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EFFECT OF LEVOTHYROXINE SUBSTITUTION THERAPY ON THE SERUM LIPID PROFILE IN PATIENTS WITH SUBCLINICAL HYPOTHYROIDISM

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Thyroid hormones modulate lipid metabolism by a variety of ways. Thyroid replacement therapy has beneficial effects on the lipid parameters in patients with overt hypothyroidism The aims of the present study were to investigate the effect of levothyroxine substitution therapy on serum lipid profile in patients with subclinical hypothyroidism. 38 patients (22 women and 16 men) with subclinical hypothyroidism (subclinical hypothyroidism refers to elevated thyroid-stimulating hormone levels in patients with normal levels of thyroid hormone) were recruited for this study. The subjects were between 48 and 61 years Serum thyroid-stimulating hormone (TSH), free thyroxin (FT4), total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol and triglycerides levels were determined before and after 6 months treatment with levothyroxine. Before treatment 14 patients (38.88%) present elevated cholesterol level, 14 patients (38.88%) borderline level and 10 patients (26.31%) normal level according the report of National Cholesterol Education Program, Adult Treatment Panels. Results show that 16 patients (42.10%) present family history of thyroid disease. and significant positive correlation was found between TSH level and age (r=0,991, p<0.001). In the present study, FT4, but not TSH, was found to be significant negatively correlated with total cholesterol (r=-0.907, p<0.001) and LDL cholesterol levels (r=-0.857, p<0.001). We found that TSH was not associated with any lipid parameters. Restoration of euthyroidism in 27 patients with subclinical hypothyroidism resulted in significant changes in serum TSH (7.72 ± 1.07 mIU/L *versus*, 4.22 ± 1.63 mIU/L, p < 0.001), FT4 (1.01 ± 0.20 ng/dL *versus*, 1.09 ± 0.20 ng/dL, p = 0.029), total cholesterol (230.37 ± 37.92 mg/dL *versus*, 216.82 ± 32.35 mg/dL, p = 0.048) and LDL cholesterol levels (152.66 ± 41.41 mg/dL *versus*, 135.24 ± 37.73 mg/dL, p = 0.029). No improvements of HDL cholesterol or triglyceride levels were demonstrated. Clinical evidence suggests that thyroid replacement therapy had beneficial effects on the serum lipid profile in patients with overt hypothyroidism the question of whether subclinical hypothyroidism should be treated or not is still pending.

Key words: subclinical hypothyroidism, lipid parameters, levothyroxine.

INTRODUCTION

It is known that thyroid hormones modulate lipid metabolism by a variety of ways: stimulation of the hepatic cholesterol synthesis by inducing the 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, upregulation of the low density lipoprotein (LDL) receptors, which results in enhanced catabolism of the LDL particles, stimulation of the cholesteryl ester transfer protein and the lipoprotein lipase, stimulation of hepatic lipase and inhibition of lecithin cholesterol acyltransferase[1–3].

Different thyroid abnormalities are accompanied by changes in the lipid profile. Hyperthyroidism is associated with a decrease in serum levels of total,

LDL and high-density lipoprotein (HDL)-cholesterol. Hypothyroidism is accompanied by increase in the serum total cholesterol concentration; hypertriglyceridemia are found less commonly in this population and patients usually exhibit elevated levels of HDL cholesterol.

Subclinical hypothyroidism is defined as the clinical status of mildly elevated serum thyroid-stimulating hormone (TSH) levels (up to 10 mU/L) with normal levels of free thyroxin (FT4) and free triiodothyronine (FT3). Certain studies have indicated that patients with subclinical hypothyroidism had significantly higher levels of total cholesterol, LDL cholesterol, apolipoprotein B (the primary apolipoprotein of low-density lipoproteins) whereas levels of triglycerides, HDL-cholesterol and apolipoprotein AI (the major protein component of high density lipoprotein in plasma) not differ significantly compared to euthyroid controls [4].

