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RESEARCH ARTICLE

Insulin resistance and serum lipid profile in hypo- and hyper-thyroidism and their relationship with serum thyroid-stimulating hormone levels

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ABSTRACT

Background: The coexistence of thyroid dysfunction and diabetes mellitus is increasing in prevalence. Thyroid dysfunction leads to alterations of carbohydrate and lipid metabolism. This study aimed at determining the association between altered thyroid hormone levels, insulin resistance (IR), and serum lipid profile. **Aims and Objectives:** The primary objective was to study fetal bovine serum (FBS), serum insulin, IR, and lipid profile in hypothyroid and hyperthyroid patients and to compare them with healthy control subjects. The secondary objective was to correlate IR and lipid profile with serum thyroid-stimulating hormone (TSH). **Materials and Methods:** A cross-sectional comparative study including 165 participants of the age group of 18–45 years. Participants were selected after proper exclusion and informed consent. Ethical clearance was obtained from the Institutional Ethics Committee. The following parameters were studied: Serum FBS, serum insulin, IR, total cholesterol, serum high-density lipoprotein, low-density lipoprotein (LDL), and TSH. Statistical analysis was performed using SPSS version 18. **Results:** IR has been found elevated in hypothyroid and hyperthyroid subjects. In hypothyroid subjects, a significant elevation in total cholesterol LDL and triglycerides has been found, while in hyperthyroid subjects, no significant alteration in serum lipid profile has been found. IR showed a positive correlation with total cholesterol, LDL, and triglycerides in the hypothyroid group. **Conclusion:** The present study showed elevated IR in hypo- and hyper-thyroidism and elevated lipid profile in hypothyroidism.

KEY WORDS: Insulin Resistance; Hypothyroidism; Hyperthyroidism; Lipid Profile; Serum Thyroid-Stimulating Hormone; Correlation

INTRODUCTION

Thyroid dysfunction is one of the most common endocrine abnormalities, with approximately 300 million people worldwide affected by it, and among them, about 42 million are residing in India. A population-based study done in Cochin, estimated the prevalence of hypothyroidism to be 3.9% and hyperthyroidism to be 1.3%.[1]

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Thyroid hormones play an important role in the metabolism of carbohydrates and lipids.[1] Thyroid hormones help in the maintenance of blood glucose by opposing the action of insulin and promoting gluconeogenesis and glycogenolysis. Hyperthyroidism promotes a hypermetabolic state characterized by increased resting energy expenditure, weight loss, reduced cholesterol levels, increased lipolysis, and gluconeogenesis. Conversely, hypothyroidism is associated with hypometabolism characterized by reduced resting energy expenditure, weight gain, increased cholesterol levels, reduced lipolysis, and reduced

gluconeogenesis.[2] Therefore, both disorders contribute to a hyperglycemic state.

Assessment of thyroid-stimulating hormone (TSH) is the single most useful test of thyroid function in the vast majority of patients in the presence of an intact hypothalamo-pituitary axis.[3] The normal range for TSH is between 0.35 mIU/mL and 4.50 mIU/mL. TSH levels above 4.50 mIU/ml are indicative of hypothyroidism, while that below 0.35 mIU/ml are found in hyperthyroidism. Sub-clinical hypothyroidism has a TSH level between 4.50 and 8 mIU/ml, while in sub-clinical hyperthyroidism, the TSH levels lie between 0.1 and 0.3 mIU/ml.[3]

The association between thyroid diseases and diabetes mellitus was first proven by Coller and Huggins in the year 1927[4] and later by several other studies.[5-8]

Thyroxine plays an integral role in the metabolism of glucose and lipids.[9] While thyroid hormones oppose the action of insulin and stimulate the hepatic gluconeogenesis and glycogenolysis, they upregulate the expression of genes such as glucose transporter type-4 (GLUT-4) and phosphoglycerate kinase, involved in glucose transport and glycolysis, respectively, thus acting synergistically with insulin facilitating glucose disposal and utilization in peripheral tissues.[10] The optimal function of thyroid maintains the euglycemic state in the body. In hypothyroidism, the levels of insulin-sensitive GLUT-4 are reduced, and the degradation of insulin is slowed. While in hyperthyroidism, there is an increase in hepatic gluconeogenesis and increased gastrointestinal absorption of glucose, which, in turn, increases the requirement of insulin. Increased requirement of insulin and insulin resistance (IR) in both hypo- and hyper-thyroidism was demonstrated in the study done by Kapadia *et al*.[10]

