Assessment of Dyslipidemia and Insulin Resistance in Patients with Thyroid Dysfunction: A Study from A Tertiary Care Hospital in India

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Abstract

Background: Thyroid dysfunction is associated with significant morbidity. Dyslipidemia and dysglycemia may increase the risk for cardiovascular disease and stroke in these patients.

Aim: current study was conducted to estimate the prevalence of aberrant serum lipids, fasting blood glucose, glycated hemoglobin and insulin resistance as TG/HDL- C ratio in patients with thyroid dysfunction including hypothyroidism and hyperthyroidism patients.

Materials and Methods: The study included randomly selected 64 newly diagnosed adult hypothyroid patients (age 39.75 ± 14.83 years) and 30 hyperthyroid (age 35.43 ± 15.45 years). History taking and general examination of participants was done, followed by collection blood samples in clot activator and EDTA vacutainer tubes as required for fasting blood glucose, lipid profile and HbA1c. Two tail independent t-test was done to compare the variables the two groups, considering P value <0.05 as statistically significant.

Results: Serum triglyceride, VLDL-C and triglyceride/ HDL-C ratio were found to be significantly higher among the hypothyroid patients. Total cholesterol was found to be higher and HDL- C was found to lower in hypothyroid patients but the difference was nearly significant. HbA1c and fasting blood glucose showed no statistically significant difference between the two groups, but T4 and HbA1c showed significant positive correlation in hyperthyroid patients.

Conclusion: We conclude that hypothyroidism poses higher risk of development of dyslipidemia and insulin resistance as compared to hyperthyroid patients. Further studies with larger sample size may be designed to validate the findings.

Key Words: Thyroid dysfunction, hypothyroidism, hyperthyroidism, dyslipidemia, insulin resistance

Introduction:

Thyroid gland secretes two major hormones 3,5,3′-Triiodthyronine (T3) and tetraiodothyronine (T4) also referred as thyroxine. Thyroid hormones play an important role in growth, development and regulation of metabolism of carbohydrates, lipids and proteins. [11]. Secretion of thyroid hormones is under precise regulation by thyroid stimulating hormone (TSH) secreted from anterior lobe of pituitary gland. Thyroid dysfunction including reduced and increased secretion of thyroid hormones referred as hypothyroidism and hyperthyroidism respectively affect nearly 2% females and 1% males in India [1].

Hypothyroidism is associated with hypometabolic state marked by reduced resting energy expenditure and weight gain [2]. On the other hand, hyperthyroidism promotes a hypermetabolic state marked by increased resting energy expenditure and weight loss [3]. As, thyroid hormones directly affect lipogenesis, lipolysis, thyroid dysfunction ultimately gets reflected in aberrations of serum lipids. Similarly, insulin sensitivity of tissues is affected by thyroid hormones. Similarly, several studies have reported development of insulin resistance in patients with thyroid dysfunction. Homeostasis model assessment for insulin resistance (HOMA-IR) index is widely used clinically as a measure of insulin resistance [4]. As for calculation of HOMA-IR, measurement of plasma fasting insulin and glucose is needed; triglyceride to high density cholesterol ratio (TG: HDL- C) is considered as an easy, low cost and precise marker for insulin resistance based on routine plasma lipid parameters [5].

Aberrations of serum lipids are known to be associated with increased risk of cardiovascular disease [6]. Similarly, a causal-effect relationship has been established between insulin resistance and cardiovascular disease [7]. Thus, current study was conducted to estimate the prevalence of aberrant serum lipids, fasting blood glucose, glycated hemoglobin and insulin resistance as TG/HDL- C ratio in patients with thyroid dysfunction including hypothyroidism and hyperthyroidism patients attending a tertiary care hospital in Chhattisgarh, India.

Materials and Methods:

Sample Size Calculation:

The minimum sample size required was 61 cases in hypothyroid group and 30 cases in hyperthyroid group at 95% confidence and 80% power considering hypothetical prevalence of dyslipidemia in hypothyroid and hyperthyroid groups as 60% and 27% respectively [8].

