

Study of Correlation of Serum Thyroid Hormones with Plasma Insulin and Insulin Resistance Index in Patients of Hypothyroidism

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ABSTRACT

Introduction: Hypothyroidism, a condition of hyposecretion of T3 and T4 with high TSH is associated with hyperinsulinaemia and increased insulin resistance index due to disturbances in insulin secretion with deranged lipid profile.

Aim: The present study was designed to find out the correlation of total Triiodothyronine (T3), total Thyroxine (T4) and Thyroid Stimulating Hormone (TSH) with plasma insulin and insulin resistance index in patients suffering from clinical hypothyroidism.

Materials and Methods: In the present study, 40 diagnosed hypothyroid patients were considered as cases and 30 age and sex matched individuals were taken as controls. ELISA techniques were used for estimation of serum TSH, total T3, total T4 and fasting plasma insulin. Homeostasis Model Assessment (HOMA) was used for calculation of insulin resistance index.

Results: There was highly significant negative correlation between plasma insulin and T3 in hypothyroid patients ($r=-0.421$, $p=0.007$). The coefficient of correlation was significantly

negative between plasma insulin and T4 in hypothyroid patients ($r=-0.354$, $p=0.025$). In hypothyroid patients, a highly significant positive correlation was found between plasma insulin and TSH ($r=0.898$, $p=0.001$). In hypothyroid patients, there was significant negative correlation between insulin resistance index and T3 in hypothyroid patients ($r=-0.385$, $p=0.014$). There was significant negative correlation between insulin resistance index and T4 in hypothyroid patients ($r=-0.355$, $p=0.025$). Correlation was highly significant positive between insulin resistance index and TSH in hypothyroid patients ($r=0.894$, $p=0.001$).

Conclusion: Plasma insulin is increased in hypothyroidism because thyroid hormones have metabolic effects on insulin sensitive organs (skeletal muscle and adipose tissue). In hypothyroidism, there is increased insulin resistance through its insulin receptor and post receptor defects. So in patients of hypothyroidism regular screening of diabetes mellitus should be required. Screening should be done for hypothyroidism in all diabetic patients.

Keywords: Homeostasis Model Assessment, Hyperinsulinaemia, Hypothyroid

INTRODUCTION

Thyroid hormones secreted by thyroid glands are important metabolic hormones regulating energy homeostasis and have control over carbohydrate and lipid metabolism [1]. Hypo and hyperthyroidism result in derangement of intermediary metabolism altering body weight, insulin resistance and lipid profile [2,3]. One of the most important causes of diabetes mellitus, metabolic syndrome and obesity is insulin resistance [4]. The thyroid axis is a classic example of an endocrine feedback loop. Hypothalamic Thyrotropin Releasing Hormone (TRH) is an important regulator of hypothalamic-pituitary thyroid gland axis, causes secretion of TSH, which in turn, stimulates thyroid hormone synthesis and secretion, all under negative feedback control [5]. Hypothyroidism is associated with decreased levels of T3, T4 and increased TSH, causing increased body weight with increased plasma lipids and

lipoproteins. It is seen that the plasma lipid profile is increased in hypothyroidism and vice versa [2,6]. Insulin resistance and oxidative stress, is induced by dyslipidaemia via a vice vicious cycle [7-13]. Thyroid disease also promotes insulin resistance, hypertension, inflammation, oxidative stress and coagulation deficits, independently of dyslipidemia. Therefore, thyroid disease with dyslipidemia plays an important role in multifactorial origin of atherosclerosis [14-17].

The present study was designed to correlate the serum total T3, total T4 and TSH with plasma insulin and insulin resistance index in patients suffering from clinical hypothyroidism.

MATERIALS AND METHODS

A case control study of total of 40 patients (within age group 15-82 years) diagnosed with hypothyroidism by the Medicine Department were included in the study group. Thirty age

and gender matched healthy individuals (within age group 14-70 years) were taken as controls. Written consent was obtained from all patients and controls and approval of Institutional Ethics Committee was also obtained. Time period of the study was 3 years from 2009-2012. Known cases of diabetes mellitus, obese patients, patients with history of steroid use, alcoholics, smokers, patients with any infection/illness and any cases under hormone replacement therapy were excluded from the study.

These patients were taken from OPD and indoor of Department of Medicine of Rajindra Hospital, Patiala, India. The sample size was calculated according to demographic factors (like socioeconomic status, environmental factors and life style) with the consultation of the statistician. All the subjects were instructed to undergo overnight fasting and advised to come to next morning for the investigations. Samples for insulin were collected subsequently in a vial containing EDTA (Ethylenediamine tetraacetate) and samples for thyroid hormones were collected in a vial containing clot activator. Serum TSH, total T3, T4 and plasma insulin were carried out in Biochemistry Department of Government Medical College, Patiala and were assayed by Enzyme Linked Immunosorbent Assay (ELISA) technique [18].