IR is defined as a glucose homeostasis disorder involving a decreased sensitivity of muscles, adipose tissue, liver, and other body tissues to insulin, despite its normal or increased concentration in blood. IR occurs as part of a cluster of cardiovascular metabolic abnormalities commonly referred to as "The IR Syndrome" or "The Metabolic Syndrome" and is characterized by type 2 diabetes, hyperglycemia-induced tissue damage, hypertension, and dyslipidemia.[11,12] Hypothyroidism is associated with disorders of glucose and insulin metabolism involving defective insulin secretion in response to glucose and hyperinsulinemia,[13,14] while hyperthyroidism shows an elevated rate of glucose metabolism by insulin and increases the rate of formation of lactate which is then used by the liver for gluconeogenesis and endogenous glucose production.[15,16]

IR in thyroid dysfunction is found to be in close association with diabetic dyslipidemia.[17] IR leads to increased production of hepatic cholesterol and very low-density lipoproteins (VLDL) and an increased high-density lipoprotein cholesterol (HDL-C) clearance, which augments the deleterious effect of hypothyroidism on the lipid profile.[17] Thyroid hormones are essential for the proper metabolism of lipids, and hence, a deficiency or an excess of thyroid hormone has a great impact on the metabolism of lipids as well as on many other cardiovascular risk factors.[18] Hypothyroidism shows hypercholesterolemia due to an increase mainly in the levels of LDL.[19-21] On the contrary, in hyperthyroidism, there are decreased levels of total, LDL, and HDL-C due to a decrease in the level of LDL cholesterol by gene expression that enhances LDL receptor-mediated catabolism of LDL particles or due to its increased oxidability due to a higher level of fT_4.[22]

The aim of this study is to analyze the relationship of IR to the serum lipid profile and TSH in patients with hypothyroidism and hyperthyroidism.

MATERIALS AND METHODS

A cross-sectional comparative study was conducted in the Outpatient Department of Government Medical College, Kozhikode, after obtaining necessary clearance from the Institutional Ethics Committee. Consecutive patients coming to endocrinology outpatient departments with newly diagnosed untreated hypothyroidism and hyperthyroidism were selected and controls from the bystander population as per the inclusion and exclusion criteria. The subjects were enrolled after obtaining informed consent. A detailed history was taken and clinical examination was done. Blood samples were collected after 8–12 h of fasting. The parameters assessed were: Serum TSH, plasma glucose, serum insulin, serum total cholesterol, serum LDL, and serum HDL.

IR was calculated according to the formula of the homeostasis model assessment (HOMA).

When glucose in molar units (mmol/L)

$$\text{HOMA} - \text{IR} = \frac{\text{Glucose} \times \text{Insulin}}{22.5}$$

When glucose in mass units (mg/dl)

$$\text{HOMA} - \text{IR} = \frac{\text{Glucose} \times \text{Insulin}}{405}$$

The baseline characteristics and blood investigation values were compared among the three groups using ANOVA and were expressed in mean ± standard deviation. The association between the various parameters in different groups was evaluated using Pearson's correlation coefficient. $P < 0.05$ was considered statistically significant.

RESULTS

The mean values of fasting blood sugar, serum insulin, and serum TSH were found to be significantly higher in the hypothyroid and hyperthyroid groups compared to the control group. Serum levels of total cholesterol, LDL, and triglycerides were significantly higher in the hypothyroid group compared to the control subjects, but there was no significant variation in these values between the hyperthyroid and control groups. Serum HDL levels were comparable among the three groups and showed no significant variation. A study of the association between serum IR and TSH levels in the three groups revealed a significant positive correlation in the hypothyroid group, while in the hyperthyroid group, there was a significant negative correlation. A positive correlation was observed between TSH levels and parameters of serum lipid profile, namely, total cholesterol, triglycerides, and LDL in the hypothyroid group, while no significant association of these parameters was observed in the hyperthyroid group [Table 1 and Figures 1-7].

DISCUSSION

In the present study, the mean fasting glucose, serum insulin, and IR values in the hypothyroid group and hyperthyroid groups are significantly elevated when compared to the control group. Assessment of lipid profile revealed significantly higher levels of serum total cholesterol, LDL, and triglycerides in the hypothyroid group in comparison with the hyperthyroid and control groups, while no significant difference was observed between the hyperthyroid and control group. There was no significant elevation in serum HDL levels in the hypothyroid group compared to the control group, but there was a significant decrease in HDL levels in the hyperthyroid group. In the present study, there was a significant positive correlation between IR and serum TSH in the hypothyroid group (r = 0.471, P = 0.000) and a negative correlation was observed in the hyperthyroid group (r = −0.311, P = 0.020). Analysis of correlation between components of lipid profile and serum TSH in the hypothyroid and hyperthyroid groups revealed a significant positive correlation between serum TSH levels and lipid parameters, namely, serum total cholesterol, triglycerides, and LDL cholesterol in the hypothyroid group. However, no significant correlation was observed in the hyperthyroid group.

