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ORIGINAL ARTICLE

Cardiovascular risk factors in middle-aged women with subclinical hypothyroidism

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Abstract

OBJECTIVES: Overt hypothyroidism (OH) is associated with premature atherosclerosis and coronary heart disease (CHD). Recently, C-reactive protein (CRP) and total homocysteine (tHct) emerged as additional independent cardiovascular risk factors. Subclinical hypothyroidism (SH), affecting as many as 15% of middle-aged women is not known to be associated with risk for CHD.

DESIGN AND MEASUREMENTS: We measured CRP and tHct levels as well as conventional cardiovascular risk markers in 44 middle-aged women with newly diagnose SH. Results were compared with those obtained in 10 patients with OH and 19 euthyroid controls.

RESULTS: In SH, tHct and CRP levels were not as augmented as compared to controls. Their mean systolic and diastolic blood pressure values were increased vs. controls ($p<0.04$;$p<0.01$, respectively). Mean values of total cholesterol (TC), high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), triglycerides, TC/HDL-C and LDL-C/HDL-C were not different in patients with SH compared to controls. Individual analysis revealed that the percentage of patients with SH having hypertension, hypertriglyceridemia, hypercholesterolemia, elevated TC/HDL-C and LDL-C/HDL-C ratios were higher than the percentage in controls. CRP positively correlated with BMI($r=0.29$,$p<0.02$), and tHct positively correlated with age ($r=0.24$, $p<0.05$).

CONCLUSIONS: Our findings suggest that subclinical hypothyroidism in middle-aged women is associated with hypertension and dyslipidemia. CRP and tHct do not appear to contribute to the increased risk for CHD in these patients.

Abbreviations & symbols

1. SH subclinical hypothyroidism
2. CRP C-reactive protein
3. tHct total homocysteine
4. FT4 free thyroxine index
5. TSH thyroid stimulating hormone
6. CHD coronary heart disease
7. TC total cholesterol
8. HDL high-density lipoprotein cholesterol
9. LDL low-density lipoprotein cholesterol
10. TG triglyceridesIntroduction

Introduction

Overt hypothyroidism is associated with increased risk for cardiovascular disease (CHD) and accelerated atherosclerosis as indicated by hypertension, hypercholesterolemia and increased low-density lipoprotein cholesterol (LDL-C) levels [1,2]. Not all patients with overt hypothyroidism have these conventional risk factors for CHD [3], suggesting that other factors may be involved. Elevated homocysteine have been reported in overt hypothyroidism [4], and have been proposed as an independent risk factor for CHD [5,6]. Women with hypopituitarism have increased levels of C-reactive protein (CRP) and IL-6 [7], both of which are inflammatory markers of atherosclerosis [8]. Subclinical hypothyroidism (SH) is highly prevalent in elderly subjects, especially in middle-aged women [9–12]. Whether SH is related to a risk for premature CHD is controversial [13,14]. Hak et al [15] have shown that SH was associated with atherosclerosis and myocardial infarction. Aortic atherosclerosis was diagnosed by radiographic detection of calcified deposits in the abdominal aorta. Recent studies have demonstrated that only serum LDL-C levels were elevated in SH [16]. Plasma Hct levels were not elevated in SH and remained unchanged during levothyroxine treatment [17].

The present study was conducted to determine whether CRP, total homocysteine and conventional risk for CHD already exist in untreated patients with SH. Thus, we studied middle-aged women with SH and compared their plasma total homocysteine, CRP, lipid profiles and blood pressure with data obtained in age-matched euthyroid control women and overt hypothyroidism.

Material and Methods

Participants

We studied 44 consecutive middle-aged women (aged 51.6±9.7 years) with subclinical hypothyroidism, defined by normal free thyroxin (FT4) and elevated thyrotropin (TSH) levels) (>4.5 Mu/L), 10 women with overt hypothyroidism (aged 50.1±8.8 years) and 19 euthyroid controls (aged 51.7±10.1 years) recruited among patients attending our outpatient clinic. The study was approved by the Institutional review board (Helsinki Committee) and all participants gave their informed consent to participate in the study. The diagnosis of subclinical and overt hypothyroidism was established by, at least two determinations of FT4 and TSH levels. Hypothyroid patients had never received thyroxin replacement therapy. Patients with subclinical hypothyroidism were asymptomatic. None had previous radioactive iodine therapy, thyroidectomy, external radiation or consumption of drugs known to cause subclinical hypothyroidism.

