ORIGINAL ARTICLE

ASSOCIATION BETWEEN INSULIN RESISTANCE AND HYPOTHYROIDISM IN FEMALES ATTENDING A TERTIARY CARE HOSPITAL

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ABSTRACT

The effect of thyroid status on insulin sensitivity is of great interest but despite various studies there is conflicting data on this subject. The study group comprised of 25 female subjects each with subclinical hypothyroidism, overt hypothyroidism and euthyroid controls. Serum samples of all the patients were assayed for thyroid profile, Insulin and lipid profile. Homeostasis model of assessment (HOMA-IR) was employed to assess the level of insulin resistance. Patients with hypothyroidism demonstrated insulin resistance and dyslipidemia as observed by the higher HOMA-IR and cholesterol and triglyceride levels respectively as compared to the controls. A significantly positive correlation between TSH and HOMA-IR level was also observed in the hypothyroidism group. Thyroid dysfunction leads to alterations in glucose and lipid metabolism which is an important risk factor for cardiovascular diseases. The dyslipidemia and insulin resistance should be managed aggressively to reduce the impending risk.

KEY WORDS

Insulin, Hypothyroidism, HOMA-IR, TSH, Dyslipidemia.

INTRODUCTION

Sub-clinical hypothyroidism (SCH) and overt hypothyroidism (OH) are established risk factors for insulin resistance, hyperlipidemia, hypercoagulability and low grade inflammation (1, 2). Several studies have proved the association between insulin resistance and hypothyroidism for overt hypothyroidism, but there is controversy as to whether this association is also present in sub clinical hypothyroidism. In a recent study it was found that insulin resistance was comparable in both SCH and OH (3, 4). It is known that overt hypothyroidism leads to an increase in plasma cholesterol levels (4, 5). Most studies in sub clinical hypothyroidism show comparable but less pronounced associations (6, 7). The extent to which various degrees of thyroid dysfunction affects cardio vascular events

and lipid profile continues to be debated.

The prevalence of thyroid disease in patients with diabetes is significantly higher than that in the general population (8). This indicates a possible interplay between thyroid status and insulin sensitivity. Homeostatic model assessment (HOMA) is a method for assessing β -cell function and insulin resistance (IR) from basal (fasting) glucose and insulin or C-peptide concentrations. The homeostasis model assessment (HOMA) for insulin resistance (HOMA-IR) derives estimates of insulin sensitivity from the mathematical modeling of fasting plasma glucose and insulin concentrations.

Insulin resistance leads to an increased production of hepatic cholesterol and very low density lipoproteins (VLDL) (9) and an increased HDL cholesterol (HDL-C) clearance (10). Insulin resistance augments the deleterious effect of hypothyroidism on the lipid profile as suggested by Bakker et al (11). Complex interplay between thyroid function and insulin resistance has been implicated in diabetic dyslipidemia (12). We aimed to investigate the relationship between thyroid function and insulin resistance in hypothyroid female population attending a tertiary care hospital in Delhi.

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MATERIALS AND METHODS

The study was conducted in the department of Biochemistry, GB Pant Hospital, New Delhi. The patients visiting the thyroid clinic were screened and 25 female patients each suffering from sub clinical and overt hypothyroidism was enrolled in the study after prior consent. Twenty five age and socio economic status matched female volunteers were enrolled as controls. The inclusion criteria adopted were: age 18 to 45 years, newly diagnosed and untreated cases for sub clinical or overt hypothyroidism. Patients suffering from diabetes, polycystic ovarian disease, Tuberculosis, other systemic illness, liver disorders, renal disorders, congestive cardiac failure, intake of oral contraceptive pills, statins and other medications that alter thyroid functions and lipid levels led to exclusion from the study. Pregnancy and menopause also accounted for exclusion from the study. Blood sample for the estimation of all the parameters was collected from the patients after an overnight fasting.

Thyroid profile (TSH, FT₃ and FT₄) and insulin levels were estimated by Roche Elecsys modular analytics Cobas e 411 using electrochemiluminescence immuno assay (Manheim Germany) using commercially available kits. Lipid profile and sugar levels were analyzed on Olympus AU 400 (Hamberg Germany) using commercially available kits. LDL was calculated using Friedwald's formula. Insulin resistance was estimated using homeostasis model assessment (HOMA-IR) from fasting serum glucose and insulin using the Oxford HOMA calculator (<http://www.dtu.ox.ac.uk/homa/index.html>).

Normal range for TSH was (0.27–4.2) μ U/ml, FT₃ was (2–4.4 pg/ml) and that for FT₄ was (0.93–1.7) ng/dl. Sub clinical thyroid disease (SCH) was defined as serum free T₄ and free T₃ levels within their respective reference ranges in the presence of abnormal serum TSH levels. Patients with high TSH and low FT₃ (<2pg/ml) and /or FT₄ levels (< 0.93 ng/dl) were classified as being overt hypothyroid. Patients with normal TSH, FT₃ and FT₄ were considered euthyroid. The normal range for fasting insulin was 2.6–24.9 μ U/ml. Informed consent was obtained from all the study participants and the ethics committee of our tertiary care hospital approved the study.