Elevation in glucose levels, serum insulin, and IR was observed in the studies done by Kapadia *et al*. and Gayoum[10,13,17,23-25] and correlation between IR and TSH levels.[10,17,26] Elevated levels of lipid parameters in hypothyroidism are in concordance with findings of Kapadia *et al*., Singh *et al.*, Abdel-Gayoum, and Alsalmi *et al*.[10,17,27,28] Findings in hyperthyroidism are similar to those in prior studies by Regmi *et al*. and Gayoum.[10,23,29]

The higher fasting blood glucose levels in hypothyroidism may be an effect of diminished insulin-mediated glucose disposal, also reduced blood flow and glucose extraction in the skeletal muscles and adipose tissue after a meal can contribute to elevation of fasting blood glucose in hypothyroid subjects,[30,31] while in hyperthyroidism, in spite of high levels of serum insulin, there is hyperglycemia possibly due to impaired processing of proinsulin, enhanced intestinal absorption of glucose, or increased in the expression of GLUT-2 that results in an increased gluconeogenesis and glycogenolysis.[30] In addition, enhanced lipolysis in hyperthyroidism increases the release of fatty acids and the availability of glycerol for gluconeogenesis.[23] The elevated levels of serum insulin may be due to either impaired insulin-stimulated glucose disposal or decreased insulin-stimulated glucose transport in monocytes due to impaired translocation of GLUT-4 glucose transporters on the plasma membrane.[10]

In hypothyroidism, persistently, elevated levels of serum insulin can lead to the downregulation of insulin receptors on the target tissues and desensitization of the post-receptor pathways. Impaired GLUT-4 transporter on the plasma membrane and impaired blood flow has been implicated in the failure of adequate glucose utilization at the level of peripheral tissues.[25]

Table 1: Correlation of thyroid dysfunction and thyroid-stimulating hormone level

Variables	IR	TC	LDL	TG	HDL	VLDL
Hypothyroid						
Pearson correlation	0.471**	0.697**	0.553**	0.674**	0.256	0.674**
Sig. (two-tailed)	0.000	0.000	0.000	0.000	0.059	00.000
Hyperthyroid						
Pearson correlation	−0.311*	0.081	0.040	0.139	0.100	0.139
Sig. (two-tailed)	0.040	0.555	0.772	0.313	0.461	0.313
Control						
Pearson correlation	0.040	0.184	0.222	0.049	−0.267	0.049
Sig. (two-tailed)	0.776	0.183	0.106	0.723	0.057	0.723

**Correlation is significant at the 0.01 level (two-tailed), *Correlation is significant at the 0.05 level (two-tailed), IR: Insulin resistance, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, VLDL: Very low-density lipoprotein

