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# The Effect of Hypothyroidism on Insulin Sensitivity and Their Influence on the Serum Lipid Profile and Renal Function

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## Abstract

The overt and subclinical hypothyroidism is more prevalent in patients with diabetes mellitus than in general population. Recently, more studies have been warranted to elucidate the relationship between thyroid hormones disorders and the insulin activity. The present study aims to investigate the correlations between the thyroid hormone levels in subclinical and overt hypothyroid patients with the insulin resistance and their impact on serum lipid profiles and kidney function.

**Methods:** A total of fifty newly diagnosed hypothyroid patients were recruited for the study and classified into: 1) Subclinical hypothyroid (SH) group: n-26; 2) Overt hypothyroid (OH) group: n=24, and control (C) group: n=18. Fasting blood was collected and serum was used for biochemical analysis.

**Results:** The fasting serum insulin, glucose levels and the estimated insulin resistance index (HOMA) of the SH and OH groups were significantly (P<0.001) elevated compared to control. The regression analysis reviled a significant negative correlation between $FT_4$ and insulin (r=-0.32, P=0.04) and significant positive correlations between TSH and insulin (r=0.57, P=0.002), between TSH and HOMA (r=0.51, P=0.001), between HOMA and uric acid (r=0.37, P=0.02), and between TSH and TG (r=0.47, P=0.002). The serum creatinine, urea and uric acid concentrations were significantly (P<0.001) elevated in the OH group but not the SH. The serum total cholesterol, TG and LDL-cholesterol were significantly elevated in both SH and OH.

**Conclusion:** Hypothyroidism is associated with insulin resistance, renal impairment, hyperurecemia and dyslipidemia, which are atherosclerotic risk indicators. The TSH had maximum impact on the changes.

Subclinical and overt hypothyroid patients with elevated TSH are at high risk of developing atherosclerosis, thus may need close monitor to contain the rise in plasma TSH.

**Keywords:** Hypothyroidism; Insulin resistance; Renal function; Dyslipidemia

## Introduction

Thyroid disorders are common in the general population, with hypothyroidism being the predominant disorder in the adult population [1,2]. The disorder is associated with impaired cardiac contractility, endothelial dysfunction, atherosclerosis and increased carotid intima-media thickness [3,4]. Several studies have shown overt and subclinical hypothyroidism being more prevalent in patients with diabetes mellitus than in general population [5], and women with subclinical hypothyroidism are believed to be at more risk to develop gestational diabetes [6]. The thyroid hormones are known to have a stimulating effect on maturation of the insulin secreting beta cells, and thyroid hormone receptors have been detected in these cells [7]. The hormones enhance gluconeogenesis and glycogenolysis in an opposing effect to insulin [8], whereas, they are known to facilitate the cellular glucose uptake by expressing the glucose transporter-4 (GLT-4) isozyme [9]. Recently researchers have become more concerned to elucidate the complex relationship between thyroid hormones and the insulin activity and more studies have been warranted to clarify the underlying pathogenic mechanisms [10]. In the light of these reports, we planned to evaluate the correlations between the thyroid function parameters (free $T_3$, free $T_4$ and TSH) in subclinical and overt hypothyroid patients with the insulin resistance and their impact on the serum lipid profiles and kidney function in patients from Hail region, Saudi Arabia.

## Patients and Methods

### Protocol of study

The study was conducted on newly diagnosed patients with thyroid disorders who were visiting the Diabetic and Endocrinology Out-Patient Unit of King Khalid Hospital, Hail, Saudi Arabia. The patients clinical data entered in the record book of the laboratory were used in this study. A total of 50 newly diagnosed hypothyroid patients were recruited for the study. Patients suffering from chronic liver or kidney diseases were excluded. Depending on their serum TSH, free T3 ($FT_3$) and free T4 ($FT_4$) levels, the patients were classified into:

- Subclinical hypothyroid (SH) group: n=26 patients (M=9, F=17) with serum TSH>4.0 mU/L and with normal $FT_4$ and $FT_3$ levels;

- Overt hypothyroid (OH) group: n= 24 patients (M=10, F=14) with TSH>4.0 mU/L and $FT_4$<9.0 pmol/L;
- The control (C) group: n= 18, (M=8, F=10) were normal subjects visiting the clinic for routine check-up. All patients had an age range of 18-77 years (mean age was 43.47 ± 11.20 years).

