The Effect of Subclinical Hypothyroidism on Blood Pressure

Narges Maleki, MSc1; Faranak Kazerouni, PhD1; Mehdi Hedayati, PhD2; Ali Rahimipour, PhD1; Mohammad Hassan Maleki, PhD3

From 1Department of Medical Laboratory Sciences, Faculty of Paramedical Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran; 2Cellular and Molecular Research Center, Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran; 3Department of operation management, Faculty of management, University of Qom, Qom, Iran.

ABSTRACT: Objectives: Overt hypothyroidism is associated with hypertension and dyslipidemia, but there is uncertainty as to whether the same is true of subclinical hypothyroidism (SCH). This study aimed to investigate alterations of blood pressure and lipid profile in patients with SCH as compared to age- and sex-matched controls. Methods: Thirty-four patients with SCH and 34 control individuals without SCH were enrolled in this study. In all participants we determined thyroid function, systolic and diastolic blood pressure, total cholesterol (TC), low density lipoprotein-cholesterol (LDL-C), high density lipoprotein-cholesterol (HDL-C), triglyceride (TG) and a ratio of TC/HDL-C. Results: Diastolic blood pressure (DBP), a main risk factor for cardiovascular disease, was significantly higher in the patients vs the controls (P<.001). In the SCH group, there was an elevated TC (P <.01) and LDL-C (P <.01) concentration and a borderline elevated TG (not reaching the limit of significance, P =.063), whereas there were no significant differences in the mean values of systolic blood pressure (SBP), HDL-C, TC/HDL-C ratio and body mass index between the two groups. Serum T4 levels were negatively correlated with SBP (P <.05) and DBP (P <.001). Significant negative correlation was also found between triiodothyronine values and diastolic blood pressure (P <.01). Conclusion: Our findings suggest that patients with SCH are at higher risk of hypertension and dyslipidemia as compared to the controls.

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Thyroid hormones have several well-recognized effects on the cardiovascular system, including decreased systemic vascular resistance (SVR) and increased resting heart rate, left ventricular contractility, and blood volume.1,2 It has long been known that some of the most characteristic and common signs and symptoms of thyroid dysfunction are those that result from the profound effects of thyroid hormones on the heart and peripheral vasculature.3 Overt hypothyroidism (OH), with its accompanying dyslipidemia and hypertension, has been known to be associated with cardiovascular disease (CVD).4,5 In these patients, increased SVR in association with decreased arterial compliance results
in elevated diastolic blood pressure (DBP). Subclinical hypothyroidism (SCH), defined as an asymptomatic state characterized by elevated serum thyroid-stimulating hormone (TSH) values with normal thyroxine (T4) and triiodothyronine (T3) levels, is common in the adult population, especially among women above 60 years of age.\textsuperscript{6,7} Certain studies have indicated that SCH has been associated with increased risk of CVD.\textsuperscript{8-10} Lipid abnormalities would suggest the most obvious explanation for this association. Some studies have reported conflicting results regarding the presence or the severity of dyslipidemia in SCH.\textsuperscript{11,12} Furthermore, blood pressure alterations may be responsible for the association between SCH and CVD. The presence of hypertension has also been investigated in certain studies, although the results are not consistent.\textsuperscript{13,14}

In the present study, we aimed to investigate alterations of blood pressure and lipid profile, which are major risk factors for CV disorders, in the patients with SCH compared with healthy euthyroid individuals.

**METHODS**

We selected 34 newly diagnosed SCH cases among the patients who were referred by the physicians to the endocrine clinic of Taleghani Hospital and also Endocrine Research Center and 34 age- and sex-matched healthy controls without any thyroid hormone abnormality from the general population according to the inclusion and exclusion criteria mentioned below. Diagnosis of SCH was based on abnormal elevation of TSH levels in the presence of normal thyroid hormone levels.