Several studies have shown that subclinical hypothyroidism has been associated with lipid abnormalities and increased risk of atherosclerotic coronary artery disease. Clinical evidence suggests that thyroid replacement therapy has beneficial effects on the serum lipid profile in patients with overt hypothyroidism, the question of whether subclinical hypothyroidism should be treated or not is still pending [5,6].

The aims of the present study were to investigate the effect of levothyroxine substitution therapy on serum lipid profile in patients with subclinical hypothyroidism.

MATERIALS AND METHODS

We evaluated 38 patients, 22 women (57.89%) and 16 men (42.10%), with subclinical hypothyroidism. The subjects were between 48 and 61 years. Patients were screened with a questionnaire detailing their family history of thyroid disease, smoking status, medical history, concomitant medications. TSH, FT4, serum total cholesterol, LDL-cholesterol, HDL-cholesterol and triglycerides levels were determined before and after 6 months treatment with levothyroxine. TSH was measured using a chemiluminescent immunometric assay (reference ranges 0.4–4.5 mIU/L) and FT4 with a direct, monoclonal antibody assay (reference ranges 0.7–1.5 ng/dL). Serum total cholesterol, LDL-cholesterol, HDL-cholesterol and triglycerides have been assessed while fasting, by enzimatic methods. Normal blood cholesterol level is defined according the report of National Cholesterol Education Program, Adult Treatment Panels as less than 200 mg of cholesterol per deciliter (mg/dL). Blood cholesterol is considered to be borderline when it is in the range of 200 to 239 mg/dL and elevated cholesterol level is 240 mg/dL or above [7].

Statistical analyses

Data are presented as mean ± SD. Clinical characteristics were compared using the t Student Test. Pearson's moment-product correlation coefficients were calculated to evaluate relationships between variables. Significance was defined at the 0.05 level of confidence. All calculations were performed using the Statistical Package for Social Sciences Software (SPSS) version 15.

RESULTS

The average age of the participants was 56.03 ± 3.40 years. 16 patients (42.10%) present family history of thyroid disease. Before treatment with levothyroxine 14 patients (38.88%) present elevated cholesterol level, 14 patients (38.88%) borderline level and 10 patients (26.31%) normal level according the report of National Cholesterol Education Program, Adult Treatment Panels. Restoration of euthyroidism in 27 patients with subclinical hypothyroidism resulted in significant changes in serum TSH (7.72 ± 1.07 mIU/L *versus*, 4.22 ± 1.63 mIU/L, $p < 0.001$), FT4 (1.01 ± 0.20 ng/dL *versus*, 1.09 ± 0.20 ng/dL, $p = 0.029$), total cholesterol (230.37 ± 37.92 mg/dL *versus*, 216.82 ± 32.35 mg/dL, $p = 0.048$) and LDL cholesterol levels (152.66 ± 41.41 mg/dL *versus*, 135.24 ± 37.73 mg/dL, $p = 0.029$). No improvements of HDL cholesterol or triglyceride levels were demonstrated. The characteristics of the patients before and after levothyroxine treatment are shown in Table 1.

Table 1

Characteristics of patients before and after levothyroxine treatment

	Baseline characteristics of subjects	**Characteristics of subjects after 6 months of treatment**	**P**
TSH (mIU/L)	7.72±1.07	4.22±1.63	p<0.001
FT4 (ng/dL)	1.01±0.20	1.09±0.20	p=0.029
Total cholesterol (mg/dL)	230.37±37.92	216.82±32.35	p=0.005
LDL cholest (mg/dL)	152.66±41.41	135.24±37.73.	p=0.029
HDL cholest (mg/dL)	42.66±6.07	43.00±5.87	NS
Triglyceride (mg/dL)	162.53±41.88	158.71±37.36	NS

Comparison is signifiant at the 0.05 level: $p < 0.05$.