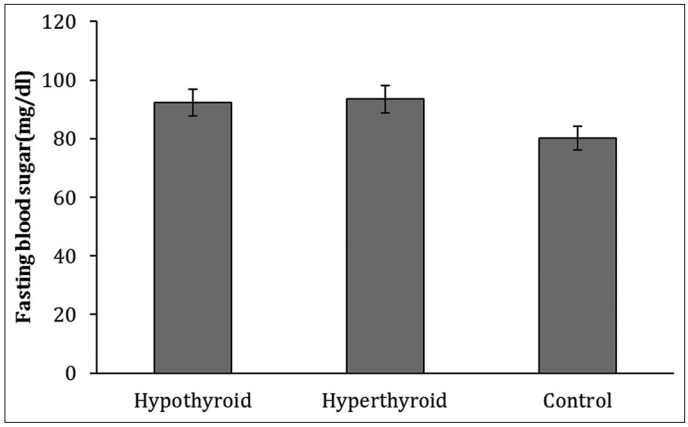

Figure 1: Fasting blood sugar (mg/dl) level in the study participants

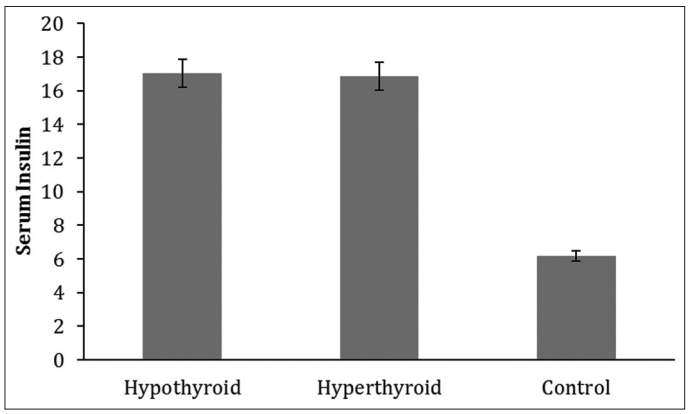

Figure 2: Serum insulin level in the study participants

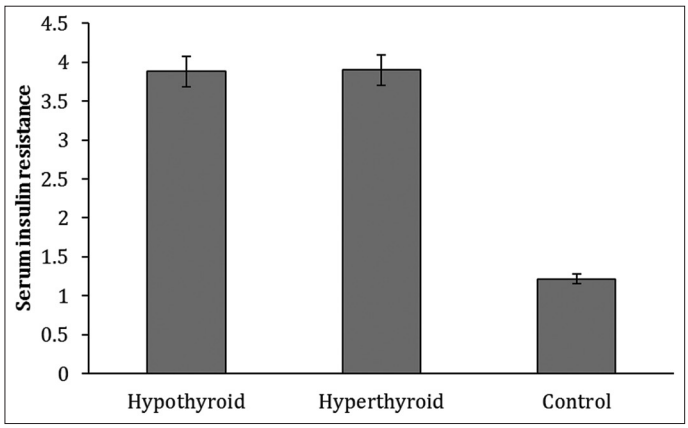

Figure 3: Serum insulin resistance in the study participants

Hyperthyroidism increases the production of endogenous glucose in the liver in the fasting state and decreases the hepatic sensitivity to insulin. Effect on hepatic cells is achieved through alteration of transcription and translation of the genes responsible for gluconeogenesis and glycogen metabolism or increased expression of the GLUT-2 glucose transporter on hepatocyte plasma membranes. An indirect effect is by increasing the activity of the parasympathetic nervous system, modulated by the hypothalamus.[30] The occurrence of glucose intolerance associated with hyperthyroidism may be explained simply by the hepatic type of IR.[32]

