Homeostatic Model Assessment-Insulin Resistance (HOMA-IR 2) in Mild Subclinical Hypothyroid Subjects

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Abstract Despite various studies with conflicting results, the effect of thyroid hormones on lipids and insulin levels in dysthyroidism is of great interest. This case control study was aimed to perceive the existence of IR and dyslipidemia in mild subclinical hypothyroid subjects ($TSH \leq 9.9 \mu IU/ml$) as compared to their age and gender matched euthyroid controls. Basic demographic information like height, weight was recorded. Serum samples of all the subjects were assayed for thyroid profile, lipid profile, blood glucose, HbA1C and insulin. BMI and insulin resistance was calculated. Compared to controls patients with mild subclinical hypothyroidism demonstrated hyperinsulinemia and dyslipidemia observed by the higher LDL cholesterol. A significantly positive correlation was observed for HOMA-IR with TSH and LDL cholesterol. Hence, even in the mild subclinical hypothyroid state assessment of thyroid function should be combined with estimation of plasma glucose, insulin and serum lipids to monitor and prevent its associated effects.

Keywords Dyslipidemia · HOMA-IR-2 · Insulin resistance · Subclinical hypothyroidism

Introduction

Insulin resistance (IR) and dyslipidemia are the central pathophysiological phenomenon underlying the metabolic syndrome, a major cardiovascular risk factor [1, 2]. In recent years the influence of thyroid hormones on insulin and lipid levels has gained prominence. It is established that clinical hypothyroidism is considered as an insulin-resistant state and is associated with increased risk of dyslipidemia [3, 4].

The exact mechanism connecting hypothyroidism to Insulin Resistance and dyslipidemia is still unclear [5]. Subclinical hypothyroidism (SCH) has been associated with disorders of altered lipids and insulin activity [6, 7], but there is controversy as to whether this association exists in mild subclinical hypothyroid state ($TSH \leq 9.9 \mu IU/ml$) [8–10].

The study was aimed to perceive the existence of IR and dyslipidemia in subjects with mild SCH ($TSH \leq 9.9 \mu IU/ml$).

Materials and Methods

In the present case control study, sixty euthyroid controls and sixty newly diagnosed mild SCH subjects with TSH ranging from (4.12–9.9 $\mu IU/ml$) with normal T3 and T4 of both genders aged between 20 and 45 years without any known thyroid disease were enrolled from those who came for a routine health check to a tertiary care hospital.

Patients with diabetes mellitus, hypertension, systemic illness, liver disorders, renal disorders, congestive cardiac failure, pregnant women, tobacco chewers, chronic alcoholics and those on medications altering the thyroid function were excluded from the study based on a

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questionnaire. Informed consent was obtained from all the study participants and the study was approved by IEC.

Basic demographic information and physical data including height, weight, systolic and diastolic blood pressure were collected. BMI was calculated. Thyroid profile—TSH (third-generation TSH assay; normal range: 0.27–4.12 μ IU/ml) T₄ (normal range: 5.1–14.1 μ g/ml), T₃ (normal range: 0.80–2.0 ng/ml), blood glucose (fasting and post prandial) and Lipid profile were estimated by Roche COBAS-6000 modular system and HbA1C by Bio-Rad D10. Insulin was estimated by ELISA using commercially available kits. Insulin resistance was calculated using homeostasis model assessment (HOMA-IR 2) from fasting serum glucose and insulin using the Oxford HOMA calculator (www.dtu.ox.ac.uk/homacalculator).

Statistical Analysis

The SPSS package program (version 16.0, Chicago, IL) was used for statistical analysis. Data were presented as mean $\pm$ SD. The results were analyzed by students 't' test and the association between variables were evaluated using Pearson's correlation test 'p' value ≤ 0.05 was considered statistically significant.

Results and Discussion

BMI, LDL-C, insulin levels and IR were found to be elevated in the SCH group (Tables 1, 2, 3). Thyroid hormones have a significant effect on glucose metabolism and the development of insulin resistance. In hypothyroidism insulin resistance of peripheral tissues prevails [1]. It is hypothesized that decrease in T₃ leads to a decreased binding of insulin to the receptors and Impaired translocation of GLUT4, resulting in decreased glucose uptake in muscles and adipose tissue [1]. Gen et al. [10] reported early insulin resistance and hyperinsulinemia in mild SCH subjects while IR in overt hypothyroidism. Al Sayed et al. [11] observed only fasting hyperinsulinemia and not IR in

Table 1 Baseline characteristics of study subjects

Parameters	Euthyroid (N = 60)	SCH (N = 60)	p value
M:F	17:43	22:48	
Age (years)	39 $\pm$ 7	41 $\pm$ 8	0.113
T ₃ (ng/ml)	1.1 $\pm$ 0.2	1.1 $\pm$ 0.2	0.288
T ₄ (μ g/dl)	8.4 $\pm$ 1.0	7.8 $\pm$ 1.3	0.002
TSH (μ IU/ml)	2.0 $\pm$ 0.8	5.6 $\pm$ 1.4	0.001
BMI (kg/m ²)	24.4 $\pm$ 3	25.5 $\pm$ 3	0.049