Biochemical methods

Blood samples were drawn at 08:00AM after a 14-hour fast. Samples were centrifuged within 30 minutes at 3000g for 5 minutes. Plasma and serum samples were stored at -20^0C until assayed. Plasma total homocysteine levels were measured with an amino acid analyzer (Pharmacia Biotech, Cambridge, UK), using a high-performance column and modified physiologic sample separation as previously described [18]. Each sample was analyzed in duplicate. The interassay coefficient of variation (CV) was 5%. The assay was validated by analysis of 186 samples with high-performance liquid chromatography (HPLC) with a correlation of 0.98 between HPLC and amino acid analyzer data. The reference range ≤ 10.98 μmol/L. CRP was determined with a highly sensitive latex-based immunoassay (Dade Behring, Newark, DE, sensitivity 0.05 mg/L). The CRP reference range ≤3 mg/L. Serum creatinine and HDL-C cholesterol were determined enzymatically (Boehringer Manheim, Germany) on a Hitachi 747 analyzer. Serum FT4 and TSH levels were determined by microparticle enzyme immunoassay (MEIA) obtained from Abott Laboratories (Abbott Park, IL). The intra-assay CVs for TSH and FT4 were 4.2% and 4.1%, respectively, and the interassay CVs were 5.2% and 4.6%, respectively. The sensitivity of the assay was 0.06 mU/L and 5.0 nmol/L, respectively. The normal range for TSH is 0.5–4.5 mU/l and for FT4 is 8.7–22.6 nmol/L. Serum antibodies for thyroid peroxidase (TPO) and thyroglobulin (TG) were determined by immunometric assays obtained from Diagnostic Products Corporation (Los Angeles, CA). The intra-assay CVs for TPO and TG were 3.5% and 2.7%, respectively, and the interassay CVs were 8.7% and 9.1%, respectively. Test results were considered positive if levels were greater than 35 IU/ml for thyroid peroxidase (TPO) and 40 IU/ml for TG.

Statistical analysis

The data of SH, OH and control groups were compared by Kruskal-Wallis test. The data of SH and control groups were compared by the Wilcoxon two-sample-test. Spearman rank correlation on the entire data as well as within group were used to test whether CRP or total homocysteine were correlated with FT4, TSH, cholesterol, LDL-C, HDL-C, triglycerides, thyroid antibodies, creatinine and blood pressure. A p value< 0.05 was considered statistically significant.

Results

Clinical and biochemical characteristics of the study subjects are given in Table I. Euthyroid, subclinical and overt hypothyroid patients were well matched

Table I. Clinical and biochemical characteristics in women with subclinical hypothyroidism

Variable	SH [N=44]	OH [N=10]	Control [N=19]	P value
Age [yr]	51.6±9.7	50.1±8.8	51.7±10.1	NS [NS]
BMI [Kg/m^2]	28.7±5.3	25.2±4.0	26.5±4.2	0.04[0.07]
Free thyroxine [pmol/L]	11.1±1.5	7.2±1.9	12.8±2.1	0.0001[0.02]
TSH [mIU/L]	9.2±4.4	46.1±30.4	2.6±1.5	0.0001[0.02]
TPO [IU/L]	575±567	228±2389	26±28	0.0001[0.01]
AT [IU/L]	89±228	468±1250	32±35	NS [0.08]
Systolic BP [mm Hg]	130.7±11.3	113.9±15.8	121.4±19.2	0.01[0.04]
Diastolic BP [mm Hg]	84.2±12.4	74.4±9.9	75.8±10.1	0.001[0.01]
Creatinine [µmol/L]	80±10	85±22	78±8	NS [NS]
Homocysteine [µmol/L]	9.1±2.4	13.0±7.9	9.8±2.6	NS [NS]
CRP [mg/L]	3.7±6.1	1.4±1.2	1.8±1.3	NS [NS]
TC [mmol/L]	5.8±1.1	5.1±1.6	5.5±1.1	NS [NS]
LDL [mmol/L]	3.4±0.8	3.8±1.4	3.4±0.8	NS [NS]
HDL [mmol/L]	1.4±0.3	1.5±0.4	1.5±0.3	NS [NS]
Triglycerides [mmol/L]	1.7±0.9	1.3±0.7	1.2±0.7	NS [0.09]
TC/HDL	4.1±0.9	4.1±1.0	3.8±0.7	NS [NS]
LDL/HDL	2.4±0.6	2.6±1.0	2.3±0.5	NS [NS]

