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SUB CLINICAL HYPOTHYROIDISM IS ASSOCIATED WITH A LOW GRADE INFLAMMATION HIGH PLASMA FIBRINOGEN LEVELS AND HIGH ATHEROTHROMBOTIC POTENTIALITY

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Summary

Overt hypothyroidism (OH) is associated with premature atherosclerosis and coronary heart disease (CHD). Recently, C-reactive protein (CRP) and plasma fibrinogen 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. We measured CRP and plasma fibrinogen levels as well as conventional cardiovascular risk markers in 30 middle-aged women with SH. Results were compared with those obtained in 40 euthyroid controls. In SH, plasma fibrinogen and CRP levels were significantly higher ($p<0.01$; $p<0.05$, respectively) in cases as compared to controls. Their Body Mass Index (BMI), mean systolic and diastolic blood pressure values were increased vs. controls ($p<0.05$; $p<0.01$; $p<0.05$, respectively). Total cholesterol (TC), low-density lipoprotein cholesterol (LDL), triglycerides (TG) was also high in patients with SH compared to controls. Serum TSH positively correlated with CRP ($r=.663$, $p<0.01$), and plasma fibrinogen ($r=.5$, $p<0.01$). Our findings suggest that subclinical hypothyroidism in middle-aged women is associated with hypertension and dyslipidemia. CRP and plasma fibrinogen appear to contribute to the increased risk for CHD in these patients.

Key ward: hypothyroidism; C-reactive protein; plasma fibrinogen; cardiovascular disease; lipids

Introduction

Hypothyroidism is a common disorder in the general population and occurs more frequently in women. Indeed, up to 11% of women of 55 years or more present with high TSH levels[1], of whom up to 18% may progress to OH [2]. Plasma lipid profile may change according to thyroid status[3].

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Hypothyroidism is associated with increased risk of atherosclerosis through high levels of serum lipids and/or haemostatic abnormalities[4]. SH, defined as an asymptomatic state characterized by normal serum concentrations of free thyroxine and elevated serum concentrations of thyroid-stimulating hormone (TSH) [5]. Whether SH is related to risk for cardiovascular disease is controversial.

OH is associated with increased risk for cardiovascular disease (CHD) and accelerated atherosclerosis as indicated by hypertension, hypercholesterolemia and increased LDL-C levels [6]. Not all patients with overt hypothyroidism have these conventional risk factors for CHD [7], suggesting that other factors may be involved. Elevated levels of fibrinogen have consistently shown as an independent predictor of initial and recurrent cardiovascular events. There are several potential mechanisms by which fibrinogen can promote the development of atherosclerosis and thrombosis. It affects the haemostatic system and is the major determinant of plasma viscosity. Fibrinogen is an acute phase reactant and therefore could also be a marker for increased inflammatory activity. T4 levels are the determinant of several components of the fibrinolytic system. T4 has an impact on the synthesis and catabolism of proteins, and the final modification of serum levels of these proteins may depend on the severity of the disease, in hypothyroidism. Plasma levels of fibrinogen was either correlated to plasma levels of T4 or altered in patients displaying normal to low free thyroxine (FT4) levels or hypothyroidism [8]. Elevated plasma fibrinogens have been reported in OH [9], and have been proposed as an independent risk factor for CHD[10, 11]. Cantürk et al. measured fibrinolytic activity in 35 SH patients and found a significantly higher fibrinogen level in SH patients than in healthy controls. Do¨rr et al also showed that decreased serum TSH is an independent risk factor for elevated plasma fibrinogen levels as a possible explanation for the high cardiovascular mortality among affected subjects[12].

The CRP, a marker of systemic inflammation, had been identified as a predictive marker of cardiovascular events and may be of stronger predictive value than LDL-C[13].

The potential relationship of inflammatory markers to the premature atherosclerosis typical of hypothyroidism is indeterminate. It has been suggested that CRP values are higher in patients with hypothyroidism as compared to euthyroid patients[14]. CRP and fibrinogen are associated with the risk of CHD and severity of atherosclerosis[15].

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

Materials and methods

The subjects of the present case control study were selected from patients attending for investigation purpose in the Bell Vue, Chittagong, during the period June 2010 to August 2010. A total 30 middle-aged women (aged 43.6±9.7 years) with subclinical hypothyroidism [TSH level greater than 4.0 μIU/ml in the presence of a normal free thyroxine level (.76-1.76 ngm/dl)] [5] were selected as case. 40 apparently healthy middle-aged (aged 42.7±8.1 years) euthyroidism [normal TSH level (.4-4 μIU/ml)] women were selected as control. Exclusion criteria were as following: Established diagnosis of ischemic heart disease, diabetes mellitus, renal insufficiency (serum creatinine above 130 mmol/L), clinical liver disease, a known history of hepatitis, or elevated transaminase levels, chronic illness or infections, those treated with lipid lowering agents or receiving menopausal hormone replacement therapy, any malignancy, transient hypothyroidism, smokers, pregnant women, and patients receiving any medication affecting hemorheological parameters (e.g. aspirine, diltiazem, pentoxyfilline, warfarine). Informed consent was obtained from all participants.