Baseline characteristics of the study participants were expressed in mean $\pm$ SD and percentage. One way Anova was used to analyze differences in baseline characteristics between the study groups and the control group. The association between the various parameters in different groups was evaluated using Pearson's correlation coefficient. $P < 0.05$ was considered statistically significant. Statistical analysis was

performed using SPSS windows version 10.0 software (SPSS Inc., Chicago, Illinois).

RESULTS

The study population was divided into three groups with 25 subjects in each group: 'Controls', 'Sub clinical Hypothyroid' and 'Overt hypothyroid' on the basis of FT₃, FT₄ and TSH levels in serum. All the patients included were females in the age group ranging from 25–45 yrs. Table 1 shows anthropometrical and biochemical characteristics of the patients. In our study TSH and FT₄ were found to be significantly high in OH (45.8 $\pm$ 20.85 μ U/ml; 0.67 $\pm$.18 ng/dl) as compared with the SCH (11.08 $\pm$ 6.65 μ U/ml ; 1.1 $\pm$ 0.6 ng/dl) and controls (1.94 $\pm$ 1.10; 1.10 $\pm$ 0.11 μ U/ml).

Table 1: Biochemical parameters of various groups

	Control (n=25)	Sub clinical (n=25)	Overt (n=25)
TSH (μ U/ml)	1.94 $\pm$ 1.10	11.08 $\pm$ 6.65	45.8 $\pm$ 20.85*#
FT ₃ (pg/ml)	2.57 $\pm$ 0.32	3.16 $\pm$ 0.35\$	2.14 $\pm$ 0.53*#
FT ₄ (ng/dl)	1.10 $\pm$ 0.11	1.1 $\pm$ 0.16	0.67 $\pm$ 0.18*#
Insulin (μ U/ml)	5.66 $\pm$ 2.9	14.2 $\pm$ 5.98\$	10.56 $\pm$ 4.02*
Sugar (mg/dl)	85.5 $\pm$ 12.38	102.5 $\pm$ 14.71	92.9 $\pm$ 17.1*
HOMA IR	0.57 $\pm$ 0.15	1.7 $\pm$.58\$	3.9 $\pm$ 1.32*#
Cholesterol (mg/dl)	128 $\pm$ 23.9	178.8 $\pm$ 35.3	219.3 $\pm$ 50.1*#
Triglycerides (mg/dl)	115.7 $\pm$ 19.3	93.2 $\pm$ 91.19\$	242.6 $\pm$ 52.5*
HDL(mg/dl)	40.7 $\pm$ 4.8	33.9 $\pm$ 11.1	31.3 $\pm$ 7.6*
LDL(mg/dl)	64.0 $\pm$ 20	106.2 $\pm$ 33.97\$	126.2 $\pm$ 40.9*
BMI (kg/m ²)	21.2 $\pm$ 1.3	26.8 $\pm$ 3.9\$	27.1 $\pm$ 3.4*
Age (yrs)	35.1 $\pm$ 3.84	34.1 $\pm$ 5.9	36.1 $\pm$ 5.2

* control vs overt hypothyroidism; \$ control vs subclinical hypothyroidism; # overt vs subclinical hypothyroidism

Mean HOMA IR in controls was 0.57 $\pm$.15. HOMA-IR was higher in OH (3.9 $\pm$ 1.32) versus SCH (1.7 $\pm$.58) as well as in both OH and SCH as compared to controls (0.57 $\pm$.15).

The total cholesterol levels were significantly higher in OH as compared to SCH and controls, whereas triglyceride and LDL levels in OH and SCH were comparable although they were significantly raised as compared to the control group (Fig 1&2).

The body mass index (BMI) of the subjects in both the OH and SCH group were significantly more than those in the control group. There was however no significant difference in the BMIs of the subjects in the OH and SCH groups.

Table 2: Pearson's correlations between different parameters in hypothyroidism

Parameters	Correlation coefficient	P value
TSH vs. insulin	0.927	<0.01
TSH vs. HOMA IR	0.835	<0.01
TSH vs. TC	0.459	0.02
HOMA IR vs. TC	0.554	0.03
Insulin vs. TC	0.462	0.03

The Pearson's correlation coefficient for the relationships between serum TSH and HOMA IR as well as TSH and lipid parameters are shown in Table 2. Our study showed that TSH levels were positively correlated with insulin and HOMA IR in patients with hypothyroidism ($r=0.927$, $P<0.01$; $r=0.835$, $P<0.01$ respectively). The serum TSH levels positively correlated with total cholesterol levels in hypothyroid subjects ($r=0.459$, $P=0.02$). Similarly, HOMA IR was also positively associated with TC with $r=0.554$ and $P=0.03$. The serum insulin levels were significantly correlated with total cholesterol ($r=0.462$, $P=0.03$). However no other significant correlations were observed in our study.

