Relationship of Thyroid Stimulating Hormone with Coronary Artery Disease in Patients Undergoing Diagnostic Coronary Angiography

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ABSTRACT

In this cross-sectional study, a sample of 150 patients (88 men and 62 women) of age 53.28±9.6 years who underwent diagnostic coronary angiography. Blood was used for the measurement of serum thyroid stimulating hormone (TSH), free thyroxine (FT4) concentration and serum lipid profile total cholesterol (TC), triglyceride (TG), low density lipoprotein-cholesterol (LDL-C) and high density lipoprotein-cholesterol (HDL-C). Mean serum concentration of lipid profile across different groups of TSH level, (<0.38, 0.38-4.31 and > 4.31 mIU/L) was calculated in order to study the association of TSH with prevalence of CAD. The severity of CAD was scored as score (0) for those with smooth normal coronary artery while score 1, 2 and 3 for those with single, double and triple-coronary artery of ≥50% stenosis, respectively. Score 4 indicated left main coronary artery with ≥50% stenosis. The mean serum TSH was significantly higher in women than men (p=0.005). There was no significant difference between mean serum TSH level across different score groups (p=0.7). High level of TSH was observed in the multi-vessel disease, (score 2, 3 and 4 p=0.03). It was found that serum TC, LDL-C and TG increased while HDL-C decreased with increased TSH level.

This study suggested that the high level of TSH is associated with multi-vessel disease and slight elevation of TSH also leads to changes in lipid profile that raise the risks of cardiovascular disorders.

Keywords: Thyroid stimulating hormone, subclinical hypothyroidism, overt hypothyroidism, coronary artery disease, coronary angiography.
INTRODUCTION

Overt hypothyroidism (OH) is associated with the abnormality of blood lipids and the increased risk of cardiovascular disease (CVD) (Becker et al., 1985). Subclinical hypothyroidism (SCH) is a symptomatic state characterized by normal serum concentrations of freeT4 (FT4) and elevated serum concentrations of thyroid stimulating hormone (TSH). Moreover, it is associated with an increase risk of CVD (Tieche et al., 1981). The SCH is increased with age and it is higher in women than men (Surks et al., 2004).

However, most of cardiovascular events occur in subjects with normal thyroid functions (Bakker et al., 2001). Thus, the question whether an association of TSH with CVD also exists in the euthyroid state or not is important. In one study addressed this question showed a significantly higher TSH level in patients with coronary heart disease (CHD) compared...
with healthy controls matched for age, sex and body mass index (BMI) (Miura et al., 1996). Interestingly, this difference could not be explained by a higher incidence of SCH.

The association of OH and SCH with hyperlipidemia might be extended to the normal range of thyroid functions (Asvold et al., 2007). Some studies have shown that serum lipids might also be altered within normal ranges of thyroid functions that is considered clinically normal (Iqbal et al., 2006). Certain authors reported that serum total cholesterol (TC), low density lipoprotein-cholesterol (LDL-C) and triglyceride (TG) increased with the increase of the TSH level while high density lipoprotein-cholesterol (HDL-C) decreased with the increase of the TSH level (Pallas et al., 1991).

In this study, we determine whether there is a relationship between the variation of TSH within the reference range and the presence and severity of CAD. Moreover, to find whether there is an association of serum lipid concentration with the level TSH.

**MATERIALS AND METHODS**

A cross-sectional study was carried out in IBN-SINA Teaching Hospital in Mosul city during the period from 1st of November 2011 to the 1st of March 2012. The protocol of this study was approved by the regional research Committees at the College of Medicine and Mosul Health Administration.

One hundred and fifty patients clinically referred for the unit of coronary angiography to evaluate their chest pain, (88 males and 62 females) aged (30 - 78) years with mean ± standard deviation (SD) of (53.3±9.6) years. Patients with a history of thyroid diseases, chronic debilitating illnesses and those receiving medications that interfere with thyroid functions and serum lipid estimation were excluded.

After obtaining informed consent, data of age, sex, coronary risk factors (hypertension, hyperlipidemia, diabetes mellitus (DM), smoking habit and obesity), Systolic (SBP) and diastolic (DBP) blood pressure were measured with standard mercury sphygmomanometer from the arm after the patient seated for five minutes prior to the measurement. Body mass index (BMI) was computed as weight divided by squared meter. Obesity was defined as BMI of ≥ 30 Kg/m² (Chan et al., 2003).