The Inclusion criteria were newly diagnosed subclinical or overt hypothyroid, male and females age ≥ 18 Yrs. Exclusion criteria were cardiovascular diseases, diagnosed diabetes mellitus on insulin or other hypoglycemic medication, chronic liver disease or known kidney disease. A sample of 5 ml venous blood was collected from each patient after an overnight fast and serum was separated and used for the biochemical analysis. The protocol of experiment was explained and the consent was obtained from the participants. The study was approved by the ethical committee, Faculty of Applied Medical Sciences, University of Hail, Hail, Saudi Arabia.

### Biochemical assays

The concentrations of serum $FT_3$, $FT_4$, TSH and insulin were assayed by Autoanalyzer (ELecsys 2010, Cobas E 411-Mannheim Germany). The serum glucose, urea, creatinine, uric acid, total cholesterol, triglyceride (TG), high density lipoprotein cholesterol (HDL-c) and low density lipoprotein cholesterol (LDL-c) were measured by the automated spectrophotometer, Hitachi-717, utilizing commercial kits supplied by Roche Diagnostic, United Kingdom. The very low density lipoprotein (VLDL) fraction was calculated by subtracting HDL+LDL from total cholesterol. The estimated homeostasis model assessment –Insulin resistance (HOMA-IR) index was calculated by the method described by Matthews et al. [11]. It was calculated by multiplying the fasting serum glucose (mmol/L) by the fasting serum insulin (mU/L) divided by 22.5. The values less than 2.5 were considered normal, and the higher values indicated insulin resistance [12].

### Statistical analysis

The presented data are means ± SD. The significance of differences between the means was computed by one way analysis of variance, followed by Multiple Comparison Analysis. Spearman's regression analysis was used to study the significance of correlation among the $FT_4$, $FT_3$, TSH, HOMA, insulin, glucose, lipids and kidney function parameters. P value less than 0.05 was considered.

## Results

### Thyroid function

Table 1 summarizes the mean age and thyroid function parameters in the experimental groups. The highest average age was that of the OH group, whereas, the mean age of SH was not different from that of control group. The serum TSH of the OH group was significantly (P<0.001) higher than that of SH, which was in turn significantly (P<0.001) higher than control. The serum $FT_3$ values of SH and OH groups were not different from that of control and were within normal range. However, the $FT_4$ of the OH group was significantly (P<0.001) lower than that of the SH and control groups, which were not different from each other.

The serum insulin levels in the SH and OH groups were significantly increased by 2.11-fold, and 2.42-fold, respectively compared to control (Figure 1). However, the fasting serum glucose concentration was significantly elevated in the OH group by 39.15% compared to control, and was not different from that of the SH group. Moreover, the estimated HOMA-IR was significantly elevated in the OH and SH groups by 3.65-fold and 2.43-fold, respectively compared to control. As shown in Figure 2, the regression analysis showed a significant negative correlation between $FT_4$ and insulin (r=-0.32, P=0.04) and a trend of negative correlation between $FT_4$ and HOMA (r=-0.27, P=0.09). It also showed a significant positive correlation between TSH and serum insulin (r=0.57, P=0.002), and between TSH and HOMA (r =0.51, P=0.001). A significant positive correlation was also shown between HOMA and uric acid (r=0.37, P=0.02), and between TSH and TG (r= 0.47, P=0.002).

### Effect on kidney function

Table 2 depicts the kidney function parameters in the experimental groups. The serum creatinine, urea and uric acid concentrations were significantly elevated in the OH group by 2.11-fold, 94.39% and 29.61%, respectively compared to control. However, none of the parameters were significantly raised in the SH group.

### Effect on serum total lipids and lipoproteins

As shown in Table 3, the serum total cholesterol was significantly increased in the SH and OH by 27.25% and 62.08%, respectively. Similarly, the serum TG was significantly elevated in the SH and OH by 60.78% and 1.01-fold, respectively compared to control.

On the other hand, the HDL-c showed a trend of decrease in the SH and OH groups, but was not statistically significant. However, the LDL-c fractions of the SH and OH groups were significantly elevated by 29.92% and 86.22%, respectively compared to control. Moreover, the VLDL was significantly elevated in the SH and OH by 59.57% and 100%, respectively.

