyzer. Reference values were 4.00–8.30 pmol/L, variation coefficient: 5.30%. Reference values for HDL cholesterolwere 40–50 mg/dL in men 50–60 mg/DL in women.

Forming study group: criterion to be enrolled in the SH group and in the controls was TSH > 4.2 IU/mL and TSH ≤ 4.2 UI/mL, respectively.

Diagnosis of MetS was based on the International Diabetes Federation (IDF) criteria. Central obesity was required condition (among European population, it is defined as waist circumference larger than 94 cm and 80 cm in males and females, respectively) plus any of two following factors: blood pressure higher than 130/85 mmHg or treated arterial hypertension which was previously diagnosed; triglycerides over 1.7 mmol/L or specific treatment of this lipid abnormality; HDL cholesterol lower than 1.03 mmol/L and 1.29 mmol/L in males and females, respectively, or specific treatment of this lipid abnormality; morning fasting plasma glucose (FPG) > 5.6 mmol/L or previously diagnosed T2DM.

Before starting statistical analysis, laboratory reports with the patients' results of analyses were anonymized and they all were granted identification numbers (for protection of patient privacy, while patient data were known only to investigators). Electronic database was created using the program SPSS version 20.0. Mean, standard deviation (SD), median, minimum and maximum as well as normal distribution of all studied continuous variables (normal distribution of values within the group was analyzed by Kolmogorov-Smirnov test) were determined. To compare the mean values of continuous variables, we used repeated-measures unifactorial ANOVA (non-parametric Kruskal Wallis test, alternative to Variance analysis F test) and dependent sample t-test in normal distribution, or alternatively, Mann-Whitney U-test (non-parametric test, alternative to t-test), and Wilcoxon matched pairs test for outcomes not following normal distribution, as well as χ^2 test for comparison of frequency of categorical (dichotomous) variables. $p < 0.05$ was statistically significant, with 95% confidence interval.

Results

Out of 105 subjects with SH, mean age 44.15 ± 11.23 years, 77 (73.3%) patients had MetS. In the control group consisting of 35 subjects, mean age 33.80 ± 10.60 years, only 3(8.6%) subjects had MetS. Accordingly, the frequency of MetS was nine times higher in the SH subjects.

Out of 77 subjects with SH and MetS, there were 72 (93.5%) females and 5 (6.5%) males. The number of women was significantly higher than men ($\chi^2 = 58.299$, $p < 0.0001$). Out of 97 females with SH, 72 (74.2%) had SH and MetS, and among a total of 8 males with SH there were 5 (62.5%) with SH and MetS. Testing of distribution of female subjects according to groups formed in relation to presence of SH and MetS confirmed a significant difference ($p < 0.0001$) while no significant difference was found between males.

Table 1 shows mean values ± standard deviation, and the results of analysis of variance (ANOVA test), as well as the result of testing the differences of mean values by Student's t-test of studied parameters both in the experimental and the control group.

Mean values of the waist circumference, morning fasting plasma glucose, parameters of lipidogram, systolic and diastolic blood pressure were higher in the SH group in comparison to the controls ($p < 0.0001$). Mean HDL-cholesterol value was significantly lower in the SH group as compared to the controls ($p < 0.05$).

Discussion

The study found that the frequency of MetS was nine times higher in the SH subjects in relation to the subjects without SH. Our results indicate that MetS should be actively searched for in the SH patients.

The patients with the SH might not be identified by symptoms and signs even if they were discreetly present. Higher frequency of SH in females than in males and older people in relation to younger age group was corresponding to higher incidence of thyroglobulin and thyroperoxidase antibodies in women and elderly people [27, 28]. In our study of 105 subjects with SH, 97 (92.4%) were women.

The relationship between SH and CVD has been examined in many studies. A more recent review of the clinical consequences of thyroid function variations within the normal reference range documented that even modest elevations of TSH might have substantial health outcomes, including cardiovascular mortality [16]. Ten-year follow-up of Korean cohort revealed that elevated serum TSH levels significantly increased the risk of CVD by approximately 20% per one standard deviation in males [7].

Studies of euthyroid individuals found positive association between the TSH levels and coronary heart disease (CHD)-related mortality [29]. The TSH levels within the normal range are inversely associated with all-cause mortality [18, 30–33]. Adult Taiwanese subjects with SH were reported to have an increased risk of all-cause mortality and CVD death over a 10-year period [34]. However, some other studies failed to establish any association with all-cause or cardiovascular mortality rates [35–39]. Such discrepancy of findings could result from different sample size and power, the inconsistent age and sex ratios of study population or varied iodine intake in different regions.

