Subclinical Hypothyroidism and the Alterations of Lipid Profile as a Cardiovascular Risk Factor

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ABSTRACT

The association between overt hypothyroidism and altered lipid profile is well known, whereas the significance of dyslipidemia in subclinical hypothyroidism (SCH) is still a matter of debate. The aim of the present study was to evaluate the lipid profile in patients with SCH in comparison to controls. Serum lipid parameters of 34 patients with SCH and 34 age- and sex-matched healthy controls were evaluated in our study. TC (198.88 ± 42.90 vs 171.40 ± 26.24 mg/dl, $P < 0.01$) and LDL-C concentrations (129.04 ± 35.44 vs 106.71 ± 26.21 mg/dl, $P < 0.01$) as well as ratio of LDL-C/HDL-C (3.51 ± 1.46 vs 2.81 ± 0.80, $P < 0.05$) were significantly higher in the patients in comparison to the controls, whereas HDL-C and TC/HDL-C ratio remained unaltered. TG concentrations were higher in the patients but this difference did not reach statistical significance (0.063). Correlation analyses revealed a significant correlation of TSH with TC, LDL-C and LDL-C/HDL-C ratio (r=0.351, r=0.345, r=0.340, respectively, $P < 0.01$) and a borderline correlation with TG (p=0.051). Our findings showed that SCH is associated with some lipid abnormalities suggesting higher risk of cardiovascular disease in these patients which seems to weigh in favor of treatment of patients with SCH.

Keywords: Subclinical Hypothyroidism; Lipid Profile; Cardiovascular Disease

INTRODUCTION

Subclinical hypothyroidism (SCH), also called mild thyroid failure, is characterized by elevated levels of serum thyroid stimulating hormone (TSH) in the presence of normal thyroxine (T4) and triiodothyronine (T3) levels [1]. This condition is one of the most common endocrine disorders that occur in 4 to 20 percent of the general population [2]. The prevalence increases with age and is higher in women [3]. SCH has clinical significance because of its high prevalence, the risk of progression to overt hypothyroidism (OH), poor quality of life related to nonspecific symptoms and potential consequences including neurobehavioral and cardiovascular disorders [4, 5]. Cardiovascular outcome in these patients is partly due to its association with unfavorable lipid profile. Thyroid hormones have varied effects on lipid metabolism, because thyroid function regulates lipids synthesis and degradation and mediates the activity of key enzymes in these pathways [6, 7]. The association between OH and dyslipidemia is well known [6], which may predispose to the development of cardiovascular disease (CVD), however it is uncertain whether SCH is also associated with lipid abnormalities [1, 8, 9]. Substantial studies on the association between SCH and lipid abnormalities have been conducted but results from these studies are not consistent [10]. In this respect, it has been reported that SCH is associated with increased levels of total cholesterol (TC), low density lipoprotein-cholesterol (LDL-C) and triglyceride (TG) [11, 12] and decreased levels of high density lipoprotein- cholesterol (HDL-C) [13]. However, some of the literature has reported no difference in the lipid parameters between SCH and healthy subjects [14]. The decision about whether to screen patients for this disorder is clouded by inconsistent evidence of association of lipid abnormalities or other risk factors of CVD with

SCH. In the presence of dyslipidemia, screening and treatment for SCH has been suggested to prevent CVD [4].

The aim of the present study was to assess the effect of SCH on fasting serum lipids in patients with SCH.

MATERIALS AND METHODS

Subjects

Thirty-four newly diagnosed SCH patients (30 women and 4 men) aged 36.20 ± 9.77 years from the endocrine clinic of Taleghani Hospital and Endocrine Research Center, and 34 sex- and age-matched euthyroid healthy controls were included to the study according to the inclusion and exclusion criteria mentioned below. Diagnosis of SCH was based on the finding of high TSH levels associated with normal T4 levels.

Inclusion criteria

Newly diagnosed individuals with SCH based on TSH level between 6-10µIU/ml and normal T4 value 4.9-12.5 µg/dl. Age and sex matched euthyroid subjects having normal TSH and T4 values.

Exclusion criteria

The patients who were diagnosed as hyperthyroid and hypothyroid were not included in this study. None of the participants was diagnosed with 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 diseases, primary or secondary dyslipidemia. Subjects receiving drugs known to cause SCH and affect lipid metabolism were excluded from the study. The protocol of study was approved by the Research Ethic Committee of Shahid Beheshti University of Medical Sciences and after a clear explanation of the study protocol. Each participant gave a written informed consent to participate.

Laboratory Procedures

After 12 hours overnight fasting, blood samples were collected from all participants for measuring biochemical parameters. The samples were immediately centrifuged at 3000 rpm for 5 min and serum was separated. The sera were stored at -20° C until assayed.

