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Research Article

Insulin resistance in sub clinical hypothyroidism

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ABSTRACT

Background: Insulin resistance (IR) is an established risk factor for cardiovascular diseases. It is an underlying phenomenon in pathogenesis of type 2 Diabetes mellitus. Recent literature proves the development of insulin resistance in Overt hypothyroidism (OH), but there is controversy as to whether this association is also present in sub clinical hypothyroidism (SCH).
Aims: Present study was designed to explore the presence IR in SCH.
Settings & design: The study included 60 hypothyroidism patients and 30 age and sex matched euthyroid controls. Hypothyroidism patients were grouped as SCH (n=30) and OH (n=30).
Methods: We examined total cholesterol levels, fasting blood glucose, fasting serum insulin levels and Insulin resistance (calculated by using HOMA-IR software).
Statistical analysis: All statistical data was analysed by ANOVA using the Graph Pad Prism software, Version 5.01.
Results: HOMA-IR values showed highly significant association between controls and SCH. TSH levels were positively correlated with insulin and HOMA IR in patients with SCH.
Conclusions: Therefore, it will be good practice to screen people &Type 2 DM patients for presence of SCH, so that early detection and prompt intervention can prevent or prolong the appearance of various fatal complications associated with IR & help in managing diabetes holistically.

Keywords: Insulin resistance, Subclinical Hypothyroidism, HOMA-IR

INTRODUCTION

Insulin resistance leads to multi organ damage through the medium of dyslipidemia and atherosclerosis. It has strong association with increase in cardiovascular morbidity & mortality. Also, it is the underline cause for complications occurring in type 2 DM. There are multiple clinical states which lead to development of insulin resistance. In this study we are focusing on effect of hypothyroidism on development of IR.

Based on severity of clinical signs & symptoms & Thyroid function test, hypothyroidism is classified as Overt & Subclinical. SCH is defined as the clinical state where patient has high TSH values but normal T_3 & T_4 levels in serum as compared to normal reference levels. These patients have very few or no clinical signs and symptoms. While, in OH distinct signs and symptoms are present along with high TSH but low T_3 & low T_4 levels in serum. Prevalence of subclinical hypothyroidism is 6-8% in women (10% over the age 60) and 3% in men. Annual risk of developing overt hypothyroidism is about 4% when subclinical hypothyroidism is associated with positive TPO antibodies.[1]

Several studies have shown an association between insulin resistance and hypothyroidism for OH, but there is lot of controversy regarding whether this association is also

present in sub clinical hypothyroidism.[2, 3] This study is being carried out to find whether an association exists between insulin resistance and subclinical hypothyroidism.

METHODS

This study was carried out in the Department of Biochemistry in collaboration with Department of Medicine. The study protocol was approved by the Institutional Ethical Committee.

Study design

A total number of 90 subjects above the age of 15 years participated in the present study. Detailed medical history and relevant clinical examination data and written consent were obtained from all subjects after explaining the study procedure. 60 clinically diagnosed patients of hypothyroidism were selected as cases. These were selected from patients attending outpatient department of internal medicine, endocrine OPD as well as patients admitted in medicine & surgery wards. These subjects were divided into 2 groups as, Overt hypothyroidism (OH) (n=30) & Subclinical Hypothyroidism (SCH) subjects (n=30). 30 age and sex matched euthyroid subjects with TFT's in normal range were enrolled in present study as control group.

Selection of study subjects

Those who had not given consent, patients suffering from diabetes mellitus, polycystic ovarian diseases, obesity, tuberculosis, other systemic illness, liver disorders, renal disorders, congestive cardiac failure, patients on oral contraceptive pills, statins and other medications that alter thyroid functions tests were excluded from the study. Alcoholics, chronic smokers & patients already on treatment for hypothyroidism were also excluded from the study.

Collection of blood sample

About 4-5 ml of fasting blood samples were collected from cubital vein in a plain vaccutainer for TFT, fasting serum insulin levels and total cholesterol estimation. About 1 ml. blood sample was collected from cubital vein in fluoride bulb for fasting plasma glucose estimation.