Table 1

Descriptive statistics of selected parameters in relation to groups with and without hypoparathyreoidism (SH)

Parameters	Experimental with SH		Controls without SH		p	Test
	mean ± stand. deviation	median	mean ± stand. deviation	median		
Age (years)	44.15 ± 11.23	43.00	33.8 ± 10.6	33.00	0.0001	2
Waist circumference (cm)	90.88 ± 11.53	90.00	77.66 ± 8.24	77.00	0.0001	1
Body height (cm)	166.47 ± 7.74	166.00	171.14 ± 8.99	170.00	0.004	1
Body mass (kg)	80.18 ± 14.26	80.60	65.81 ± 10.42	63.80	0.0001	1
Body mass index	28.89 ± 5.02	28.41	22.35 ± 2.11	22.97	0.0001	1
FT3 (pmol/L)	4.98 ± 0.86	4.96	4.71 ± 0.64	4.77	ns	1
FT4 (pmol/L)	14.45 ± 2.37	14.32	14.94 ± 2.38	14.90	ns	1
TSH (mIU/ml)	6.87 ± 1.34	6.67	1.9 ± 0.88	1.62	0.0001	2
Morning fasting glycemia (mmol/L)	5.42 ± 0.74	5.30	4.98 ± 0.47	4.95	0.001	1
Total cholesterol: mmol/L	6.06 ± 0.88	6.00	4.98 ± 1.06	4.83	0.0001	1
Triglycerides (mmol/L)	2.17 ± 0.84	2.15	1.22 ± 0.51	1.14	0.0001	2
HDL cholesterol (mmol/L)	1.23 ± 0.33	1.15	1.39 ± 0.29	1.38	0.013	1
LDL cholesterol (mmol/L)	3.98 ± 0.79	3.94	3.04 ± 0.97	3.01	0.0001	2
Arteriosclerotic index: LDL-C/HDL-C	3.43 ± 1.21	3.27	2.33 ± 1.01	2.26	0.0001	2
Relation: TC/HDL-C	5.25 ± 1.6	5.00	3.75 ± 1.19	3.60	0.0001	2
Systolic BP (mmHg)	138.48 ± 16.96	120.00	119 ± 11.49	140.00	0.0001	1
Diastolic BP (mmHg)	92.38 ± 10.61	80.00	78.29 ± 7.47	100.00	0.0001	2

SH– subclinical hypothyreoidism; FT3 – free triiodothyronine; FT4 – free thyroxine; TSH – thyroid stimulating hormone; LDL-C – low density lipoprotein-cholesterol; HDL-C – high density lipoprotein-cholesterol; TC – total cholesterol; BP – blood pressure; 1 – ANOVA F-test; 2 - Kruskal Wallis test, ns – not statistically significant.

In the study, SH was associated with the increased cardiovascular risk. Mean values of the waist circumference, morning fasting plasma glucose, triglycerides, systolic and diastolic blood pressure were higher in the SH group than in the controls ($p < 0.0001$). Mean values of HDL-cholesterol were lower in the SH group in comparison to the controls ($p < 0.002$).

Cardiometabolic risk is a comprehensive risk of T2DM and CVDs, as a result of co-effect of multiple risk factors such as atherogenic dyslipidemia, impaired glucose tolerance, hypertension, augmented intra-abdominal fat tissue as well as the presence of prothrombotic and proinflammatory conditions. This human population is exposed to two times higher risk of death as well as to acute myocardial infarction, that is, the frequency of having acute myocardial infarction and stroke is as high as three times. The frequency of T2DM development is five times higher in people with MetS [22, 40].

There is currently controversial data regarding the prevalence of MetS among the SH patients. The geographic location, age, gender, diet, intake of iodine and other genetic and environmental factors might possibly account for these discrepancies in patterns and relationships.

Our study shows a high prevalence of MetS in patients with SH. The results of meta-analyses of Yang et al. [41] demonstrated that SH was significantly associated with a higher risk of MetS. Lai et al. [42] found the subclinical thyroid dysfunction was present in about 8% of Taiwanese elderly population, one-third of whom had MetS. According to Pangaluri et al. [43], 43.3% of the SH patients were found to satisfy the criteria for MeTS. In a cross-sectional study, Choudhary and Iani [44] found that the overall prevalence of thyroid dysfunction in patients with MetS was 41.5% with a high prevalence of SH (27%). In a Nigerian study, Udenze et al. [45] found that a third of patients with MetS had SH. Similar results were published by Gyawali et al. [46] in their Nepalese study. In a study conducted in South India, Agarwal et al. [47] found that 76 (53%) women with MetS had SH.

However, in a study in Turkey, TSH was not related to any MetS [48].

Moreover, cross-sectional and longitudinal follow-up studies from Japan noted high associations between SH and MetS [49]. One cross-sectional analysis of cohort studies emphasized that the probability of having MetS was positively associated with TSH levels within the reference range [16].

Upon their systemic review, Iwen et al. [50] documented convincing evidence supporting the major impact of SH on all MetS components. In addition, another study of 2,760 young Korean female volunteers with normal TSH levels established that the high-TSH group had two-fold higher risk of MetS compared to subjects in the low-TSH group [51].

Conclusion

The results of our study suggest that patients with the subclinical hypothyroidism, although having a moderate

form of thyroid dysfunction, represent a whole category of people with the increased cardiovascular risk, and, consequently, metabolic syndrome should be searched for in any of these patients. Proper timing and precise identification of cardiometabolic risk in patients with the subclinical hypothyroidism opens up the opportunities for specific therapeutic interventions directed against individual atherogenic risk factors.

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