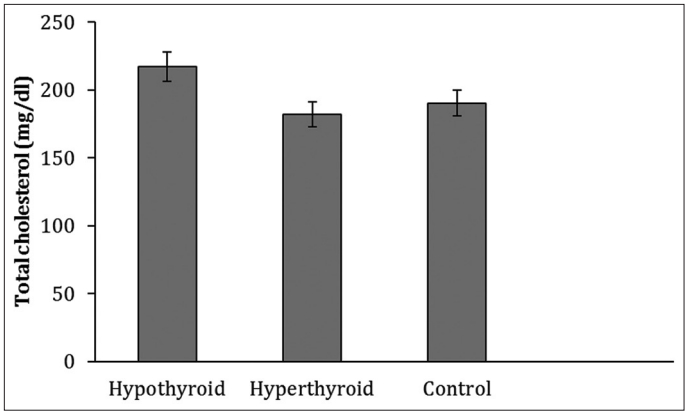

Figure 4: Total cholesterol (mg/dl) level in the study participants

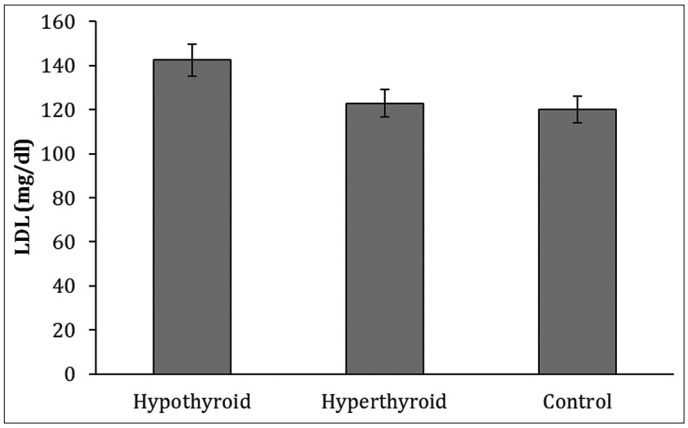

Figure 5: Low-density lipoprotein (mg/dl) level in the study participants

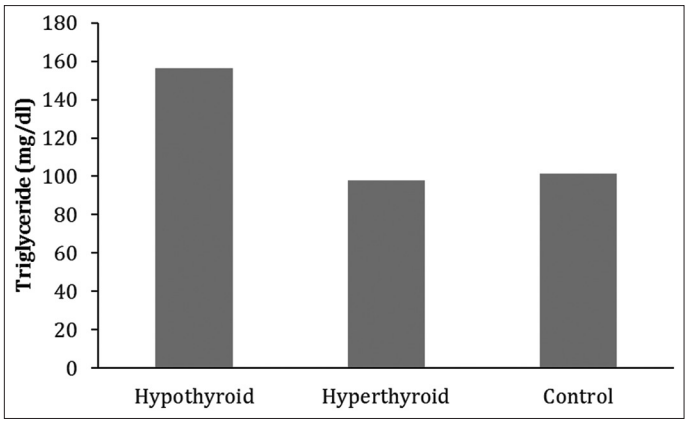

Figure 6: Triglyceride (mg/dl) level in the study participants

In spite of the reduced HMG-COA reductase activity in hypothyroidism, there is an increase in the levels of serum LDL cholesterol and intermediate-density lipoprotein (IDL) levels. Decreased activity of LDL receptors resulting in decreased receptor-mediated catabolism of LDL and IDL is the main cause of the hypercholesterolemia observed in hypothyroidism.[33]

Hypertriglyceridemia in hypothyroidism is due to decreased activity of lipoprotein lipase (LPL), which results in decreased

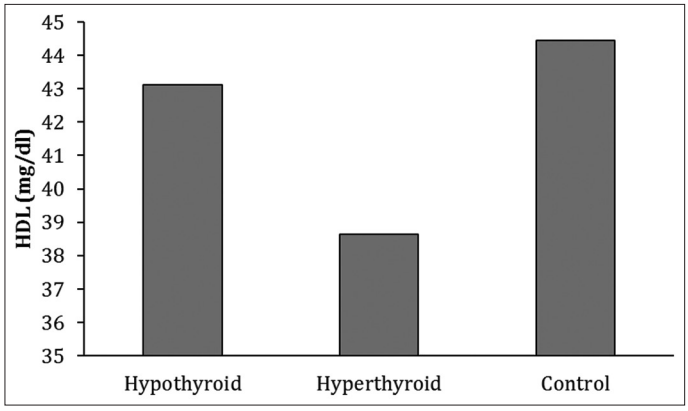

Figure 7: High-density lipoprotein (mg/dl) level in the study participants

clearance of triglyceride-rich lipoproteins,[34] while in hyperthyroidism there is an increase in the activity of LPL.[27] Thyroid hormones *per se* have only a minor influence on plasma triglyceride levels, but they induce an acceleration of triglyceride turnover and chylomicron clearance.[35]

Plasma HDL concentrations may be normal or decreased in hyperthyroidism, and normal or even elevated in severe hypothyroidism.[36] These conflicting results are partly due to the regulation of cholesteryl ester transfer protein (CETP) and hepatic lipase (HL) activity by thyroid hormone.[36] CETP transports cholesteryl esters from HDL_2 to VLDL and IDL and it also transports triglycerides to HDL_2. HDL_2 is then converted to HDL_3 by HL. CETP and, more specifically, HL seem to be dependent on the status of thyroid function, and they are low in severe thyroid failure and increased in hyperthyroidism.[36]

The results of the study would have been more conclusive if free T_4 and free T_3 levels were compared and correlated with IR and lipid profile, and, a larger sample size would ensure more accuracy.

CONCLUSION

From the present study, it is concluded that hypothyroidism and hyperthyroidism are associated with IR and atherogenic lipid profile. The present study showed a significant increase in mean IR value in both the study groups compared to the control subjects. IR in hypothyroidism may be the result of reduced blood flow, impaired insulin signaling or oxidative stress, and in hyperthyroidism, there is increased IR in the liver, aggravation of general peripheral IR, and increased glucose uptake in muscles.[32]

In the present s tudy, lipid parameters and IR have a significant positive correlation with serum TSH levels in the hypothyroid group, while in the hyperthyroid group, a negative correlation was observed between IR and serum TSH. Thyroid dysfunction predisposes to the development of IR, which is a risk factor for the development of diabetes mellitus, and altered lipid profile predisposes to the development of cardiovascular diseases. Screening for IR in thyroid dysfunction together with adequate management can reduce the risk of development of diabetes mellitus and cardiovascular diseases in these patients.

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