DISCUSSION

Subclinical hypothyroidism is a prevalent condition among adult population. A higher prevalence has been reported among women, caucasian populations, those over 50 years of age, men and women with a family history of thyroid disease [8,9]. Results show that 16 patients (42.10%) present family history of thyroid disease. and significant positive correlation was found between TSH level and age ($r = 0.991$, $p < 0.001$). The American Thyroid Association advocates for earlier screening, recommending measurement of TSH beginning at age 35 and every 5 years thereafter [10].

In the present study, FT4, but not TSH, was found to be significant negatively correlated with total cholesterol ($r = -0.907$, $p < 0.001$) and LDL cholesterol levels ($r = -0.857$, $p < 0.001$). Our results are consistent with several, studies that have reported that circulating levels of FT4, was found to be negatively correlated with total cholesterol and LDL cholesterol levels. Data collected from Roos *et al*. reported that FT4 was negatively associated with total cholesterol, LDL-cholesterol in 2703 adult euthyroid subjects [11]. In his research published in the Kathmandu University Medical Journal Dr. Risal and his colleagues have identified that FT4 was significant negatively correlated with total cholesterol in 169 cases, 32.5% of the patients were having thyroid disorder [12].

We found that TSH was not associated with any lipid parameters (total cholesterol, LDL-cholesterol, or HDL-cholesterol, triglycerides).

Treatment of subclinical hypothyroidism improves significant thyroid function tests (TSH, FT4), total cholesterol and LDL cholesterol levels No improvements of HDL cholesterol or triglyceride levels were demonstrated. Our results are consistent with short-term studies that have demonstrated that thyroid replacement therapy has beneficial effects on the serum lipid profile in patients with subclinical hypothyroidism [13, 14].

In 2000, Danese MD *et al.* published a clinical review about the effect of thyroxine therapy on serum lipoproteins in patients with mild thyroid failure. "All studies reported serum total cholesterol concentration changes during T4 treatment, 12 reported triglyceride changes, 10 reported high-density lipoprotein (HDL) cholesterol changes, and 9 reported low-density lipoprotein (LDL) cholesterol changes. There were 247 patients in 13 studies. The mean decrease in the serum total cholesterol concentration was -0.20 mmol/L (-7.9 mg/ dL), with a 95% confidence interval of -0.09 to -0.34. The decline in serum total cholesterol was directly proportional to its baseline concentration. The change in serum LDL cholesterol concentration was -0.26 mmol/L (-10 mg/dL), with a 95% confidence interval of -0.12 to -0.41" [15].

Several studies have indicated that subclinical hypothyroidism has been associated with increased risk of cardiovascular diseases. Subclinical hypothyroidism induced lipid abnormalities impairs ventricular function, cardiovascular adaptation to effort and, decreases heart rate variability, impairs endothelial function [16–18].

Certain studies have shown conflicting results concerning the effect of levothyroxine substitution therapy in patients with subclinical hypothyroidism [19–21]. Efstathiadou Z. [21] and our group have found that restoration of euthyroidism in 37 patients with subclinical hypothyroidism resulted in no significant changes in serum lipid parameters except for a significant decrease in HDL cholesterol concentration. The decrease of HDL cholesterol concentration could undermine the beneficial effect of total and LDL cholesterol reduction in patients treated with levothyroxine. Treatment with levothyroxine in patients with angina pectoris or heart disease, may exacerbate angina or promote cardiac arrhythmia.

Extensive studies designed to answer the question as to whether subclinical hypothyroidism are associated with increased risk for cardiovascular diseases and whether therapy with levothyroxine might influence cardiovascular mortality are neded.

CONCLUSION

Thyroxine therapy, in a thyrotropin suppressive dose, leads to a considerable improvement of the lipid profile in patients with subclinical hypothyroidism.

Hypercholesterolemic patients with subclinical hypothyroidism may be treated with thyroxin substitution.

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