Serum T3, T4 and TSH levels were measured by the enzyme-linked immunosorbent assay (ELISA) method using commercial kits (Diaplus INC, USA). The intra-assay coefficient of variations (CVs) for T3, T4 and TSH were 4.1%, 4.1%, and 4.2%, respectively, and the inter assay 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 0.39-5.95 µIU/ml and for T3 and T4 are 55-200 ng/ dl and 4.9-12.5 µg/ dl, respectively. Serum levels of TC, TG and HDL-C were measured using a spectrophotometric assay with commercial kits (Pars Azmoon, Tehran, Iran) at 546 nm. Intra assay CVs for TC, TG and HDL-C were 1.4%, 1.61% and 1.04%, respectively. Serum levels of TC and TG were determined by enzymatic colorimetric assay using CHOD-PAP and GPO-PAP method, respectively. HDL-C was determined enzymatically in the supernatant after dextran–magnesium-induced precipitation of other lipoproteins. LDL-C was calculated using the Friedewald formula: LDL-C= serum total cholesterol –HDL cholesterol – one-fifth of the TG concentration [15]. The TC-to- HDL-C and LDL-C- to- HDL-C ratios were also calculated.

Statistical Analysis

All data were presented as mean± standard deviation and were evaluated with the Kolmogrov-Smirnov test for normality. Independent- t test was used for the comparison of mean values between control and patient groups. Pearson's correlation coefficient was used to evaluate the correlations between two variables. For all the tests, p-value less than 0.05 was considered as statistically significant. Statistical analyses were conducted using the Statistical Package for Social Sciences (SPSS) version 22.

RESULTS

In this study, 34 patients with SCH and 34 healthy subjects were analyzed. They were 36.20 ± 9.77 vs 36.38 ± 9.62 years old. There were not any differences in age (P=0.940) and gender between SCH and control group. The results of TSH, T3 and T4 are summarized in Table1. As seen, compared with the healthy control group, TSH level was significantly higher in the SCH patients (7.13 ± 3.43 vs 2.55 ± 1.36 µIU/ ml, P < 0.001). T4 concentrations was significantly (P=0.026) lower in the patients, while T3 levels showed no significant difference in the SCH patients compared with the healthy subjects (P = 0.855). Differences in lipid status between SCH and control group are shown in Table 2. Subjects with SCH had significantly higher levels of TC and LDL-C as compared with the healthy individuals (198.88 ± 42.90 vs 171.40 ± 26.24 mg/dl, 129.04 ± 35.44 vs 106.71 ± 26.21 mg/dl, respectively, P<0.01). LDL-C/HDL-C ratio was

also higher in the patients compared with the controls (3.51 ± 1.46 vs 2.81 ± 0.80, P<0.05). Serum concentrations of TG were higher in the SCH patients when compared with the controls, but this differences did not reach the limit of significance (P= 0.063). There were no significant differences in HDL-C and ratio of TC/ HDL-C between patients with SCH and controls (P = 0.602, P= 0.335, respectively).

The Pearson's correlation coefficients for the relationships between TSH and lipid parameters are shown in Table 3. Our study showed that TSH levels were positively correlated with TC, LDL-C and ratio of LDL-C/HDL-C (r=0.351, r=0.345, r=0.340, respectively, for all cases P=0.004). Moreover, we also observed borderline association between TG levels and TSH (r=0.251, P=0.051). TSH was not significantly correlated with HDL-C and ratio of TC/ HDL-C.

Table 1. Hormonal status of the subclinical hypothyroidism patients and healthy controls

Variable	Subclinical hypothyroid subjects	Control subjects	P value
TSH, µIU/ml	7.13 ± 3.43	2.55 ± 1.36	0.000**
T4, µg/dl	5.06 ± 2.19	6.02 ± 1.18	0.026*
T3, ng/dl	97.12 ± 26.15	98.15 ± 20.53	0.855

Data are expressed as mean ± standard deviation. TSH: thyroid-stimulating hormone; T4: tetraiodothyronine; T3; triiodothyronine.
*Statistically significant.
* P<0.05, **P <0.001.

Table2. Lipid parameters of the groups involved in the study

Variable	Subclinical hypothyroid subjects	Control subjects	P value
Age, years	36.20 ± 9.77	36.38 ± 9.62	0.940
TC, mg/dl	198.88 ± 42.90	171.40 ± 26.24	0.003**
LDL-C, mg/dl	129.04 ± 35.44	106.71 ± 26.21	0.004**
HDL-C, mg/dl	40.48 ±12.46	39.12 ± 8.76	0.602
TG, mg/dl	146.76 ± 71.70	119.44 ± 38.53	0.063
LDL-C/HDL-C ratio	3.51 ± 1.46	2.81 ± 0.80	0.018*
TC /HDL-C ratio	5.18 ± 2.50	4.71 ± 1.29	0.335

Data are expressed as mean ± standard deviation. TC: total cholesterol; LDL-C: low density lipoprotein- cholesterol; HDL-C: high density lipoprotein- cholesterol; TG: triglyceride.
*Statistically significant.
* P<0.05, ** P <0.01.