After 12 hrs of fasting period, coronary angiography was performed by percutaneous transfemoral technique according to the Judkins method (Judkins, 1976). The results of coronary angiography are classified according to the scoring system (Ringqvist et al., 1983).

The severity of CAD was scored as (0) for smooth normal coronary arteries, score (1, 2 and 3) for those with single, double, triple- coronary artery of ≥ 50% stenosis, respectively. Score (4) designated left main disease was applied on left main coronary artery of ≥ 50% stenosis.

Biochemical parameters including TC, TG, HDL-C were measured enzymatically using kits supplied from (Biolabo, France). Serum LDL-C was calculated by Friedewald equation (Friedewald et al., 1972; Burtis et al., 2006) as follows:

\[
\text{LDL-C} = \text{TC} - (\text{HDL-C}) - \text{TG} /2.22 \text{ mmol/l}.
\]

Atherogenic Index (AI) is calculated by the following equation:

\[
\text{AI} = \text{TC} /\text{HDL-C} \quad \text{(Bishop et al., 2005)}.
\]

Serum TSH and FT4 was measured by Automated enzyme immunoassay system, AIA-360 TOSOH analyzer (Tosoh, Japan)
Patients were classified into three groups according to their TSH levels (< 0.38, 0.38-4.31 and > 4.31mIU/L), then a score of CAD was assessed for each group. The statistical analysis was performed as follows:

- Data were expressed as mean± (SD).
- Paired and unpaired Student’s $t$-test for the differences between groups for continuous variables.
- Analysis of one way variation (ANOVA) test was applied when more than two groups were compared.
- Chi-square( $X^2$ ) was used to compare the proportions in qualitative variables and to analyze the relations between TSH levels and score of angiography.

The results were considered statistically significant at $p<0.05$.

**RESULTS**

The severity of CAD was scored as 0, 1, 2, 3 and 4 in 51, 45, 23, 27 and 4 patients, respectively (Fig.1).

![Fig.1: Severity of CAD in the overall patients](image)

Table (1) shows patients characteristics according to angiography scores regarding the history of the underlying disease and smoking. Among the conventional risk factors for CAD, patient’s age ($p=0.007$), male ($p=0.001$), hypertension ($p=0.05$), diabetes mellitus ($p=0.02$), hyperlipidemia ($p=0.05$) and smoking ($p=0.001$).

**Table 1: Characteristics of patients according to angiography scores**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Angiography Scores</th>
<th>Total N=150</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Score(0)</td>
<td>Score(1)</td>
</tr>
<tr>
<td></td>
<td>N=51</td>
<td>N=45</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male (n)%</td>
<td>(14) 9.3%</td>
<td>(34) 22.7%</td>
</tr>
<tr>
<td>Female (n)%</td>
<td>(37) 24.7%</td>
<td>(11) 7.3%</td>
</tr>
<tr>
<td>Hypertension (n)%</td>
<td>(28) 18.7%</td>
<td>(24) 16.0%</td>
</tr>
<tr>
<td>Diabetes Mellitus (n)%</td>
<td>(8) 5.3%</td>
<td>(12) 8.0%</td>
</tr>
<tr>
<td>Hyperlipidemia (n)%</td>
<td>(18) 12.0%</td>
<td>(18) 12.0%</td>
</tr>
<tr>
<td>Smoker (n)%</td>
<td>(6) 4.0%</td>
<td>(16) 10.7%</td>
</tr>
</tbody>
</table>

(43) 28.7%
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The data are expressed as number (n) and percentage (%). The differences in frequencies were performed by \( \chi^2 \) test.

Table (2) shows patients characteristics according to the angiography score regarding age, SBP, DBP, BMI, TSH, FT4, TC, HDL-C, LDL-C, TG and AI. The severity of CAD increased significantly with age, BMI increases significantly with the increase of the angiography score. Also TC, LDL-C, TG and AI show a significant increase across angiography score, while HDL-C significantly decrease. Although TSH insignificantly increased with the severity of CAD as in (score 3 and 4).

Moreover, there was no significant difference regarding the mean TSH level across different score groups \((p=0.7)\). Free T4 shows non significant decrease across the angiography score. The mean SBP and DBP show non significant difference among angiography score.