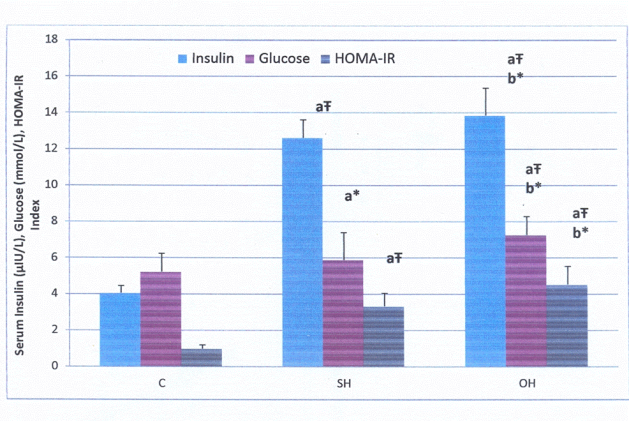


**Figure 1:** The serum insulin, glucose and estimated insulin resistance index (HOMA-IR) in subclinical hypothyroid (SH), overt hypothyroid (OH) and control (C) groups. Columns and vertical bars represent means ± SD. ∓P<0.001; a: significantly different from C; b: significantly different from SH.

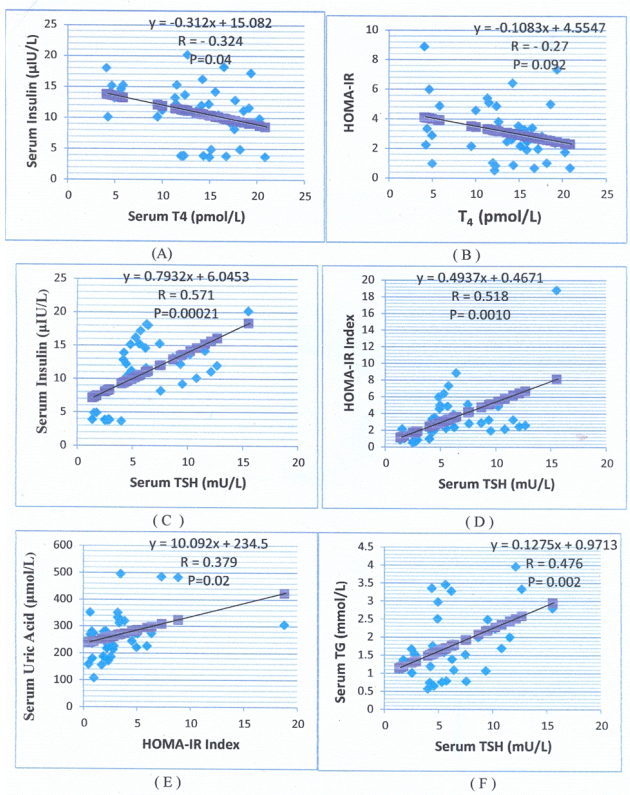


**Figure 2:** Straight line plot of the regression analysis for ; (A): the serum $FT_4$ values with serum fasting insulin levels, (B): the serum $FT_4$ values with the estimated homeostasis model assessment – Insulin resistance (HOMA-IR) index; (C): The serum TSH values with serum insulin levels; (D): The serum TSH values with HOMA-IR index; (E): HOMA-IR index with serum uric acid levels and (F): The serum TSH values with serum triglyceride (TG) levels in pooled control, subclinical and overt hypothyroid patients.

| | C | SH | OH |
|---|---|---|---|
| Gender | M=8 F=10 | M=9 F=17 | M=10 F=14 |
| Age (Yrs) | 33.11 ± 10.18 | 38.94 ± 8.81 | 48.00 ± 14.66 |
| TSH (mU/L) | 2.49 ± 0.81 | 7.88 ± 3.46a$^{\mp}$ | 14.89 ± 3.48 a$^{\mp}$b$^{\mp}$ |
| $FT_4$ (pmol/L) | 14.10 ± 4.47 | 15.17 ± 3.16 | 4.84 ± 0.63 a$^{\mp}$b$^{\mp}$ |
| $FT_3$ (pmol/L) | 6.17 ± 3.31 | 5.29 ± 1.01 | 7.23 ± 3.02 |
| Presented data are mean ± SD; $^{\mp}$P<0.001. a: significantly different from C; b: significantly different from SH | | | |