Table 3. Correlation between lipid parameters and TSH

Variable	TSH	
	r values	p value
TC	0.351	0.004*
LDL-C	0.345	0.004*
HDL-C	-0.025	0.841
TG	0.251	0.051
LDL-C/HDL-C ratio	0.340	0.004*
TC/HDL-C ratio	0.197	0.105

TSH: thyroid-stimulating hormone; TC: total cholesterol; LDL-C: low density lipoprotein- cholesterol; HDL-C: high density lipoprotein- cholesterol; TG: triglyceride.
*Statistically significant. P <0.01.

DISCUSSION

OH is associated with increased risk of CVD [16], while evidence regarding the association of SCH and the risk of CVD appear conflicting in previous studies [16-22]. Increased risk for atherosclerosis and CV disorders in hypothyroidism can be attributed primarily to dyslipidaemia. Although there was a clear relationship between dyslipidemia and OH [6], the significance of dyslipidemia in SCH especially in subjects with serum TSH levels less than 10 µIU/ ml remains controversial [1, 23]. Some studies reported higher levels of TC or/and LDL-C in SCH subjects [24, 25], whereas others demonstrated no association of SCH and increased levels of TC and LDL-C [9,

14]. These conflicting reports in the literature may be a result of differences in sex and age of patients and, the degree and duration of hypothyroidism, as well as differences in population studied. The Colorado Study revealed that patients with SCH had significantly higher TC and LDL-C concentrations compared with euthyroid subjects [26]. Consistently, findings from Tromso Study showed increased levels of LDL-C in SCH subjects [27]. In line with the above, results from several smaller studies demonstrated an association between unfavorable lipid profile and SCH [12, 28, 29]. As in previous studies, our data revealed that patients with SCH had increased TC and LDL-C levels compared with age and sex matched healthy subjects. Elevation of serum LDL-C and TC is due to decreased cholesterol excretion and mainly to impaired clearance of LDL, probably reflecting decreased LDL receptor expression [30]. By contrast, National Health and Nutrition Examination Survey III (NHANES III) reported no significant differences in lipid parameters in subjects with SCH compared with euthyroid individuals when adjusted for age and sex and the use of lipid-lowering agents [31]. The LDL-C/HDL-C ratio is a better predictor for risk of heart disease than LDL-C alone [32]. In this regard, our data showed elevated LDL-C/ HDL-C ratio in the SCH patients compared with the controls which is in agreement with Althaus et al study [33]. Luboshitzky et al concluded that SCH in middle-aged women is associated with hypertriglyceridemia and elevated TC/HDL-C ratio [8]. In contrast, our data showed no significant difference in TC/HDL-C ratio between SCH patients and controls. Some studies have indicated that SCH dyslipidemia may also be accompanied by increased TG levels [13]. In hypothyroidism, lipoprotein lipase activity in the adipose tissue has been shown normal or decreased, in addition to decreased hepatic lipase activity resulting in normal or increased levels of TG [34]. Toruner et al [11] have reported that the TG concentrations of SCH patients are higher than control subjects. As in previous studies, our data revealed that patients with SCH had higher TG levels compared with the healthy subjects but did not reach to the statistical significance. Small size of samples and short duration of illness state may be possible reasons for insignificancy of our result. There is also conflicting data with regard to the effect of SCH on HDL-C levels, since normal [1] as well as decreased levels [35] have been reported. Our data showed that the SCH and control groups did not differ in their HDL-C values. Elevated serum TSH values may be a risk factor for dyslipidemia and CV disease as we observed a significant positive correlation between TC, LDL-C, LDL-C/HDL-C ratio and TSH. A border line correlation between TG and TSH was also observed in our study. In agreement with our results, Iqbal et al revealed that serum TSH concentrations were positively correlated with TC and LDL-C levels [27]. Moreover, serum lipids may be significantly affected by thyroid function even in euthyroid individuals. In this regard, Lee et al study revealed a positive correlation of TSH within the normal range and TC, LDL-C and TG in subjects with no history of thyroid dysfunctions or relevant treatment, even after adjustment for age, sex and obesity [36]. Given the high prevalence of SCH in general population and association between dyslipidemia and TSH, screening of patients with dyslipidemia for thyroid dysfunction may be justifiable before starting hypolipidemic drug therapy. However, large-scale randomized studies are needed for evidence-based recommendations with respect to screening for mild thyroid failure and substitution therapy for this condition. It is currently uncertain whether SCH should be treated [37]. The evidence provided by different studies is controversial and concerns different aspects of this condition [38, 39].

However, based on the data available, it appears that substitution therapy should be considered in patients with mild hypothyroidism in the presence of dyslipidemia and other associated CV risk factors in the attempt to reverse these undesirable prognostic factors [40].

CONCLUSION

Our data showed that SCH is associated with some lipid abnormalities including higher levels of serum TC and LDL-C, which are risk factors for CVD. These findings could justify the increased risk of CVDs in subjects with SCH. Hence, based on the results of the current study, careful screening of subjects with SCH with respect to the dyslipidemia seems necessary and need to be addressed. However, further studies are needed to evaluate a larger series of patients, with a longer duration of SCH.

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