Recruitment of Patients and sample collection:

A total of 94 patients newly diagnosed with thyroid dysfunction were recruited for this study after obtaining written informed consent. The study was approved by the institutional ethics committee and we followed the guidelines of Helsinki declaration. History taking and general examination of participants was done. The thyroid function status of patients was confirmed through chemiluminiscence immunoassay (CLIA) using the Access 2 Immunoassay system (Beckman Coulter Inc., USA) as per manufacturer's guidelines. Out of 94 recruited patients, 83 were females and 11 were males. Only the patients aged more than 18 years were included in this study. Among these 64 were hyperthyroid and 30 were hypothyroid patients. We excluded patients with known history and/or already under treatment for thyroid dysfunction, diabetes mellitus, polycystic ovarian disease from this study. We also excluded pregnant and lactating mothers.

Hypothyroid and hyperthyroid patients were defined as those having TSH value > 5.0 µIU/ml and <0.5 µIU/ml respectively. About 5 ml peripheral venous blood was collected in EDTA (K2) PET Blood collection tubes for further testing after 10-12 hours overnight fasting.

Assessment of biochemical parameters:

A total of 12 parameters including 3 thyroid function parameters and 5 lipid profile parameters, fasting blood glucose, glycated hemoglobin (HbA1c) and insulin resistance were measured. Thyroid function parameters including were assessed using CLIA on the Access 2 Immunoassay system (Beckman Coulter Inc., USA) as per manufacturer's guidelines. Lipid profile parameters including serum triglyceride (TG), total cholesterol (TC), high density lipoprotein cholesterol (HDL- C), low density lipoprotein cholesterol (LDL- C), fasting blood glucose and HbA1c were analysed using spectrophotometry on ILaB 650 Clinical Chemistry System (Werfen, USA) as per manufacturer's protocol. Very low density lipoprotein cholesterol (VLDL-C) was calculated by dividing the triglyceride value in mg/dl by five [9]. Similarly, insulin resistance was calculated as TG/HDL-C ratio [5].

Statistical analysis

R version 4.4.0 was used for all the computations and statistical analysis [10]. Descriptive data were expressed as mean ± standard deviation (SD) of the mean. Shapiro-Wilk normality test was followed by comparison of values for biochemical parameters among the two groups using Student's t-test. P value <0.05 was as considered statistically significant.

Results:

Hypothyroid and hyperthyroid patients were found to be comparable with mean age 39.75 years and 35.43 years respectively and p>0.05 using Student's t test. Highest number of patients with thyroid dysfunction were observed in 18-31 years age group (Figure 1). Out of 94 recruited patients, 83 were females and 11 were males. Among hypothyroid patients, 8 were males and 56 were females. Similarly, among hyperthyroid patients, 3 were males and 27 were females.

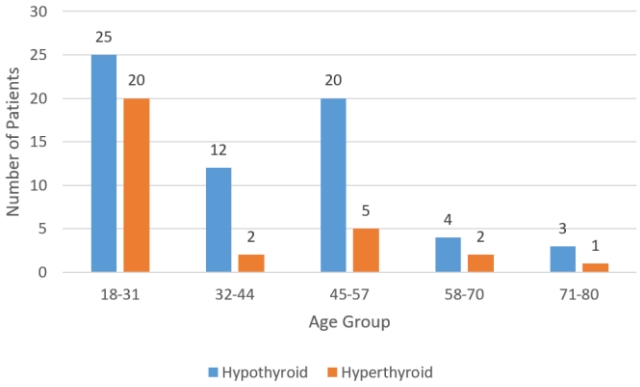

Figure 1: Age group- wise distribution of hypothyroidism and hyperthyroidism patients

Among hypothyroid patients, only one patient had all the lipid profile parameters simultaneously in normal range. Similarly. among hyperthyroid patients only one patient had all the lipid profile parameters simultaneously in normal range. Among hypothyroid patients, majority were found to have above normal LDL- C levels. On the other hand, HDL- C was found to be normal in most of the hypothyroid patients.

TG / HDL-C ratio was found to be above normal range in majority i.e., 59.37% of hypothyroid patients. On the contrary, among hyperthyroid patients, HDL- C was found to be normal in most of the patients also. Similarly, TG/ HDL- C ratio was found to normal in 66.67% hyperthyroid patients (Table 1).