Data are given as Mean±SD. NS, not significant; TC, total cholesterol; LDL, low density lipoprotein; HDL, high density lipoprotein; x Comparison between the 3 groups [SH vs. control]

Table II. Risk factors for cardiovascular disease in women with subclinical hypothyroidism

Variable	SH [N=44]	OH [N=10]	Control [= 19]
Homocysteine [a] [≥10.98 µmol/L]	29.5	50.0	26.3
CRP [≥3.0 mg/L]	20.4	10.0	15.7
Systolic BP [≥ 140 mm Hg]	34	0	21
Diastolic BP [≥ 90 mm Hg]	27.2	0	5.2
TC [≥5.2 mmol/L]	29.5	10.0	5.7
LDL [≥3.4 mmol/L]	38.6	60.0	5.2
Triglycerides [≥2.3 mmol/L]	27.2	20.0	5.2
TC/HDL [b] [≥ 5.51]	9.0	20.0	0
LDL/HDL [b] [≥3.46]	4.5	10.0	0

Data are given as percent of subjects. [a] The values are the 75 th percentile of the controls.
[b] The values are 2 SD above the mean in controls

with respect to age. SH patients had higher BMI values compared with OH and controls. Patients with SH had significant lower fT4 (although within the normal range) and higher TSH levels than the control group. Positive tests to TPO were detected in 73% of SH, in 100% of OH and in 21% of controls. Antibodies to TG were observed in 32% of SH, 40% of OH and in 16% of control women. Patients with SH had significant higher systolic ($p<0.01$) and diastolic ($p< 0.001$) blood pressure. The mean plasma tHct levels in SH (9.1±2.4 µmol/L) were not different from the values in controls (9.8±2.6). In OH, total homocysteine levels (13.0±7.9) were higher than the values in the other two groups, although statistically not different. In OH 50% of patients had total homocysteine ≥10.98 µmol/L, compared with 29.5% in SH and 26.3% in controls. The mean plasma CRP levels in SH (3.7±6.1 mg/L) were higher than the values in controls (1.8±1.3) or in OH (1.4±1.2) but statistically not significantly different. Elevated CRP levels (≥ 3 mg/L) were detected in 20.4% of SH, compared with 15.7% in controls and 10% in OH. In SH with TSH levels > 10 mIU/L, the mean CRP levels were higher than in patients with TSH levels < 10 mIU/l or in controls (figure 1). Across all participants, CRP positively correlated with BMI($r=0.29, p<0.02$). There was no significant correlation with fT4($r=0.02$, $p=0.8$) or with TSH ($r=–0.01$, $p=0.9$). Total homocysteine positively correlated with age ($r=0.24$, $p<0.05$) but not with fT4($r= –0.16$, $p=0.2$) or TSH ($R= 0.03$, $P<0.79$).

Serum mean levels of total cholesterol (5.8±1.1 mmol/L), LDL-C (3.4±0.8 mmol/L), HDL-C (1.4±0.3 mmol/L), triglycerides (1.7±0.9 mmol/L) as well as the ratios TC/HDL-C (4.1±0.9) and LDL-C/HDL-C (2.4±0.6) were not significantly different from the values in controls (5.5±1.1; 3.4±0.8; 1.5±0.3; 1.2±0.7; 3.8±0.7; 2.3±0.5, respectively). The percentages of patients and controls with elevated blood pressure, abnormal lipid profiles, CRP and tHct are given in table II. The percent of patients with SH having hypertension (≥ 140/90 mmHg), elevated TC (>5.2 mmol/L), TC-HDL-C (≥5.51) and triglycerides (≥ 2.3 mmol/L) was significantly higher in SH than in controls ($p<0.03$). Across all participants cholesterol was negatively correlated with fT4 ($r=–0.26$, $p<0.04$) and positively with TPO($r= 0.24$, $p<0.05$). No significant

