

Biochemical Changes in Serum Lipid Fractions, Calcium, Magnesium and Phosphorus Levels in Women with Subclinical Hypothyroidism

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Abstract: There is a growing evidence that subclinical hypothyroidism is an indicator of increased risk for atherosclerosis and myocardial infarction in women. However, the association of subclinical hypothyroidism (SCH) with changes in serum lipids is still question. The aim of this study was to assess whether SCH is associated with abnormal lipid levels and changes in serum cations, calcium, magnesium and phosphorus as atherogenic parameters. Thirty women age; 40 ± 3 years who did not previously have a diagnosis of hypothyroidism or take any medicine were enrolled in the study, divided into euthyroid control (group included women with TSH value in a normal range between 0.27- 4.2 μ IU/ml and subclinical hypothyroidism group with TSH value of 6.7- 12.5 μ IU/ml. we measured total cholesterol (TC), low density Lipoprotein cholesterol (LDL-c), high density Lipoprotein cholesterol (HDL-c), triglycerides (TG), calcium, magnesium and phosphorus in both groups. SCH subjects showed significantly higher TC, LDL-c and TG levels than control. While, HDL-c was significantly lower in subjects with SCH than euthyroid. There was decrease in serum calcium level and increase in serum magnesium and phosphorus in SCH group. In conclusion, subclinical hypothyroidism is associated with elevated TC, LDL-c and TG levels and decreased HDL-c level and disturbance in serum electrolytes. This may increase the risk of atherosclerosis.

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1. Introduction

subclinical hypothyroidism (SCH) defined as an elevated serum thyroid Stimulating Hormone (TSH) level associated with serum total free thyroxin (T_4) and triiodothyroxine (T_3) concentrations within the reference range with few or no symptoms of hypothyroidism (Surks *et al.*, 2004). It is referred to as a state of mild thyroid failure and is essentially a laboratory diagnosis (Cooper, 1998). Subclinical hypothyroidism is much more common than overt hypothyroidism (Danese *et al.*, 2000), therefore early diagnosis and treatment may prevent the onset of overt hypothyroidism. This condition is more common in the elderly and is found twice as often in women as in men (Sawin *et al.*, 1985). Lipid abnormalities are reported to be more common in patients with overt hypothyroidism and are thought to contribute to the disproportionate increase in cardiovascular risk in these persons (Morris *et al.*, 2001). A reversible impairment of systolic and diastolic myocardial function has also been reported in subclinical hypothyroidism (Biondi *et al.*, 1999 and Monzani *et al.*, 2001) and the condition has been claimed to be a risk factor for coronary heart disease and peripheral arterial disease (Althaus *et al.*, 1988 and Hak *et al.*, 2000).

However, whether an altered lipid conveys this risk is uncertain because the relationship between SCH and serum lipid is controversial (Yanis *et al.*, 1996, Baur *et al.*, 1998 and Cooper, 1998). Some studies reported positive correlation and prompt reversal of changes following treatment (Althaus *et al.*, 1988; Monzani *et al.*, 2001) and other studies refuting any correlation between the two (Danese *et al.*, 1996). Other studies have found that persons with subclinical hypothyroidism who are given L-thyroxine experience some improvements in their energy level and feeling well being (Cooper *et al.*, 1984 and Jaescheke *et al.*, 1996).

Although the changes in analytes, including magnesium and calcium may be slight in thyroid disease, it is possible that these disturbances will be important for a patient in the long term (Ford *et al.*, 1989). Recently, it has been suggested that some of metabolic disorders, hypertension and cardiovascular disease are linked by common defects in metabolism of divalent cations such as calcium and magnesium (Hagstrom *et al.*, 2007 and Huerta *et al.*, 2005).

The positive relationship between serum calcium and cardiovascular disease (Slinin *et al.*, 2005), metabolic syndrome (Lind *et al.*, 1988) or myocardial infarction (Lind *et al.*, 1997) has been reported. On a parallel note, several studies have

reported an inverse relationship between serum magnesium concentration and lipid profile (Guerrero and Rodriguez, 2002).

Low serum magnesium is associated with cardiovascular events and metabolic syndrome (Nadler *et al.*, 1993). Although, the exact mechanism underlying these relationships is not fully understood, potential mechanism is the basic role of these cations in metabolic pathways (Resnick, 1989).

From the above introduction, lipid profile, serum calcium and magnesium are considered as risk factor for cardiovascular disease. So, the aim of this study was to determine whether lipid abnormalities and calcium, magnesium and phosphorus changes are more common in women with subclinical hypothyroidism when compared to euthyroid individuals as there are only few studies related to women with subclinical hypothyroidism in Egypt that can be essential for treating them to prevent the onset of hypothyroidism and cardiovascular diseases.