Table 2: Characteristics of patients according to angiography scores.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Score (0) N=51</th>
<th>Score (1) N=45</th>
<th>Score (2) N=23</th>
<th>Score (3) N=27</th>
<th>Score (4) N=4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Years)</td>
<td>52.01±9.68 (30.00-76.00)</td>
<td>51.77±8.43 (33.00-67.00)</td>
<td>53.30±10.24 (34.00-78.00)</td>
<td>55.92±8.68 (36.00-72.00)</td>
<td>68.25±11.84 (51.00-76.00)</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>135.68±20.64 (100.00-185.00)</td>
<td>126.66±19.94 (80.00-170.00)</td>
<td>135.86±18.06 (110.00-185.00)</td>
<td>138.70±21.68 (100.00-180.00)</td>
<td>135.00±26.45 (100.00-160.00)</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>79.50±11.36 (60.00-120.00)</td>
<td>78.66±19.14 (50.00-185.00)</td>
<td>79.13±9.49 (70.00-100.00)</td>
<td>81.85±12.33 (60.00-110.00)</td>
<td>73.75±7.50 (65.00-80.00)</td>
</tr>
<tr>
<td>BMI (Kg/m²)</td>
<td>31.53±6.87 (20.43-55.55)</td>
<td>29.85±5.43 (22.49-42.65)</td>
<td>27.87±4.38 (19.75-37.77)</td>
<td>28.86±3.37 (23.66-34.89)</td>
<td>28.22±3.16 (23.88-31.39)</td>
</tr>
<tr>
<td>TSH (mIU/L)</td>
<td>2.09±1.93 (0.30-13.41)</td>
<td>1.79±1.09 (0.26-5.47)</td>
<td>1.72±0.97 (0.42-4.55)</td>
<td>1.89±1.14 (0.79-5.25)</td>
<td>1.38±0.40 (1.02-1.74)</td>
</tr>
<tr>
<td>FT4 (ng/dl)</td>
<td>1.44±0.30 (0.69-2.15)</td>
<td>1.40±0.28 (0.89-2.01)</td>
<td>1.47±0.32 (1.01-2.06)</td>
<td>1.40±0.31 (0.75-2.17)</td>
<td>1.23±0.23 (0.95-1.44)</td>
</tr>
<tr>
<td>TC (mmol/L)</td>
<td>3.97±1.07 (2.44-6.19)</td>
<td>4.19±1.24 (1.84-7.31)</td>
<td>4.58±1.11 (2.18-8.06)</td>
<td>4.53±1.29 (2.76-7.04)</td>
<td>4.33±1.02 (3.11-5.49)</td>
</tr>
<tr>
<td>HDL-C (mmol/L)</td>
<td>1.09±0.32 (0.56-2.20)</td>
<td>0.94±0.20 (0.31-1.37)</td>
<td>0.85±0.18 (0.51-1.29)</td>
<td>0.92±0.11 (0.69-1.23)</td>
<td>0.93±0.11 (0.85-1.10)</td>
</tr>
<tr>
<td>LDL-C (mmol/L)</td>
<td>2.19±0.93 (1.05-4.35)</td>
<td>2.38±1.11 (0.24-5.30)</td>
<td>2.80±1.01 (0.83-5.70)</td>
<td>2.60±1.19 (0.87-5.00)</td>
<td>2.32±0.66 (1.43-2.93)</td>
</tr>
<tr>
<td>TG (mmol/L)</td>
<td>1.52±0.61 (0.55-3.47)</td>
<td>1.92±0.93 (0.63-4.92)</td>
<td>2.04±0.76 (0.89-3.93)</td>
<td>2.22±1.04 (0.61-5.13)</td>
<td>2.41±0.98 (1.84-3.88)</td>
</tr>
<tr>
<td>AI (mmol/L)</td>
<td>4.38±1.29 (2.03-7.52)</td>
<td>4.55±1.37 (1.96-8.61)</td>
<td>4.88±1.80 (2.58-10.31)</td>
<td>4.97±1.51 (2.87-8.38)</td>
<td>4.64±1.15 (3.65-6.31)</td>
</tr>
</tbody>
</table>

Data are expressed as mean± (SD) and (ranges). Analysis of mean difference between groups were performed by ANOVA test.

Table (3) shows that the mean serum TSH level was higher in women than men but there was no statistical significant difference between mean TSH level in person with and without CAD in each sex group.
Table 3: Gender distribution and mean TSH level in relation to coronary stenosis score.

<table>
<thead>
<tr>
<th>Gender</th>
<th>Without coronary stenosis</th>
<th>With coronary stenosis</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>N</td>
<td>14</td>
<td>74</td>
</tr>
<tr>
<td>TSH (mIU/L)</td>
<td>1.31±0.67</td>
<td>1.68 ±0.96</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>N</td>
<td>37</td>
<td>25</td>
</tr>
<tr>
<td>TSH(mIU/L)</td>
<td>2.10±1.26</td>
<td>2.39 ±2.17</td>
<td></td>
</tr>
</tbody>
</table>

Data are expressed as mean ± SD.