**Table 1:** The mean ages and thyroid function parameters in subclinical hypothyroid (SH), overt hypothyroid (OH) and control (C) groups.

| | C | SH | OH |
|---|---|---|---|
| Creatinne (umol/L) | 63.46 ± 13.71 | 70.56 ± 22.36 | 134.12 ± 15.46a$^{\mp}$b$^{\mp}$ |
| Urea (mmol/L) | 4.46 ± 0.94 | 5.53 ± 1.16 | 8.62 ± 2.01a$^{\mp}$ |
| Uric acid (umol/L) | 232.83 ± 33.15 | 249.47 ± 25.36 | 301.79 ± 26.36a$^{\mp}$b$^{\mp}$ |
| The presented data are means ± SD; $^{\mp}$P<0.001; a: significantly different from C; b; significantly different from SH | | | |

**Table 2:** The kidney function parameters in the subclinical hypothyroid (SH), overt hypothyroid (OH) and control (C) groups.

| | C | SH | OH |
|---|---|---|---|
| Total cholesterol (mmol/L) | 4.22 ± 0.47 | 5.37 ± 1.28a$^{**}$ | 6.84 ± 1.25a$^{‡}$b$^{*}$ |
| TG (mmol/L) | 1.02 ±0.41 | 1.64 ± 0.55a$^{‡}$ | 2.06 ± 0.72a$^{‡}$b$^{‡}$ |
| HDL-c ( mmol/L) | 1.40 ± 0.21 | 1.35 ± 0.21 | 1.26 ± 0.17 |
| LDL-c ( mmol/L) | 2.54 ± 0.54 | 3.30 ± 1.22a$^{‡}$ | 4.73 ± 0.99a$^{‡}$b$^{‡}$ |
| VLDL-c (mmol/L) | 0.47 ± 0.18 | 0.75 ± 0.25a$^{‡}$ | 0.94 ±0.33a$^{‡}$b$^{‡}$ |
| The presented data are means ± SD; $^{*}$P<0.05, $^{**}$P<0.01, $^{\mp}$P<0.001; a: significantly different from C; b: significantly different from SH | | | |

**Table 3:** The serum lipids and lipoprotein levels in the subclinical hypothyroid (SH), overt hypothyroid (OH) and control (C) groups.

## Discussion

The present study revealed that our patients of the overt hypothyroid group were older in age with the percentage of females being higher than males. This is a commonly observed trend in thyroid disorders, where hypothyroidism is shown to be more prevalent among older ages and particularly in women [13]. Although the mean value of FT4 in the overt hypothyroid group was below normal, but the mean FT3 value was within the normal range (normal range 3.5-7.8 pmol/L). It is known that about 85% of the circulating T3 is synthesized in extra-thyroid tissues by deiodination of T4 where metabolic factors prevailing in these tissues may influence its plasma levels. This probably explains its maintenance within normal range in spite of fall in the levels of FT4. In our study we addressed the possible influence of the thyroid hormones and TSH on insulin sensitivity. In a cohort study, Gronich et al. [4] indicated that overt and subclinical hypothyroidism were related to increased risk for the development of diabetes mellitus, whereas, treatment with thyroxine replacement therapy alleviated that risk.

In the present study there was a several fold increase in the fasting insulin level of the hypothyroid patients with significant increases in the serum glucose concentrations. The estimated insulin resistance index (HOMA) exhibited a significant increase in both subclinical and overt hypothyroid patients. Our results were in agreement with those of Kapadia et al. [10] who found significantly increased fasting serum insulin level with lower insulin sensitivity in the hypothyroid patients. Our data also indicated a significant negative correlation between $FT_4$ and serum insulin values (r=-0.32, P=0.04), and a more significant positive correlation between TSH and the serum insulin values (r=0.57, P=0.0002). Similarly, TSH exhibited a highly significant positive correlation with HOMA (r= 0.518, P=0.001). This indicates a strong influence of TSH on the fasting insulin levels and the insulin resistance. Some studies have indicated the effect of TSH on insulin action and that even a subtle increase in plasma TSH levels within the normal range can affect insulin secretion [14,15] and may cause insulin resistance and metabolic syndrome [16,17]. Moreover,