Inclusion criteria were newly diagnosed individuals with SCH based on a TSH level between 6 µIU/mL and 10 µIU/mL and normal T4 value 4.9-12.5 µg/dL. Age- and sex-matched euthyroid subjects had normal TSH and T4 values. Excluded from the study were patients with history of diabetes mellitus or other endocrine disease such as polycystic ovary syndrome, renal and hepatic dysfunction, heart failure, stroke or ischemic heart disease or other systemic disease, primary or secondary dyslipidemia and hypertension in any of the participants included in the study. Subjects were taking lipid- and pressure-lowering drugs, were smokers, and had known hypothyroidism; previous radioactive iodine therapy and consumption of drugs known to cause SCH such as methimazole were excluded from the study. The Research Ethic Committee of Shahid Beheshti University of Medical Sciences approved the protocol of the study, and all subjects gave informed consent.

**LABORATORY PROCEDURES**

After an overnight fasting period, blood samples were drawn with minimal trauma from an antecubital vein. The samples were centrifuged for 5 minutes at 3,000 rpm, and sera were separated. The serum samples were immediately stored at −20° C until assayed. Thyroid profile was assessed by estimation of serum TSH, T3, and T4 that were measured by the enzyme-linked immunosorbent assay (ELISA) method using commercial kits (Diaplus Inc.). The intra-assay coefficient of variations (CVs) for T3, T4, and TSH were 4.1%, 4.1%, and 4.2%, respectively. The interassay CVs were 4.3%, 5.2% and 4.6%, respectively. The sensitivity of the assay was 0.4 ng/dL, 0.4 µg/dL and 0.078 µIU/mL, respectively. The normal range for TSH is 0.39 µIU/mL to 5.95 µIU/mL and for T3 and T4 the normal ranges are 55 ng/dL to 200 ng/dL and 4.9 µg/dL to
12.5 µg/dL, respectively.

Serum levels of total cholesterol (TC), triglyceride (TG), and high-density lipoprotein cholesterol (HDL-C) were measured using a spectrophotometric assay with commercial kits (Pars Azmoon) at 546 nm. Intra-assay CVs for TC, TG, and HDL-C were 1.4%, 1.61% and 1.04% respectively. Low-density lipoprotein cholesterol (LDL-C) was calculated using the Friedewald formula:

\[
LDL \text{ cholesterol} = TC - HDL \text{ cholesterol} - \frac{1}{5} \times \text{TG concentration}
\]

Body mass index (BMI) was calculated as weight (kg) divided by height squared (m²). Systolic and diastolic blood pressure values were measured twice on the right hand using a standard random-zero sphygmomanometer while participants were in a seated position. There was a 3-min interval between the two measurements for each participant and the mean value of the two measurements was used. In the case of hypertension (≥140/90 mmHg), the measurement was repeated after 5 minutes.

**STATISTICAL ANALYSIS**

Data were presented as mean ± standard deviation.
Normality of the data was tested using the Kolmogorov-Smirnov test. The independent t test was used to compare the mean values between cases and controls. The Pearson correlation test was applied to assess the relationship between thyroid hormones and blood pressure parameters. P value of less than .05 was considered statistically significant at a 95% confidence interval. All statistical analyses were performed using the statistical package for social sciences (SPSS) version 22.

**RESULTS**

No differences were found between the patients with SCH and the controls with respect to age and gender (36.20 ± 9.77 vs 36.38 ± 9.62, P=.940). There were 30 (88.23%) females and 4 (11.76%) males in each group of participants.

The biochemical characteristics of subjects are summarized in Table 1. As shown, TSH levels were significantly higher in the SCH groups compared to the healthy control group (7.13 µIU/mL ± 3.43 µIU/mL vs 2.55 µIU/mL ± 1.36 µIU/mL, P<.001). Concentrations of T4 were significantly lower in the SCH patients (5.06 µg/dL ± 2.19 µg/dL vs 6.02 µg/dL ± 1.18 µg/dL, P<.05), while there was no significant difference in T3 levels between the two groups (P=.855).