Evidence suggests that SCH carried a risk of CAD. Thus, the classification in the present work was done according to TSH level into three groups (<0.38, 0.38-4.31 and >4.31 mIU/L). The relationship between TSH and the prevalence of CAD was assessed. Although there is no significant difference of mean TSH across different groups of angiographic score but TSH levels showed a trend toward higher levels in the patients with multivessel disease as in group with score (2, 3 and 4) compared to that with score (0 and 1). The extent of CAD and the incidence of multivessel disease increase with the increased of TSH levels (p=0.03) (Fig.2).

![Fig. 2: The relationship between groups of TSH levels and angiography scores.](image)

Table (4) showed patients characteristics according to groups of TSH levels. There was a significant difference regarding gender (p=0.01), BMI (p=0.05) and DM (p=0.02) across different TSH groups. There was an increase in the concentration of TC, LDL-C, TG and AI, and a reduction in HDL-C with the increase TSH level.
Table 4: Characteristics of patients according to groups of TSH levels.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>TSH groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;0.38</td>
</tr>
<tr>
<td></td>
<td>N=5</td>
</tr>
<tr>
<td>Age (Years)</td>
<td>53.80±5.26 (47.00-60.00)</td>
</tr>
<tr>
<td>Gender</td>
<td>Male (n)% 3.3% (5)</td>
</tr>
<tr>
<td></td>
<td>Female (n)% 0% (0)</td>
</tr>
<tr>
<td>Hypertension (n)%</td>
<td>1.3% (2)</td>
</tr>
<tr>
<td>Diabetes Mellitus (n)%</td>
<td>2.0% (3)</td>
</tr>
<tr>
<td>Hyperlipidemia (n)%</td>
<td>0.7% (1)</td>
</tr>
<tr>
<td>Smoker (n)%</td>
<td>1.3% (2)</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>126.00±25.09980 (110.00-170.00)</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>74.00±5.47 (70.00-80.00)</td>
</tr>
<tr>
<td>BMI (Kg/m²)</td>
<td>27.9±2.72 (22.79-39.79)</td>
</tr>
<tr>
<td>FT4 (ng/dl)</td>
<td>1.61±0.16 (1.38-1.76)</td>
</tr>
<tr>
<td>TC (mmol/L)</td>
<td>4.05±1.10 (2.27-5.29)</td>
</tr>
<tr>
<td>HDL-C (mmol/L)</td>
<td>0.98±0.09 (0.82-1.07)</td>
</tr>
<tr>
<td>LDL-C (mmol/L)</td>
<td>2.49±1.07 (0.88-3.87)</td>
</tr>
<tr>
<td>TG (mmol/L)</td>
<td>1.17±0.32 (0.73-1.64)</td>
</tr>
<tr>
<td>AI (mmol/L)</td>
<td>4.31±1.10 (2.76-5.81)</td>
</tr>
</tbody>
</table>
DISCUSSION

This study showed that variation of TSH within normal range might influence the extent and the severity of CAD but not the presence of CAD. Thus, the higher levels of TSH were associated with multivessel disease (p=0.03).

Accordingly, the results of this work are in agreement with those obtained by other studies of (Auer et al., 2003), who studied 100 patients (59 men and 41 women) (63.7±11.0 years), whom underwent coronary angiography. They concluded that higher TSH concentrations were associated with increasing severity of coronary atherosclerosis (p=0.049).

Yun et al., (2005), studied 125 patients (84 males and 41 females) their age (60±11.1) years whom underwent diagnostic coronary angiography, they found that TSH was significantly higher (p=0.053) in patients with multivessel diseases compared to those with normal coronary arteries.

Moreover, Yun et al., (2007), studied 344 patients aged (62.5±9.72), 50% were male who underwent elective coronary angiography. The incidence of multivessel disease was statistically higher (p=0.03) in patients with high TSH.

In the present study, there was no association between TSH level and the presence of CAD. Although the mean TSH was higher in women than men, but there was no statistical significant difference between mean TSH levels in person with and without CAD in each sex group.

This result was similar to that of (Shams et al., 2005) whom performed a cross sectional study on 390 patients (239 males and 151 females) with mean age of (55.12±10.52) years who had referred to the unit of coronary angiography. They reported that mean serum TSH was significantly higher in women. Moreover, there was no correlation (p=0.37) between TSH level and the presence of CAD in either sex.