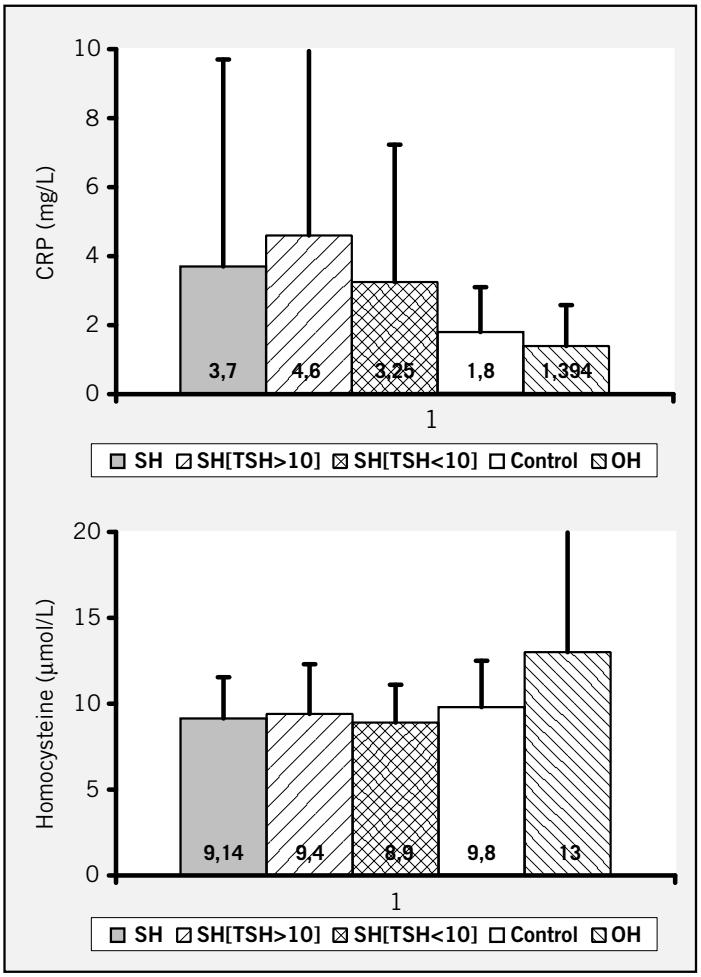

Figure 1. Plasma total homocysteine and CRP levels in subclinical hypothyroidism, overt hypothyroidism and control women.

Table III. Spearman correlation coefficients between blood pressure and lipid profiles in women with subclinical hypothyroidism

Variable	Systolic BP		Diastolic BP		Triglycerides	
	R	P	R	P	R	P
TC	0.26	0.03	0.18	0.15	0.52	0.0001
LDL	0.16	0.22	0.12	0.31	0.22	0.07
HDL	–0.27	0.02	–0.19	0.13	–0.24	0.05
Triglycerides	0.42	0.0007	0.31	0.01	_	

correlations were observed between cholesterol and TSH. Blood pressure was positively correlated with age (r= 0.34, p<0.005) and BMI(r= 0.38, p<0.002). A significant positive correlation was observed between blood pressure and TC or triglycerides. Serum triglycerides were positively correlated with TC and negatively correlated with HDL-C (table III).

Discussion

In this study we have demonstrated that middle-aged women with subclinical hypothyroidism (SH) have mean blood CRP, total homocysteine levels, lipid profiles similar to values observed in age-matched euthyroid controls. Their blood pressure values were significantly higher compared with controls. However, a significant percentage of women with SH had hypertension, hypertriglyceridemia, hypercholesterolemia and elevated TC/HDL-C ratio.