2. Material and Methods

Subjects:

A total number of thirty women with age 40 ± 3 years were participated in our study. Subjects were recruited from hormonal unit, Faculty of Medicine, Zagazig University, subjects were classified according to their TSH values into subclinical hypothyroidism women ($n= 15$, TSH ranges from 6.7- 12.5 $\mu\text{IU/ml}$) and euthyroid control group ($n= 15$, TSH value ranges from 0.27- 4.2 $\mu\text{IU/ml}$) their thyroid hormone profile is shown in Table (1). All subjects were in good health; all were premenopausal with regular menses and none was pregnant. Obese subjects and those with primary or secondary dyslipidemia, diabetes mellitus, renal and hepatic failure or other systemic disease also with post myocardial infarction, and with congestive cardiac failure were excluded from the study, none was taking any drugs and all subjects were on free diets.

Laboratory Measurements:

Blood samples were withdrawn from subjects of SCH and control after overnight fasting. The samples were centrifuged at 3000 rpm for 10 min. and the separated sera were kept at -20°C until used in the biochemical analysis.

Serum concentrations of thyroid hormones (T_3 , T_4 and TSH) were estimated by radioimmunoassay using kits purchased from Siemens Medical Solutions Diagnostics, Los Anglos, USA. Serum lipids and serum calcium, magnesium and phosphorus levels were determined by enzymatic methods using Hitachi 902- Biochemical analyzer using kits purchased from Roch Diagnostic, GMBH, Mannheim, Germany.

Total cholesterol, HDL-c and Triglycerides were measured by an enzymatic method. LDL-c was calculated using Friedwald *et al.*, (1972) formula: $\text{LDL-c} = \text{Total serum cholesterol} - (\text{HDL-c} + \frac{1}{5} \text{ of the triglycerides concentrations})$.

Statistical Analysis:

Data are expressed as mean \pm S.D. comparison between patients and control for all variables was performed by t-test according to Steel and Torrie (1980).

3. Results

At base line, TSH level was higher in SCH women than euthyroid control, where as serum T_3 and T_4 levels, although still within the normal range, were significantly lower ($p < 0.05$ and $p < 0.001$), respectively as shown in Table (1).

Table (2) showed that, SCH women have significantly higher serum TC (245.86 ± 15.79 vs. 201.46 ± 15.44), LDL-c (162.65 ± 16.10 vs. 119.78 ± 15.62) and TG (184.4 ± 30.05 vs. 131.0 ± 20.90) concentrations than control. However, HDL-c level was significantly lower in SCH subjects (46.33 ± 5.61 vs. 55.48 ± 7.54). Significant decrease in serum calcium was observed in SCH women than control (8.42 ± 0.42 vs. 9.01 ± 0.27), meanwhile serum phosphorus and magnesium both recorded significant increase in SCH group (4.01 ± 0.14 vs. 3.80 ± 0.14) and (2.23 ± 0.10 vs. 2.05 ± 0.15), respectively.

Table (1): Thyroid hormones (TSH, T_3 and T_4) levels in control and subclinical hypothyroid women

Group parameter	Control	SCH
TSH ($\mu\text{IU/ml}$)	1.86 ± 0.26	$9.29 \pm 1.38^{**}$
T_3 (ng/ml)	123.13 ± 10.92	$114.0 \pm 8.56^*$
T_4 ($\mu\text{g/ml}$)	8.38 ± 0.87	$5.56 \pm 0.50^{**}$

- Data are presented as mean \pm SD
- Values with superscript are significant ($*p < 0.05$), ($**p < 0.001$)

Table (2): level of lipid profile in control and subclinical hypothyroid women

Group parameter	Control	SCH
Total Cholesterol (mg/dl)	201.46 ± 15.44	245.86 ± 15.79**
LDL-c (mg/dl)	119.78 ± 15.62	162.65 ± 16.10**
Triglycerides (mg/dl)	131.0 ± 20.90	184.4 ± 30.05**
HDL-c (mg/dl)	55.48 ± 7.54	46.33 ± 5.61**

- Data are presented as mean ± SD
- Values with superscript are significant (** $p < 0.001$)

Table (3): serum level of Calcium, Phosphorus and Magnesium in control and subclinical hypothyroid women

Group parameter	Control	SCH
Calcium (mg/dl)	9.01 ± 0.27	8.42 ± 0.42**
Phosphorus (mg/dl)	3.80 ± 0.14	4.01 ± 0.14**
Magnesium (mg/dl)	2.05 ± 0.15	2.23 ± 0.10**

- Data are presented as mean ± SD
- Values with superscript are significant (** $p < 0.001$)

4. Discussion

The nature and degree of dyslipidemia in overt hypothyroidism has been demonstrated in many studies and there is no doubt about the beneficial effects of thyroid substitution on serum lipids and on the risk of cardiovascular disease (Pucci *et al.*, 2000). Early clinical studies have suggested an association between subclinical hypothyroidism and coronary heart disease (Fowler *et al.*, 1970 and Bastenie *et al.*, 1971). Furthermore, in an early survey subclinical hypothyroidism emerged as an independent risk factor for aortic atherosclerosis and myocardial infarction (Hak *et al.*, 2000). However, the possible effects of subtle alterations of subclinical hypothyroidism on lipid profile and atherogenesis remain unclear (Kahaly, 2000).