Thyroid hormones regulate the expression of enzymes involved in all steps of lipid metabolism leading to the development of qualitative and quantitative changes of lipids. (Zhu et al., 2010). Dyslipidemia coexist with other metabolic abnormalities, including hypertension, insulin resistance and oxidative stress, all of them being risk factor for CVD. (Peppa et al., 2011).

It was reported that thyroid function tests were altered in patients with a cute coronary syndrome (ACS). These changes are characterized by euthyroid sick syndrome. However, thyroid functions were not associated with the widespread of coronary artery disease according to coronary angiography (P>0.05). (Tuzun et al., 2010).

The abnormality of thyroid hormones that lead to CAD through different mechanisms including effects on endothelial functions, relaxation of smooth muscles and blood rheology. (Fazio et al., 2004).

In notice, regarding our study results, most of the major risk factors had a clear significance as a predictors for developing (CAD patient’s age p=0.007, male p=0.001, hypertension p=0.05, DM p=0.02, hyperlipidemia p=0.05, smoking p=0.001 and BMI p=0.05), this is in accordance with the common medical knowledge. (Kaspar et al., 2005).

Risk for CAD increases steeply with advancing age in both sex. The principal reason is that age is a reflection of the progressive accumulation of coronary atherosclerosis. (Wilson et al., 1998). Also, at any age male are at a greater risk of CAD than female, this
can be explained by earlier onset of risk factor in male such as elevation of LDL-C, blood pressure and reduction of HDL-C. (Mendelson and Karas, 1999)

Hypertension is a major independent risk factor for CAD, it may induce endothelial injury to the walls of coronary arteries, it also increases the workload on the heart (Padwal et al., 2001). People with DM are at a greater risk of CAD, High blood glucose levels over time can lead to increase the deposits of fatty materials on the inside of the blood vessel walls. These deposits may affect blood flow, increasing the chance of clogging and hardening of blood vessels (Herlitz et al., 1992).

There is a positive association between the increased BMI and the risk of CAD. The increased BMI is associated with an adverse effect on all major CAD risk factors including dyslipidemia, DM and hypertension (Fava et al., 1996). The relationship of smoking to CAD is dose dependent and observed in men and women (Campisi et al., 1998).

From this study, it was observed that the extent of CAD that is represented by the angiography score is positively associated with the atherogenic lipids (TC, LDL-C, TG) and negatively associated with antiatherogenic HDL-C. This agrees with the study performed by (Tarchalski et al., 2003).

The synthesis of TSH might be affected by the mass of adipose tissue. It was found that there were receptors expressed for TSH in adipose tissue (Kershaw and Flier, 2004). In the present work, it was observed that there is a significant increase in BMI with the elevation of TSH level. This observation was in accordance with (Nyrnes et al., 2006) which found a positive association between TSH within normal range and BMI.

The current study shows that TSH level significantly increased in patients with DM (p=0.02) and this is comparable to one study (Chubb et al., 2005). The research demonstrated that at a low insulin sensitivity, relatively minor differences in TSH are associated with the marked change in lipid levels that is a risk factor for CVD.

The observation drawn from this study regarding serum TC, LDL-C and TG increased with increasing TSH level, while HDL-C decreased. These results were comparable to those obtained by other researchers (Asvold et al., 2007; Patidar et al., 2012). They reported that mild elevation of TSH is associated with changes in lipid profile that significantly raised the risk of cardiovascular disorders.

The pathophysiological process behind the abnormality of thyroid functions on lipid metabolism including: 1- High serum TC and LDL-C might be caused by fewer cell-surface receptors for LDL, resulting in reduced LDL catabolism (Cappola and Ladenson, 2003). 2- High serum TG might be caused by reduced activity of lipoproteins lipase (Lithell et al., 1981) or impaired clearance of lipoproteins dependant on LDL receptor function (Liu et al., 1998) might result in higher levels.

CONCLUSION

This cross sectional study suggested that the high level of serum TSH is associated with multi-vessel disease, but it was not the determinant of CAD in patients with the normal range of thyroid functions.

The positive association between the TSH in reference range and concentration of serum TC, LDL-C and TG, and a negative association of TSH and HDL-C was found.

Although clinically and biochemically levels of TSH indicate normal thyroid functions but it might have long term harmful effects on cardiovascular health by the association with the abnormal serum lipids.
REFERENCES