Facilities and Equipment

All the required facilities and equipment were available in the department of biochemistry. The study did not involve any harm to the any patient involved.

METHODS

Estimation of Serum TSH, T_3, T_4 & insulin was done by Sandwich ELISA method using kit by LDN diagnostika.[4-7] ELISA reader and washer (Erba Lisa Scan 2) were used for measurement. Fasting Glucose was measured by GOD-POD kit method & Total cholesterol by CHOD-PAP kit method on Auto analyzer (ERBA XL—640).[8-11] Insulin Resistance was calculated by using values of fasting serum insulin level & fasting plasma glucose level in Homeostasis Model Assessment for Insulin Resistance (HOMA-IR) calculator developed by diabetes trials unit, endocrinology dept. university of Oxford.[12]

Statistical analysis

All the calculations were done using Microsoft Office Excel 2010 and statistical analysis was done using the Graph Pad Prism software, Version 5.01. All statistical data was analysed by ANOVA (one way analysis of variance) test with Bonferroni as post test. P-value less than 0.05 ($P < 0.05$) was considered to be statistically significant (S). P-value of less than 0.001 ($P < 0.001$) was considered to be statistically highly significant (HS). P-value more than 0.05 ($P > 0.05$) was considered to be statistically non-significant (NS).

RESULTS

Table 1 shows values of various biochemical parameters in different groups. Comparison is done between control & SCH ($), Control & OH (*), OH & SCH (#). Results which are statistically significant with $P < 0.05$ are denoted by various signs ($,*, #) in the table. In present study HOMA-IR is highly significantly elevated in OH as compared to control (2.2 ± 0.91, 0.76 ± 0.36, P value <0.001), highly significantly elevated in SCH as compared to control (1.7 ± 0.71, 0.76 ± 0.36, P value <0.001) & it's significantly elevated in OH as compared to SCH (2.2 ± 0.91, 1.7 ± 0.71, P value <0.05). Figure 1 shows the above mentioned finding.

Table 1: Biochemical characteristics of various groups.

Parameters	Control	SCH	OH
Age (Years)	34.1 ± 9.4	33.6 ± 11.3	36 ± 9.9
Serum TSH (µIU/ml)	3.1 ± 1.32	12.3 ± 5.2$	18.4 ± 6.4*#
Serum T_3 (ng/dL)	111 ± 32	108 ± 31	58 ± 11*#
Serum T_4 (µg/dL)	8.8 ± 1.6	7.7 ± 2.2	3.1 ± 1.5*#
Serum Cholesterol	134 ± 14	176 ± 47$	222 ± 53*#
Fasting Plasma Glucose	87 ± 8.7	101 ± 11$	93 ± 12#
Fasting Serum Insulin (µIU/ml)	5.9 ± 2.7	13 ± 5.8$	17 ± 7.1*#
HOMA-IR	0.76 ± 0.36	1.7 ± 0.71$	2.2 ± 0.91*#

$ control vs SCH; * control vs OH; # OH vs SCH

Table 2 show correlation between TSH, HOMA- IR, Insulin & TC. Our study showed that TSH levels were positively correlated with insulin and HOMA IR in

patients with SCH (Figure 2) (r=0.693, P<0.001; r=0.712, P<0.001 respectively). Also, values of HOMA IR were positively correlate with TC (r=0.560 and P<0.05. The serum insulin levels were significantly correlated with total cholesterol (r=0.553, P<0.05). This indicates that insulin resistance is present not only in overt hypothyroidism but also is significantly present in sub clinical hypothyroidism patients. It also indicates that levels of insulin resistance directly correlate with level of TSH and cholesterol.

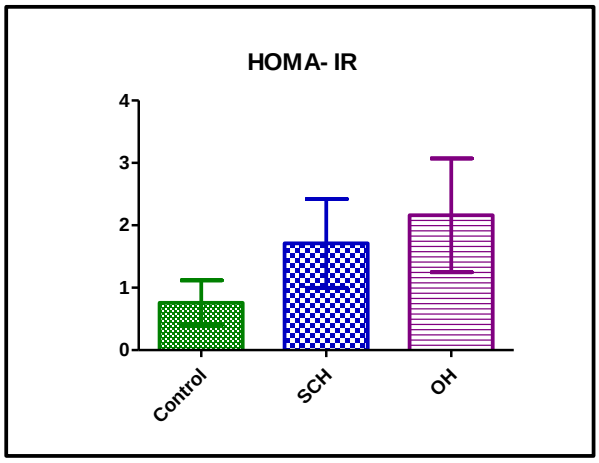

Figure 1: HOMA- IR In different study groups.