T₃ free triiodothyronine, T₄ thyroxine, TSH thyrotropin, BMI body mass index

Table 2 Comparison of biochemical parameters between SCH and controls

Lipid parameters (mg/dl)	Euthyroid (N = 60)	SCH (N = 60)	p value
TC	178 $\pm$ 30	187 $\pm$ 34	0.128
TG	109 $\pm$ 59	119 $\pm$ 50	0.336
HDL	48 $\pm$ 10	45 $\pm$ 8	0.117
LDL	120 $\pm$ 26	131 $\pm$ 31	0.039

TC total cholesterol, TG triglyceride, LDL-C LDL-cholesterol, HDL-C HDL cholesterol

Table 3 Comparison of Glycemic indices between the groups

Parameters	Euthyroid (N = 60)	SCH (N = 60)	p value
FBS (mg/dl)	96 $\pm$ 11	99 $\pm$ 10	0.071
PPBS (mg/dl)	96 $\pm$ 14	101 $\pm$ 21	0.154
A _{1c} (%)	5.7 $\pm$ 0.4	5.7 $\pm$ 0.4	0.645
Insulin (μ IU/ml)	15.3 $\pm$ 4.1	19.1 $\pm$ 4.0	0.001
IR-2	1.97 $\pm$ 0.53	2.45 $\pm$ 0.59	0.001

FBS fasting blood sugar, PPBS post prandial blood sugar, A_{1c} glycated hemoglobin, IR2 insulin resistance

SCH. This latter observation may be interpreted as an early sign of impaired glucose metabolism seen at the SCH stage.

Insulin resistance can lead to high blood sugar levels, and it is closely linked to overweight and obesity. SCH had higher IR without any significant variations in blood glucose or A_{1c} levels (Table 3). Wide variety of cutoff values are defined in different studies [12, 13] ranging from 1.8 to 2. Values applicable to our study population were not defined hence HOMA 2 IR value ≥ 2 was taken as the cutoff.

BMI was used as a measure to identify overweight/obesity and was found to be elevated in the SCH group (Table 1). Controversy still prevails on association of elevated TSH with BMI suggesting that TSH might be important in determining excess body weight [14–16]. In contrast, studies also supported the concept that obesity by itself leads to changes in circulating thyroid function parameters [17].

Patients with overt hypothyroidism are known to have dyslipidemia [18]. Some reports have also suggested that even high normal serum TSH values may adversely affect serum lipids [19]. SCH has been shown to be associated with increased total and LDL cholesterol, and reduced HDL-cholesterol in most, but not all studies [20, 21]. In this study, only LDL-cholesterol levels were found to be significantly higher in SCH subjects.

It has been found that thyroid hormones stimulate the synthesis and activity of hepatic and peripheral LDL

Fig. 1 Correlation analysis between HOMA-IR with TSH and LDL-C in SCH subjects (N = 60)

receptors, and thereby induce an increase in LDL-cholesterol clearance in combination with stimulation of HDL-cholesterol synthesis [22, 23]. It may be thus hypothesized that mild thyroid failure in SCH may lead to attenuation of LDL-C clearance possibly leading to increased levels of LDL-C levels in the subclinical hypothyroid state.

Earlier studies have shown that 30–40% of individuals with metabolic syndrome are known to have SCH [24, 25] SCH subjects of the present study were found to have condition comparable to MS with higher insulin, IR, BMI and LDL-C without any changes in glycemic profile and other lipid parameters. Several studies as discussed above, have shown an association between thyroid function and insulin resistance.

In the present study, IR2 was found to correlate with TSH ($r = 0.300$; $p < 0.01$) and LDL ($r = 0.218$; $p < 0.050$), and the degree of association was greater with the former (Fig. 1). Studies [12–14] linking HOMA-IR with BMI levels have yielded controversial findings. Increased visceral adipose tissue is considered the major cause of insulin resistance. Although we cannot ascertain whether the primary dysfunction lies on thyroid or visceral fat, the mere existence of this vicious cycle necessitates future studies.

Measurement of free thyroxine would have added further information on the subject's thyroid status. Furthermore, the influence of waist circumference and thyroid autoimmunity on insulin metabolism and lipids also needs to be considered. Despite these limitations, the associations found were in accordance with the previous studies.

We believe that the combined results of the present work and previous studies on the same lines, provide compelling evidence of presence of insulin resistance and altered lipids in mild SCH. Hence, screening for thyroid function testing should be combined with estimation of plasma glucose, insulin and serum lipids to monitor and prevent associated effects.

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Compliance with Ethical Standards

Conflict of interest Authors declare that they have no conflict of interest.

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