DISCUSSION

In the present study we have addressed the possible linkage among TSH, insulin resistance, and serum concentrations of lipids in hypothyroid female population attending the tertiary care hospital in Delhi. Thyroid disease is much more prevalent in women than men—women are five to eight times more likely to develop hypothyroidism and eight to 10 times more likely to

develop hyperthyroidism. Thyroid disease can increase the risk of cardiovascular disease, infertility, and osteoporosis.

Hypothyroidism is one of the most common functional disorders of the thyroid gland. The condition can be identified by measuring the thyroid stimulating hormone (TSH) concentration in serum, which should be above the reference range of 0.27–4.2.0 mIU/ml. Further serum FT_4 may or may not be decreased; these thyroid disorders are known as overt (OH) and sub-clinical hypothyroidism (SCH), respectively. SCH represents a condition of mild to moderate thyroid failure characterized by normal serum levels of thyroid hormones with mildly elevated serum TSH concentrations (1, 2). The prevalence of SCH has been reported to be between 4 and 10% of adult population samples (8, 13–16).

In recent times tremendous interest has been raised in the influence of thyroid hormone action on insulin levels. Conflicting data are available on how insulin levels change in thyroid dysfunction. The development of insulin resistance leads to many of the metabolic abnormalities. Although clinical hypothyroidism is associated with insulin resistance, there is little information on insulin action in sub clinical hypothyroidism. The main pathophysiological basis underlying glucose intolerance, dyslipidemia, abdominal obesity and hypertension has been attributed to insulin resistance (11, 17). Insulin resistance is a cardinal feature of type 2 diabetes mellitus and increased risk of dyslipidemia along with relatively frequently found mild thyroid dysfunction (18).

In our study, FT_3 and insulin were significantly higher in OH as well as in SCH as compared to controls. TSH and FT_4 were significantly high in OH group only. HOMA IR was significantly raised in OH as compared to controls and SCH. Cholesterol, TG, LDL were significantly raised in OH as compared to control where as HDL level was significantly lower. TG and LDL showed significantly higher levels in SCH group. This is in consistence with the well known association of hypothyroidism with lipid profile (19). Shantha et al have observed that females with insulin resistance have significant association with SCH and overt hypothyroidism (20).

In a study, Owecki et al have concluded that insulin concentrations correlate with FT_4 but not with FT_3 or TSH in profound hypothyroidism (13). Annemieke et al found from their study that a low normal FT_4 level was significantly associated with increased insulin resistance (14). Similarly Tuzcu et al observed that sub clinical hypothyroidism may be associated with fasting hyperinsulinemia (15). Our study also illustrates the complex interplay between thyroid hormonal

Fig 1: Box plots showing the levels of TSH, Insulin and HOMA-IR in the study population

status and insulin levels in the pathogenesis of insulin resistance.

Insulin resistance is assessed by the calculation of HOMA-IR. Homeostatic model assessment (HOMA) of β -cell function and insulin resistance (IR) is a method for assessing β -cell function and IR from basal glucose and insulin or C-peptide concentrations (21). The relationship between glucose and insulin in the basal state reflects the balance between hepatic glucose output and insulin secretion, which is maintained by a feedback loop between the liver and β -cells (22). The use of HOMA to estimate insulin sensitivity and β -cell function helps to compare β -cell function and insulin sensitivity in subjects with abnormal glucose tolerance. Our study demonstrated that hypothyroidism leads to a state of insulin resistance. Maratou et al (4) conducted a similar study and concluded that insulin resistance is associated with hypothyroidism with comparable HOMA IR values in OH and SCH. However in our study patients with OH had significantly higher HOMA IR values than those with SCH. Bakker et al (11) demonstrated significant interactions between insulin resistance and thyroid function in euthyroid nondiabetic adults. The findings of our study are in accordance with the above mentioned investigations. Demidova and Galieva reported from their study on obese hypothyroid females that high TSH levels are associated with the dyslipidemia observed in metabolic syndrome (23). Khan et al reported a significant correlation of triglyceride and HDL levels with HOMA-IR values in human subjects with insulin resistance syndrome (24).

The interaction between insulin resistance and high TSH has profound clinical implications. At low insulin sensitivity, relatively minor differences in TSH are associated with marked changes in lipid risk factors and thus cardiovascular risk (12).

In this hospital based study we found significant positive correlation between TSH and insulin as well as TSH and HOMA IR in female population suffering from both SCH and OH. TSH and HOMA IR showed significant correlation with total cholesterol and TG in OH study subjects whereas insulin was positively correlated with total cholesterol in OH. Hence it may be a good practice to screen females with hypothyroidism for evidence of metabolic syndrome.

Our study has limitations. Our study was cross-sectional, so its ability to infer causality is limited. We are unable to comment on the effect of hormone replacement on insulin resistance in patients with SCH and OH due to lack of follow up data. Population based studies are required to validate our study findings in a broader perspective. Despite these limitations,

the associations we found were highly significant and consistent with other studies addressing the above mentioned association.

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