Table 2: Correlation between different parameters in SCH.

Parameter	Coefficient of correlation	P value
TSH vs. HOMA-IR	0.712	<0.001
TSH vs. Insulin	0.693	<0.001
TSH vs. TC	0.602	<0.001
HOMA-IR vs. TC	0.560	<0.05
Insulin vs. TC	0.553	<0.05

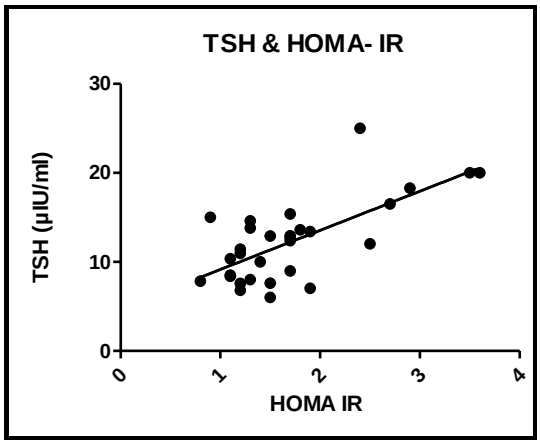

Figure 2: Linear Regression analysis between TSH & HOMA-IR.

DISCUSSION

Hypothyroidism is a clinical state resulting from a deficiency of thyroid hormones, which leads to generalized slowing down of metabolic processes. Thyroid disease is much more prevalent in women than men. Classic symptoms of hypothyroidism are tiredness, weakness, dry skin, feeling cold, hair loss, difficulty concentrating and poor memory, constipation & weight gain with poor appetite. It is caused by a complex interaction of genetic, environmental, immunologic and lifestyle factors. The condition can be diagnosed by measuring the thyroid stimulating hormone (TSH) concentration in serum, which should be above the reference range of 0.4 -4 µIU/ml. Further, serum T_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.[13,14] The prevalence of SCH has been reported to be between 4 and 10% of adult population samples.[15-18]

Nowadays, tremendous interest has been raised in the influence of thyroid hormone action on insulin levels. Confusing data are available on how insulin levels change in thyroid dysfunction. The development of insulin resistance leads to many of the metabolic abnormalities. Hypothyroidism can increase the risk of cardiovascular disease, infertility and osteoporosis. Although overt hypothyroidism is associated with insulin resistance, there is little information available on insulin action in sub clinical hypothyroidism. Insulin resistance is underline pathology of type 2 diabetes mellitus & is relatively frequently found in mild thyroid dysfunction with increased risk of dyslipidemia.[19] In the present study, we have explored the possible linkage among TSH, insulin resistance and serum concentrations of total cholesterol in sub clinical hypothyroidism patients. Based on serum TSH, T_3 & T_4 patients were classified into 3 groups as OH, SCH & Controls. In this study total cholesterol levels are highly significantly elevated in OH as compared to Control and SCH, and highly significantly elevated in SCH as compared to control (P value <0.001) (Table 1). The serum TSH levels positively correlate with total cholesterol levels in SCH subjects (r=0.602, P <0.001). The serum insulin levels also correlate significantly with total cholesterol (r=0.553, P<0.05) in SCH subjects (Table 2). This indicates that along with OH, patients of SCH also develop hypercholesterolemia.

Insulin resistance in Control, SCH & OH groups

Thyroid hormones exert profound effects in the regulation of glucose homeostasis. These effects include modifications of circulating insulin levels, counter-regulatory hormones, intestinal absorption, hepatic production and uptake of glucose by peripheral tissue (fat

and muscle). All these changes produce insulin resistance which is the culprit for many complications mainly cardiovascular.