ELISA Immunoassay: Competitive enzyme immunoassay -upon mixing immobilised antibody, enzyme antigen conjugate and a serum containing the native antigen, a competition reaction results between the native antigen and the enzyme-antigen conjugate for a limited number of insolubilised binding sites. After equilibrium is attained, the antibody bound fraction is separated from unbound antigen by decantation or aspiration. The enzyme activity in the antibody bound fraction is inversely proportional to the native antigen concentration.

Serum TSH, Total T3 and T4 were evaluated by using ERBA-thyroid kit. Plasma Insulin was assayed by using DRG insulin ELISA kit.

Fasting plasma glucose was assayed by Glucose-Oxidase/Peroxidase (GOD-POD) method [19]. Evaluation of insulin resistance index was done using the Homeostasis Model Assessment (HOMA). It was first described by Matthews et al., in 1985 [20].

STATISTICAL ANALYSIS

Data was analysed using software SPSS version 23.0. Student's t-test was employed. The p-value 0.05 and

0.01 were taken as significant and less than 0.01 as highly significant.

RESULTS

The present study shows that in the study group there were 35 (87.5%) females and 5 (12.5%) males. There was female preponderance due to more prevalence of hypothyroidism in females. In hypothyroid patients, mean value of fasting plasma glucose was 80.4 ± 8.3 (mg%) and in control group mean value of fasting plasma glucose was 82.7 ± 9.9 (mg%). This parameter was comparable in both the groups [Table/Fig-1].

Parameters	Group	Range (mg%)	Mean SD	p-Value
Fasting Plasma Glucose	Study	62-98	80.4 ± 8.3	0.298
	Control	62-98	82.7 ± 9.9	Non-significant

[Table/Fig-1]: Association of fasting plasma glucose in hypothyroid patients and control group (Students' paired t test applied).

In hypothyroid patients, mean value of plasma insulin was 21.07 ± 8.4 (μ IU/mL) and in control group, mean value of plasma insulin was 6.26 ± 1.76 (μ IU/mL). The plasma insulin was found to be higher in hypothyroid patients with compared to control and this was statistically highly significant ($p < 0.001$). Also, the mean insulin resistance index was 4.15 ± 1.61 in hypothyroid patients and in control group, the mean insulin resistance index was 1.26 ± 0.38 . The Insulin resistance index thus was found to be statistically highly significant ($p < 0.001$).

It was clear that the T3 and T4 values were significant when compared hypothyroid patients to that of controls with $p < 0.01$, whereas, the TSH value was found to be highly significant in hypothyroid patients when compared to that of controls with $p < 0.01$ [Table/Fig-2].

There was significant negative correlation between plasma insulin and T3 in hypothyroid patients. The coefficient of correlation was significantly negative between plasma insulin and T4 in hypothyroid patients. And there was highly significant positive correlation between plasma insulin and TSH in hypothyroid patients [Table/Fig-3].

Coefficient of correlation was significantly negative between insulin resistance index and T3 in hypothyroid patients. Also, there was significant negative correlation between insulin

Group	Parameters	No. of patients	Range	Mean SD	t	p	s
Study	T3	40	0.09-2.00	0.71 ± 0.46	3.034	0.003	S
Control	(ng/mL)	30	0.51-2.80	1.03 ± 0.42			
Study	T4	40	3.70-11.80	5.6 ± 2.1	2.638	0.010	S
Control	(μ g/dL)	30	5.03-9.3	6.86 ± 1.24			
Study	TSH	40	0.60-33.0	9.2 ± 8.3	-4.661	0.001	HS
Control	(μ IU/mL)	30	0.60-3.40	2.09 ± 0.87			

[Table/Fig-2]: Comparison of thyroid hormones between hypothyroid patients and controls. (Students' paired t test applied).

resistance index and T4 in hypothyroid patients. Coefficient of correlation was highly significant positive between insulin resistance index and TSH in hypothyroid patients [Table/Fig-4].

Parameters	r Value	p Value	Significance
Serum T3 levels (ng/mL)			
Plasma insulin (IU/mL)	-0.421	0.007	S
Serum T4 levels (µg/dL)			
Plasma insulin (IU/mL)	-0.354	0.025	S
Serum TSH levels (IU/mL)			
Plasma insulin (IU/mL)	0.898	0.001	HS

[Table/Fig-3]: A correlation of fasting plasma insulin and T3, T4 and TSH in hypothyroid Patients. (two-tailed Pearson correlation applied).

Parameters	r Value	p Value	Significance
Serum T3 levels (ng/mL)			
Insulin Resistance Index	-0.385	0.014	S
Serum T4 levels (µg/dL)			
Insulin Resistance Index	-0.355	0.025	S
Serum TSH levels (IU/mL)			
Insulin Resistance Index	0.894	0.001	HS

[Table/Fig-4]: A correlation of Insulin resistance index and T3, T4 and TSH in hypothyroid patients. (two-tailed Pearson's correlation applied).