hypothyroid patients are known to experience a decrease in glucose transporters $GLUT_4$ leading to a reduction of glucose uptake and promoting insulin resistance [18,15]. The relationship between thyroid hormonal status and insulin levels in the pathogenesis of insulin resistance is complex. The higher fasting serum insulin concentrations were believed to develop as a compensation result of the insulin resistance [19]. Many authors accept the concept that a patient suffering from an autoimmune disorder is more prone to be affected by an autoimmune disorder of insulin resistance. Tina et al. [20] observed more prevalence of elevated fasting insulin levels among a group of hypothyroid patients with highly elevated levels of anti-thyroid peroxidase antibodies (above 1000 IU/ml) which might support the concept of autoimmunity role in insulin resistance. Other investigators relate the occurrence of insulin resistance among hypothyroid patients to the high prevalence of obesity and the high fat deposits in this population [21]. All proposed underlying causes of insulin resistance among the hypothyroid patients are commonly present, where the majority of these patients are obese and the circulating abnormal antibodies are normally detected.

The present data exhibited significant impairment of kidney function in the overt hypothyroid group as evidenced by elevations of the serum creatinine, urea and uric acid concentrations. As frequently observed in the diabetic population, there is also high prevalence of hypothyroidism among the kidney disease patients [22,23]. Some authors suggest that hypothyroidism leads to impairment of kidney function through alterations in the renal hemodynamics and tubular structure [24]. However, our data exhibited a significant correlation between HOMA and uric acid but not creatinine. It has been indicated that hyperinsulinemia may contribute to hyperuricemia by blocking uric acid excretion, whereas, hyperuricemia has also been reported to precede the development of hyperinsulinemia. In the experimental animals high plasma uric acid levels were shown to directly induce insulin resistance *in vivo* and *in vitro* by inhibiting insulin receptor substrate-1. The generation of reactive oxygen species is believed to play a key role in hyperurecemia-induced insulin resistance [25]. Hyperurecemia was also shown to inhibit the insulin signaling and induce insulin resistance in the cardiomyocytes, which was suggested to be a mechanism of hyperuricemic-related cardiovascular disease [26].

The present results also revealed significant elevations in serum total and LDL-cholesterol levels as well as the serum TG levels in the overt hypothyroid group. Interestingly, the TSH exhibited a significant positive correlation with TG but not with cholesterol. However, Xu et al. [27] found a significant positive correlation between TSH and the serum total cholesterol levels. Other investigators have reported that hypothyroidism is associated with increased serum total and LDL-c, the small dense lipoprotein (a) and TG levels [28]. Moreover, the plasma total cholesterol and LDL-C were also reported to be elevated in the subclinical hypothyroid patients with elevated atherogenic lipid parameters [1,21]. This was observed particularly in subclinical hypothyroid patients with TSH levels ≥ 10 showing increased risk of cardiovascular disease and mortality [29]. The investigators attributed these changes to decreased clearance of LDL particles from circulation due to reductions in the hepatic LDL receptors, and decreased hepatic cholesterol catabolism by the T3-regulated cholesterol 7-α-hydroxylase enzyme [30]. Moreover hypothyroidism is associated with increased oxidation of LDL particles. Such modification of the LDL particles can impair their receptor-mediated uptake causing accumulation [31]. Such elevated levels of circulating oxidized-LDL in hypothyroidism are believed to increase the vascular systemic and pulmonary resistances causing pulmonary hypertension [32]. Results of the present study have emphasized the significant impact of TSH to increase the TG and possibly total cholesterol levels independent of the thyroid hormones. It highlights the importance of maintaining an appropriate TSH level in patients susceptible to atherosclerotic diseases.

## Conclusion

Hypothyroidism is associated with insulin resistance, renal impairment, hyperurecemia and dyslipidemia, all of which are risk factors for cardiovascular diseases.

TSH showed more influence on these changes independent of the thyroid hormones.

Subclinical and overt hypothyroid patients with elevated TSH are at high risk of developing atherosclerosis, thus may need close monitor to contain the rise in plasma TSH level.

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