In present study HOMA-IR is highly significantly elevated in OH as compared to control (2.2 ± 0.91, 0.76 ± 0.36, P value <0.001), highly significantly elevated in SCH as compared to control (1.7 ± 0.71, 0.76 ± 0.36, P value <0.001) & it's significantly elevated in OH as compared to SCH (2.2 ± 0.91, 1.7 ± 0.71, P value <0.05) (Table 1) (Figure 1).

Our study showed that TSH levels were positively correlated with insulin and HOMA IR in patients with SCH (r=0.693, P<0.001; r=0.712, P<0.001 respectively). Also, values of HOMA IR were positively correlate with TC (r=0.560 and P<0.05). The serum insulin levels were significantly correlated with total cholesterol (r=0.553, P<0.05) (Table 2) (Figure 2). This indicates that insulin resistance is present not only in overt hypothyroidism but also it is significantly present in sub clinical hypothyroidism patients. It also indicates that levels of insulin resistance directly correlate with level of TSH and cholesterol. Dessein PH et al (2004), Annemieke et al (2007), Owecki et al (2008), Eirini Maratou et al(2009), Amati F et al (2009) & Singh B M et al (2010) reported similar results which are in good agreement with our findings.[16,17,20-23] On the contrary, Bakker et al (2001), Tuzcu A et al (2005), M. Owecki et al (2006) & Al Sayed A et al (2006) found no significant correlation between insulin resistance and SCH.[15, 24-26]

Presence of insulin resistance in SCH and OH can be explained by the various studies & hypothesis.

It has long been known that thyroid hormones act differently on liver, skeletal muscle and adipose tissue – the main targets of insulin action. Thyroid hormones up-regulate the expression of genes for GLUT-4 and phosphoglycerate kinase, involved in glucose transport and glycolysis respectively, thus acting synergistically with insulin in facilitating glucose disposal and utilization in peripheral tissues.[27, 28] In patients with hypothyroidism**,** because of altered metabolism of lipid and insulin, binding of insulin to insulin receptor decreases.[29] Impaired translocation of GLUT 4 glucose transporters on plasma membrane occurs, resulting in decreased glucose uptake in muscles and adipose tissue.[21] The recent identification of a gene regulated by thyroid hormones in cultured human fibroblasts,[30] the transcription factor HIF-1a, responsible for elevated expression of glycolytic enzymes and glucose transporters, is an example that the field of thyroid diabetes is still open to new discoveries.

Decreased glucose disposal (as compared with euthyroid subjects) has been proved in hypothyroid patients by different methods including clamp studies,[31] the arteriovenous difference technique in the anterior abdominal subcutaneous adipose tissue and forearm muscles after the consumption of a mixed meal,[32] the insulin tolerance test[33] and following intravenous or oral administration of glucose.

Apart from our study, Patricia Wu et al (2000), Duntas et al (2002), Serter et al (2004) & A Squizzato et al (2005) found that there is hypercholesterolemia & dyslipidemia in hypothyroidism patients.[13, 34-36] It was postulated that elevated total cholesterol levels and dyslipidemia may act as one of the main culprits for development of insulin resistance in hypothyroidism. Mechanism of fatty acid induced insulin resistance is well studied by Randle et al and Gerald et al.[37, 38] Still, there is scarcity of data available on cellular mechanisms of insulin resistance due to dyslipidemia. Further studies are required to find out the molecular and genetic basis of hypercholesterolemia and more precisely dyslipidemia induced insulin resistance in hypothyroidism patients.

Despite some limitations, the associations we found were highly significant and consistent with other studies addressing the above mentioned associations.

We believe that the results of our present work combined with previous studies provide compelling evidence of presence of significant insulin resistance in SCH patients. These findings may have important clinical relevance.

Hence, it will be good practice to screen people for presence of SCH and insulin resistance, so that early detection and prompt intervention can prevent or prolong the appearance of various fatal complications associated with insulin resistance. Also, along with diabetes treatment, if we check and treat hypothyroidism even in subclinical stage then it will take care of its contribution to total insulin resistance.

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