DISCUSSION

In increased plasma insulin condition in hypothyroidism, there is defective secretion of insulin hormone because of glucose load which will ultimately affect the glucose delivery to the tissues, thereby establishing the insulin resistance state [21]. Thyroid function and insulin resistance association has been shown by several studies.

In present study, the plasma insulin levels and insulin resistance index were highly significant among hypothyroid patients when compared to controls. This findings were in consistent with study done by Maratou E et al., who concluded that the fasting and postprandial plasma insulin levels, as well as, HOMA index were significantly increased in hypothyroidism subjects as compared to euthyroid individuals, however, the plasma glucose was not significant among the groups [22].

Correlation was significantly negative between plasma insulin and serum T3 and T4 in hypothyroid patients. Thyroid hormones have insulin agonistic actions on peripheral tissue. Insulin acts synergistically with thyroid hormones on peripheral tissues. Expression of genes such as Glucose Transporter-4 (GLUT4) and phosphoglycerate kinase, involving glucose transport and glycolysis respectively has been upregulated by thyroid hormones. Thyroid hormones, together with insulin hormone produce combined effects to make an ease of glucose delivery and utilization in peripheral

tissues [23,24].

In the present study, hypothyroid patients had highly significant positive correlation between insulin resistance index and TSH which was in accordance with the study done by Singh BM et al., that concluded with significant positive correlation between TSH levels and HOMA-IR in hypothyroid patients [25]. Carbohydrate and lipid Metabolism are also affected by hypothyroidism. These are risk factors for cardiovascular disease [26].

Insulin and HOMA-IR were moderately positively correlated with mean TSH levels [27]. There was significant negative correlation between insulin resistance index and T3 and T4 in hypothyroid patients in the present study. In hypothyroidism, negative regulation of one or more intracellular enzymes involved in glucose catabolism results in insulin resistance [28]. Hypothyroidism causes malfunctioning of glucose transporter protein like GLUT4 on monocyte's plasma membrane as there is decreased insulin mediated glucose uptake [22]. In hypothyroidism, due to Insulin resistance there is diminished blood flow in adipose tissue and skeletal muscle [29]. There is an important fact on adipocyte-myocyte crosstalk that the adipokines-cytokines secreted by adipose tissue partially produce insulin resistance in skeletal muscle in hypothyroidism, partially is responsible for insulin [30].

Thus, in hypothyroidism, Insulin resistance is associated with various physiologic phenomenon like altered blood flow, malfunction of GLUT4, diminished glycogen synthesis and decreased muscular oxidative capacity [31].

At both cellular and molecular levels, thyroid hormone T3 and insulin have a synergistic role in glucose homeostasis [32]. In patients of hypothyroidism, reduced intracellular content of serum T3 affects insulin stimulated glucose disposal. Therefore, HOMA-IR is inversely correlated with the levels of thyroid hormones, as seen in SCH [33]. A decrease in the insulin mediated glucose disposal results from decrease in the thyroid hormones that improved upon treatment [34]. Stanick S et al., also show same type of results [35].

Handisurya A et al., established these findings by using the euglycaemic-hyperinsulinaemic clamp technique and also measuring glucose tolerance and beta-cell activity with an Oral Glucose Tolerance Tests (OGTT). They also found that glucose induced insulin secretion is diminished by thyroid replacement corresponding well with the observed improvement of insulin sensitivity [36].

The precise role of thyroid hormones towards insulin resistance is not understood. However, the association of immune cells, skeletal muscles and adipose tissue, the ability of macrophages to produce thyroid hormones, the ability of T3 to induce M2 macrophage polarisation, the proinflammatory role of thyroid hormones and the anti-inflammatory effect of insulin constitute an important event where the interference in thyroid hormones secretion may exert insulin resistance [37].

The recently discovered novel gene, the transcription factor

HIF-1(α) which is regulated by thyroid hormones in cultured human fibroblasts, is responsible for elevated expression of glycolytic enzymes and glucose transporters. However, it needs further elaborated studies to explore the scenario in the case of thyroid diabetes association [23,24].

Thus, hyperinsulinaemia results from increased demand of β -cells due to presence of insulin resistance in peripheral tissues in hypothyroidism. Since, the present study was taken in consideration with the small sample size; it should be emphasised on large sample study in larger population to get the solid results for the implementation on the clinical practice.

CONCLUSION

Fasting plasma insulin and insulin resistance index are significantly augmented in hypothyroid patients. With low T3 and T4 and High TSH as in hypothyroidism, there is increase in fasting plasma insulin and insulin resistance index. Due to insulin receptor and post receptor defects in hypothyroidism, there is presence of insulin resistance. Metabolic functions of insulin sensitive target tissues like skeletal muscles, adipose tissue and liver itself, thus increasing plasma insulin are affected by thyroid hormones.

Based on the current understanding of this relationship, screening for hypothyroidism should be done in all diabetic patients because correcting hypothyroidism helps in improving glucose homeostasis and therefore hypothyroid patients should undergo screening for diabetes mellitus. Similarly, patients of uncontrolled diabetes mellitus should undergo a thyroid function assessment.

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