The evidence provided by different authors is controversial and concerns different aspects of this condition. Caron *et al.*, 1990 reported that lower HDL-c levels in SCH patients than in a control group and demonstrated a significant increase in HDL-c levels after I-T₄ therapy with normalization of the TC/HDL-c ratio. In a substantial number of studies, TC and LDL-c seem to be elevated in SCH compared with control (Yildirimkaya *et al.*, 1996; Bauer *et al.*, 1998 and Efstathiadou *et al.*, 2001). Earlier, in a double-blind, placebo-controlled trial Meier *et al.*, (2001) demonstrated the effectiveness of I-T₄ therapy in both reducing LDL-c level and improving clinical symptoms of hypothyroidism in SCH patients. In this respect, the present study demonstrated that subjects with SCH have higher levels of TC, LDL-c and triglycerides thus displaying a more atherogenic lipid profile when compared with control subjects.

The present results appear to confirm results of studies about elevated serum lipid levels in SCH subjects. These studies showed significant increase in

TC, LDL-c (Efstathiadou *et al.*, 2001; Ganotakis *et al.*, 2003 and Adriana Santi *et al.*, 2012) and triglycerides and significant decrease in HDL-c. Concerning the risk of dyslipidemia, our results showed that SCH subjects were more likely to have hypercholesterolemia. Therefore, screening of lipid profiles is quite reasonable in subjects with subclinical hypothyroidism is our setting to prevent cardiovascular diseases.

The detailed mechanism responsible for the effect of TSH on lipid profile remained unclear. The main function of TSH is to stimulate the synthesis and release of thyroid hormones in the thyroid gland via the specific cell membrane receptor TSHR, that is expressed widely in a variety of extra thyroidal organs including kidney, adipose tissue and bone marrow (Williams, 2011). More importantly, emerging evidence suggest that TSH not only acts on the thyroid gland but also targets on several other organs.

The mechanism for the regulation of cholesterol homeostasis includes effects on biosynthesis, uptake and elimination (Norlin and Wikvall, 2007). Tian *et al.* (2010) revealed that TSH promoted the expression of HMGCR, the rate-limiting enzyme in cholesterol synthesis in liver. Based on these findings, TSH might act through expressed TSHR expressed on hepatocytes to up-regulate the expression of HMGCR resulting in increased TC level (Wanjia *et al.*, 2012).

Another reported mechanism for the development of hypercholesterolemia in subclinical hypothyroidism is the decrease of fractional clearance of LDL-c by a reduced number of LDL receptors in the liver, in addition to decreased receptor activity (Duntas, 2002 and Rush *et al.*, 2006) HDL-c metabolism is complex and changes in plasma levels are due to remodeling of HDL-c

particles by hepatic lipase and cholesterol ester transfer protein (Bakker *et al.*, 1998). The activity of both enzymes decreases with the increase of TSH level resulting in reduction in HDL-c level (Tall, 1993). The reduction in HDL-c level causes an increase in the LDL-c/ HDL-c ratio, atherogenic index that is important marker for cardiovascular disease.

Thyroid hormone is a central regulator of body haemodynamics, thermoregulation and metabolism. Therefore, it has an influence on renal haemodynamics, glomerular filtration and electrolyte handling (Mariani and Berns, 2012). The present results demonstrated a significant decrease in serum calcium of SCH group than control. Roopa and Soans (2012) reported that thyroxin normally regulates blood calcium level by releasing calcium from cells, by decreasing thyroxin level in blood, less T₄ enters the cells and less calcium is released.

Additionally, renal calcium excretion was increased in rats with high TSH (Kumar and Prasad, 2002). Also, hypercalcemia was described in patients with hyperthyroidism due to an enhanced bone turn over (Iqbal *et al.*, 2003). Alcalde *et al.* (1999) reported that thyroid hormones regulate phosphorus metabolism. In the study, phosphorus level is increased significantly in SCH subjects than in control group which is in accordance with Schwarz *et al.* (2012) who reported significant positive correlation between phosphorus and TSH level. Also, AL-Tonsi *et al.* (2004) investigated the occurrence of dyslipidemia and altered serum phosphorus concentrations in patients with thyroid disorders.

Evaluation of serum Mg concentrations has become important in recent years in human (Dube and Granory, 2003). Serum Mg in some papers showed a negative correlation with the level of thyroid hormones (Koch *et al.*, 2002). Thyroid hormones affects the glomerular filtration rate, blood flow and tubular sodium transport and has a direct effect on Ca and Mg resorption (Mc Caffrey and Quamme, 1984). Present data demonstrated significant increase in serum Mg in SCH group than controls, which in agreement with Schwarz *et al.*, 2012 and Frizel *et al.*, 1967.

Conclusion

From the previous results, subclinical hypothyroidism is associated not only with elevated TC, LDL-c levels and low HDL-c but also with changes in serum electrolytes. This may further increase the risk of development atherosclerosis and may conclude that it is of almost importance to follow up thyroid function at least one or twice/ year in order to avoid hypothyroidism with consequent

heart disease in subjects suffered from hypothyroidism without any clinical manifestation.

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