A statistically significant increase was observed in DBP (87.67 mmHg ± 8.37 mmHg vs 80.57 mmHg ± 6.32 mmHg, P<.001) in the subclinical hypothyroid patients in comparison to the healthy controls. Patients with SCH also had significantly higher levels of TC (198.88 mg/dL ± 42.90 mg/dL vs 171.40 mg/dL ± 26.24 mg/dL, P<.01) and LDL-C (129.04 mg/dL ± 35.44 mg/dL vs 106.71 mg/dL ± 26.21 mg/dL, P<.01) compared with the controls, whereas systolic blood pressure (SBP) (115.29 mmHg ± 7.60 mmHg vs 112 mmHg ± 7.76 mmHg, P=.08), HDL-C (40.48 mg/dL ± 12.46 mg/dL vs 39.12 mg/dL ± 8.76 mg/dL, P=.60), ratio of TC:HDL-C (5.18±2.50 vs 4.71±1.29, P=.335) and BMI (24.45±1.33 vs 23.99±1.21, P=.146) did not differ significantly between the two groups. Serum concentrations of triglycerides was higher in the SCH patients when compared to the controls, although not reaching the limit of significance (146.76 mg/dL ± 71.70 mg/dL vs 119.44 mg/dL ± 38.53 mg/dL, P=.063).

The Pearson correlation coefficients for the relationships between thyroid hormones levels and blood pressure parameters are shown in Table 2. This study showed that T4 levels were inversely correlated with SBP (r=−.270, P<.05) and DBP (r=−.650, P<.001) (Figure 1). Levels of T3 showed a significant inverse
correlation with DBP \((r=−.344, P<.01)\) (Figure 2). Based on these results, TSH was not significantly correlated with blood pressure parameters.

**DISCUSSION**

Overt hypothyroidism has been found to be associated with accelerated atherosclerosis and increased risk of CVD.\(^8\) However, studies concerned with the association between SCH and CVD have controversial results.\(^{16-18}\) Some studies have associated this subtle change in thyroid function with increased risk of CVD. Hak et al revealed that SCH is a strong indicator of risk for atherosclerosis and myocardial infarction in elderly women.\(^8\) Meanwhile, Völzke et al revealed that the current evidence for the association of SCH with mortality is weak.\(^{18}\) Increased risk of atherosclerosis and CV disorders in SCH can be attributed primarily to dyslipidemia. Inconsistent results have been reported in the literature regarding the association between SCH and lipid abnormalities. Some studies reported an atherogenic disturbance in the lipid metabolism in patients with SCH,\(^{19-21}\) whereas other studies did not.\(^{22,23}\) These inconsistent results might be due to differences in terms of cause and duration of SCH, sex, and age of patients, as well as differences in population evaluated.

In the present study, the TC and LDL-C levels were found to be significantly higher in the SCH patients than the controls, which is in concordance with Erem et al.\(^{24}\) The data showing elevated TC and LDL-C in SCH provide a possible pathophysiologic explanation for the reported association of CVD with SCH, and could suggest the necessity of measurement of serum TSH values in the screening of patients with dyslipidemia.

The primary mechanism for hypercholesterolemia in hypothyroidism is an accumulation of LDL cholesterol due to the reduction in the number of cell surface receptors for the LDL and the decreased activity of these receptors, resulting in decreased catabolism of LDL.\(^{25}\)
Previous studies have shown more conflicting results concerning the HDL-C values in SCH. In this regard, HDL-C has been found to be low\textsuperscript{26,27} or unchanged\textsuperscript{21} in SCH. Kung et al\textsuperscript{28} reported lower levels of HDL-C in SCH patients compared with healthy controls. In contrast, we found no effect of SCH on HDL-C. Several studies have reported increased TG levels related to SCH.\textsuperscript{12,29} Luboshitzky et al concluded that SCH in middle-aged women is associated with hypertriglyceridemia and elevated TC/HDL-C ratio.\textsuperscript{4} However, there have been studies showing no significant differences between SCH patients and healthy controls regarding TG levels.\textsuperscript{11} The data in this study revealed that fasting TG levels did not show a significant difference in the SCH patients compared to the control group, although they did have a tendency to increase. The small sample size in our study and the short duration of the patients’ illness state may be possible reasons for the insignificance of this observation. Furthermore, hypothyroidism may contribute to the development of atherosclerosis by other mechanisms such as hypertension. Hypothyroidism has long been presumed as one of the secondary causes of hypertension.\textsuperscript{30}