Venous blood samples were withdrawn from the brachial vein after a 12 h overnight fast, between 7.30 and 9.30 a.m. Arterial blood pressure was measured using Erka sphygmomanometer after at least 20 minute rest. Serum glucose levels and lipid profile levels were measured using KoneLab autoanalyzer. Plasma fibrinogen was measured by using the thrombin–time–titration method [15]. CRP (reference value .6 mg/dl) was determined with a highly sensitive latex-based turbidimetric immunoassay (Humalyzer, sensitivity 0.05 mg/dl). Free T4 (FT4) levels were measured using Chemiluminescence Immulyte 2000 (Los Angeles, USA), TSH levels were measured using Immulyte 2000 Chemiluminescence Sandwich (Los Angeles, USA).

Results & observations

There was no significant age difference in between case & control group. Table-I showed the concentrations of serum TSH ($p < 0.001$), plasma fibrinogen ($p < 0.01$), CRP ($p < 0.05$), Serum total cholesterol ($p < 0.001$), triglyceride ($p < 0.001$) & LDL-C ($p < 0.05$) of cases were significantly higher than that of controls. But no significance difference of was found in HDL-C ($p > 0.05$) concentration between cases and controls.

Table I: Serum TSH, FT4, plasma fibrinogen, CRP, & lipid profile is higher in cases than in controls group

Parameters	Case (n=30) Mean ± SD	Control(n=40) Mean ± SD	t-value	p-value
TSH	8.72 ± 5.75	2.39 ± .87	5.632	.001 ***
FT4	1.04 ± 0.318	1.27 ± 0.216	3.55	0.007**
Cholesterol (mg/dl)	195.86 ± 24.19	177.53 ± 24.53	2.918	.007 **
TG (mg/dl)	172.46 ± 22.67	141.7 ± 42.24	3.982	.002 **
LDL-C (mg/dl)	125.33 ± 22.64	109.3 ± 21.14	2.854	.008 **
HDL-C (mg/dl)	38.07 ± 3.94	40.86 ± 4.69	-2.593	.015 *
Fibrinogen (mg/dl)	291.62 ± 39.01	267.72 ± 30.97	3.016	.005 **
CRP (mg/dl)	1.04 ± .57	.77 ± .3	2.25	.028

- $p < 0.05$, ** $p < 0.01$, ***$p < 0.001$

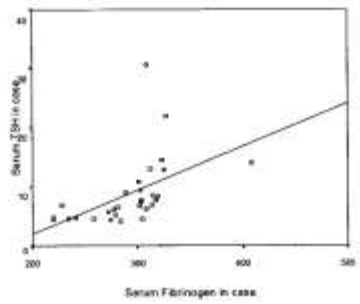
Table-II showed BMI ($p<.05$), SBP ($p<.01$) & DBP ($p<.05$) in cases are significantly higher in cases than that of control group.

Table II: Comparison of serum BMI & Blood pressure in study subjects

Parameters	Case (n=30) Mean ± SD	Control(n=40) Mean ± SD	t-value	p-value
BMI	26.52 ± 1.49	25.71 ±1.21	2.095	.045 *
Systolic Blood Pressure (SBP)	122.83 ± 10.22	116.86 ± 4.22	3.017	.005 **
Diastolic Blood Pressure (DBP)	80 ± 6.43	77 ± 4.66	2.262	.031 *

- $p < 0.05$, ** $p < 0.01$, ***$p < 0.001$

Fig 1: Correlation of TSH with Fibrinogen in cases [R = .5; P = 0.01]



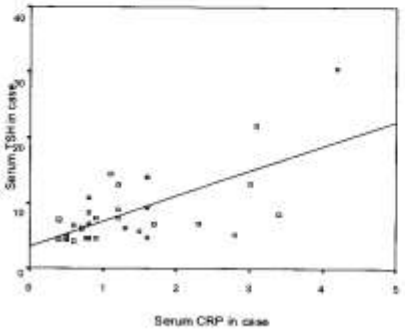
'Pearson's correlation coefficient analysis' [Table III, figure 1&2] showed a significant positive correlation between serum TSH & total cholesterol ($p < 0.05$), LDL-C ($p < 0.05$), CRP ($p < 0.01$) and plasma fibrinogen ($p < 0.01$) but no significant correlation was observed between fasting plasma glucose & triglyceride ($p > 0.05$), HDL-C ($p > 0.05$), BMI & Blood pressure.