Several reports indicated that SH is associated with elevated homocysteine levels. Replacement therapy with L-T4 was associated with lowering of homocysteine concentrations [4,19–22]. On the other hand, others found no significant difference between patients with SH and controls in basal homocysteine levels and during LT4 replacement therapy [17,23–24]. Our findings of elevated homocysteine levels in 50% of patients with overt hypothyroidism are in agreement with previous studies [23]. The percent of patients with SH having hyperhomocysteinemia was similar to that observed in euthyroid controls. This may suggest that homocysteine level is not a determinant to start LT4 replacement therapy in SH. Probably, studies of larger population are needed.

Recently, CRP and IL-6 levels were shown to be higher in women with hypopituitarism than in healthy women suggesting high risk of cardiovascular disease in these patients [17]. Since these patients had in addition to hypothyroidism other pituitary hormone deficiencies, it is not clear whether elevated CRP levels are related to hypothyroidism per se. Others have found elevated CRP levels in overt hypothyroidism and in SH. Yet, LT4 replacement therapy had no significant effect on CRP levels. Moreover, no significant correlation of CRP with fT4 or TSH was observed [23]. We have found that the percent of patients with SH having elevated CRP levels (> 3.0 mg/L) was significantly higher than in overt hypothyroidism. Thus in contrast with previous study [23]. This discrepancy may be due to the smaller number of hypothyroid patients studies by us. Interestingly, increased CRP levels were detected in 24.1% of patients with TSH< 10 mIU/L compared with 13% in patients with TSH> 10 mIU/L .Our data show a significant correlation of CRP with BMI. It is known that higher BMI values are associated with an increase in cardiovascular risk in healthy women [25]. It is of note that SH women in our study had higher BMI values than euthyroid controls. Elevation in CRP levels could be related to inflammatory thyroid disease. Recently, CRP levels were determined in inflammatory and noninfalammatory thyroid diseases. Only patients with subacute thyroiditis had elevated CRP levels [26]. . In the present study, CRP levels were well below the values observed in subacute thyroiditis. Furthermore, participants in our study were free of clinically apparent inflammatory thyroid disease.

There is substantial evidence that overt hypothyroidism increases the risk of atherosclerosis via increases in LDL-C, induction of diastolic hypertension, altered coagulability and direct effect on vascular smooth muscle. Overt hypothyroidism may also increase the risk of cardiovascular

morbidity through the effects of cigarette smoking, insulin resistance, hyperhomocysteinemia and elevated CRP levels [2,27]. The relationship between SH and atherosclerosis is still controversial. Patients with subclinical hypothyroidism exhibit increased levels of LDL-C and lipoprotein a (Lp a) levels [28]. Other studies have shown significantly higher total cholesterol, LDL-C and apolipoprotein B in SH. Elevated Lp (a) levels were more frequent than in euthyroid controls [16,29]. Replacement therapy had not demonstrated an effect of LT4 on HDL-C or apolipoprotein A1 [29]. Beneficial effects of LT4 therapy were observed with LDL-C levels with the largest treatment effect were evident in patients with TSH levels greater than 10–12 mU/l. The average LDL-C decline was 0.26 nmol/l (10 mg/dl) [14]. Serum triglycerides levels in SH were reported to be similar to values in euthyroid controls [16,23,29]. Changes in serum triglycerides during LT4 replacement therapy were observed in several studies [14]. In our study we found that the percentage of patients with atherogenic lipid profiles (elevated total cholesterol/HDL-C and LDL-C/HDL-C) were higher than in controls. Diastolic hypertension and hypertriglyceridemia were also prevalent in SH.

Whether to treat SH to reduce risk of future cardiovascular events is controversial. It seems that in most patients with coexisting hypercholesterolemia, LT4 therapy is recommended, especially in those with higher serum TSH levels. Meier et al [29], have suggested that an important risk reduction of cardiovascular mortality of 9%–31% can be estimated from the improvement in LDL-C.

In conclusion, the prevalence rates for hypertension, elevated triglycerides and undesirable lipid profiles found in the present study, and the unpredictable rate to progression of overt hypothyroidism seem to weigh in favor of treatment all patients with SH.

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