As mentioned above, hypertension, most commonly diastolic, is increased in patients with hypothyroidism because of increased SVR. The putative associations between SCH and hypertension are not well established and in this regard, data are scarce and controversial.\textsuperscript{14} In the past few years, some studies reported higher DBP, or higher prevalence of hypertension in SCH subjects,\textsuperscript{4,13} whereas others reported no association of SCH and hypertension.\textsuperscript{14,31,32} Duan et al demonstrated that SCH is an independent predictor of increased SBP and pulse pressure in females.\textsuperscript{33} Consistent with Nagasaki et al, the data in this revealed that subjects with SCH had a higher DBP than the euthyroid subjects.\textsuperscript{33} It has been revealed that serum TSH concentrations are positively associated with increasing BMI.\textsuperscript{34} However, in accordance with Garduno-Garcia et al, our data showed no difference in BMI between the SCH and euthyroid subjects.\textsuperscript{35} This finding suggests that the elevation of DBP may be independent of BMI. Pyati et al revealed that serum TSH values were positively correlated with DBP.\textsuperscript{36} Even within the range of TSH that is considered clinically normal, Asvold et al reported a linear positive correlation between TSH and both systolic and diastolic blood pressure.\textsuperscript{37} Conversely, the results of this study showed no significant correlation between TSH and blood pressure. However, this study revealed an increasing trend of DBP as thyroid function declined. In this respect, study investigators observed inverse correlations between thyroid hormones and blood pressure parameters suggesting that the lower the thyroid hormone levels, the higher blood pressure that may predispose to the long-term implications for CV health.

As a novel vasodilator, thyroid hormones directly affect the vascular smooth muscle cells that promote relaxation and decreased SVR.\textsuperscript{38} Conversely, hypothyroidism promotes contraction of these cells thereby increasing SVR, which might be an explanation for this observation.\textsuperscript{39} Therefore, in the initial evaluation of the hypertensive patients, secondary hypertension based on thyroid dysfunction should always be considered. Some studies suggest that substitution therapy with L-thyroxine in SCH may relieve certain symptoms of hypothyroidism, improve lipid levels, prevent progression to OH, and potentially decrease CVD events and
mortality. However, there is currently no consensus on the treatment benefit in subjects with SCH, and this remains to be proven in randomized controlled studies.

In conclusion, the data from the present study revealed that TC and LDL cholesterol levels as well as DBP were significantly higher in the SCH patients as compared to the healthy subjects. The results suggest that patients with SCH are at higher risk of dyslipidemia and elevated blood pressure as compared to the controls. On this basis, screening and treatment of dyslipidemia and hypertension in these patients could be useful in decreasing risk of atherogenic CV disorders at a very early stage. Large population-based studies are needed to confirm these findings; it is also essential to consider the associated genetic factors related to SCH and dyslipidemia in further studies.

Editor’s note: The authors have completed and returned the ICMJE Form for Disclosure of Potential Conflicts of Interest. The authors report no financial relationships or conflicts of interest regarding the content herein.

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Address for correspondence: Faranak Kazerouni, PhD, Department of Medical Laboratory Sciences, Faculty of Para-medical Sciences, Shahid Beheshti University of Medical Sciences, Medical Laboratory Sciences, Tehran, Iran. Email: f.kazerouni@sbmu.ac.ir

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