Table III: Correlation of serum TSH with lipid profile, plasma fibrinogen, CRP, Blood pressure and BMI in cases:

Independent variable / Dependent variable	r-value	p-value
TSH (μIU/ml)		
LDL-C (mg/dl)	.407	<0.05 (.026) *
TSH (μIU/ml)		
Total Cholesterol (mg/dl)	.487	<0.01 (.006) **
TSH (μIU/ml)		
TG (mg/dl)	.296	>0.05 (.112)
TSH (μIU/ml)		
HDL-C (mg/dl)	.267	>0.05 (.154)
TSH (μIU/ml)		
Plasma fibrinogen (mg/dl)	.5	<0.01 (.005) **
TSH (μIU/ml)		
CRP (mg/dl)	.663	<0.01 (.001) **
TSH (μIU/ml)		
SBP (mm Hg)	.083	>0.05 (.664)
TSH (μIU/ml)		
DBP (mm HG)	.113	>0.05 (.554)
TSH (μIU/ml)		
BMI	.122	>0.05 (.522)

* $p < 0.05$, ** $p < 0.01$

Fig 2: Correlation of TSH with CRP in cases [R= .663; P = 0.01]



Discussion

It was reported that, hypothyroidism is a strong indicator of risk for atherosclerosis in elderly women. Hypothyroidism was associated with a greater prevalence of aortic atherosclerosis (odds ratio, 1.7 [95% CI, 1.1 to 2.6]) and myocardial infarction [16]. Several small case-control studies in living patients have also demonstrated an association between hypothyroidism and atherosclerosis. In a hospital-based study, men and women with a TSH level of 4.0 mU/liter or greater had higher prevalence of coronary artery disease than age matched controls (48% *vs.* 38% for men and 37% *vs.* 20% for women) [17]. In a report of nursing home residents, 56% of 18 patients with subclinical hypothyroidism and 44% of 18 patients with treated hypothyroidism had histories consistent with coronary artery disease, compared with 16% of the 231 euthyroid residents [18]. Our case control study was designed to see the association of CRP & plasma fibrinogen with SH & explore the atherothrombotic potentiality (high CRP, high plasma fibrinogen and abnormal lipid profile) of SH. Serum TSH, FT4, CRP, plasma fibrinogen concentration, fasting lipid profile, blood pressure & BMI were measured and compared between 30 SH patients and age and sex matched 40 controls of apparently healthy individuals.

Fibrinogen plays an active role in the development and progression of atherosclerotic plaques [19]. Plasma fibrinogen level gets often high in hypothyroid patients. C-reactive protein (CRP), a marker of systemic inflammation, is emerging as an independent risk factor for cardiovascular disease. High CRP levels have been linked to an increased risk of thrombotic events including myocardial infarction [20]. Hypothyroid patients exhibit a significant increase in serum CRP levels compared to normal controls. Moreover, increased serum CRP might have an important independent role in an increase of arterial stiffening in hypothyroid patients[21].

The current study reveals that circulating levels of CRP is positively and significantly correlated with those of TSH in SH patients. Our population was carefully selected in order to exclude parameters which may interact with CRP levels. Indeed, none of the patients presented a recent history of infection or inflammatory disease. Moreover, none were receiving lipid lowering agent, which are known to reduce CRP levels [22], nor menopausal hormone replacement therapy which may induce elevation in CRP [23]. Our data is in good agreement with a previous report [24].

In our study mean systolic pressure, diastolic pressure, BMI, total cholesterol, LDL cholesterol, triglycerides and TSH values were significantly higher in the SH group compared to the control group. Similar observation was also shown by Shantha et al [25]. Our study has also shown a strong correlation between TSH & CRP & fibrinogen in cases. This finding was consistent with the observation of many other studies[26].

An elevated level of fibrinogen was consistently shown as an independent predictor of initial and recurrent cardiovascular events [13]. Our study found high level of plasma fibrinogen (P<.001) in SH patients. Strong positive correlation of fibrinogen with TSH also revealed in cases. Our study was well in agreement with many other studies done abroad [8]. Discrepant view had been showed by some studies. They found no differences between the SH & euthyroid control groups with respect to fibrinogen[27].

Conclusion

From all data it was evident that SH patients are highly associated with low grade inflammation (high serum CRP level) high plasma fibrinogen levels and atherothrombotic potentiality (abnormal lipid profiles). We are optimistic that findings of this study will help many SH patients in our country early identification of the risk of development of atherosclerosis in future. Then, it will be possible to lower down the development of CAD, a deadly health problem in the society at large.

Disclosure

All the authors declared no competing interestes.

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