Parameter	Hypothyroid (n %)			Hyperthyroid (n %)		
	<Normal	Normal	>Normal	<Normal	Normal	>Normal
TG	0	41 (64.06)	23 (35.94)	0	27 (90)	3 (10)
TC	14 (21.87)	35 (54.69)	15 (23.44)	6 (20)	21(70)	3 (10)
LDL-C	0	15 (23.44)	49 (76.56)	0	10 (33.33)	20 (66.67)
HDL-C	2 (3.12)	62 (96.87)	0	2 (6.67)	27 (90)	1 (3.33)
VLDL-C	6 (9.37)	25 (39.06)	33 (51.56)	4 (13.33)	18 (60)	8 (26.67)
TG/HDL-C Ratio	NA	26 (40.62)	38 (59.37)	NA	20 (66.67)	10 (33.33)
HbA1c	2 (3.12)	52 (81.25)	10 (15.62)	1 (3.33)	25 (83.33)	4 (13.33)
FBG	7 (10.74)	41 (64.06)	16 (25)	3 (10)	17 (56.67)	10 (33.33)

Table 1: Distribution of biochemical parameters in hypothyroid and hyperthyroid patients

For confirming the consistency of overall thyroid function data, correlation analysis was done for TSH with T3 and T4 levels. Results of the Pearson correlation indicated that there is a significant medium negative relationship between TSH and T3, ($r(92) = .426$, $p < .001$) and a significant large negative relationship between TSH and T4, ($r(92) = .591$, $p < .001$) indicating towards consistency and robustness of data. Mean TSH was found to be higher in hypothyroid patients (14.47 ± 15.01 µIU/ml) as compared to hyperthyroid patients (0.13 ± 0.16 µIU/ml) and the difference was statistically significant ($p< 0.05$). Mean T3 and T4 were found to be lower in hypothyroid patients as compared to hyperthyroid patients and the difference was statistically significant ($p< 0.05$). (Table 2)

As the patients with diabetes mellitus were excluded from the study, mean fasting blood glucose and HbA1c were found to be in normal range in both the hypothyroid and hyperthyroid groups. Although the values were higher in hypothyroid patients, the difference was not statistically significant. (Table 2)

Variable	Hypothyroid	Hyperthyroid	P value
T3 (ng/dl)	98.19 ± 40.24	163.91 ± 92.28	0.000005
T4 (µg/dl)	8.93 ± 4.29	14.53 ± 6.55	0.000003
TSH (µIU/ml)	14.47 ± 15.01	0.13 ± 0.16	0.000001
FBG (mg/dl)	101.03 ± 47.13	96.4 ± 34.24	0.63
HbA1c (%)	5.30 ± 1.65	5.19 ± 1.14	0.7363
Total Cholesterol (mg/dl)	188.45 ± 55.72	165.43 ± 56.33	0.06598
Triglyceride (mg/dl)	190.87 ± 119.47	124.13 ± 62.30	0.004999
LDL- C (mg/dl)	111.97 ± 38.46	103.7 ± 39.94	0.3397
HDL- C (mg/dl)	44.84 ± 11.49	50.1 ± 15.26	0.06667
VLDL- C(mg/dl)	38.17 ± 23.89	24.83 ± 12.46	0.004999
TG/HDL- C ratio (mg/dl)	4.65 ± 3.53	2.64 ± 1.36	0.003391

Table 1: Biochemical parameters in hypothyroid and hyperthyroid patients

Among lipid profile parameters, mean triglyceride was found to higher in hypothyroid patients (190.87 ± 119.47 mg/dl) as compared to hyperthyroid patients (124.13 ± 62.30 mg/dl) and the difference was found to be statistically significant ($p< 0.05$). Similarly, VLDL cholesterol was found to be significantly higher ($p< 0.05$) in hypothyroid patients (38.17 ± 23.89 mg/dl) as compared to hyperthyroid patients (24.83 ± 12.46 mg/dl). Further, mean total cholesterol was found to be higher in hypothyroid patients, but the difference was nearly significant ($p= 0.06$). Mean LDL cholesterol was found to be higher in hypothyroid patients, but the difference was not statistically significant.

Mean TG/HDL ratio was found to be higher in hypothyroid patients (4.65 ± 3.53) as compared to hyperthyroid patients (2.64 ± 1.36) and the difference was statistically significant ($p< 0.05$). (Table 1) A total 39 (60.94%) out of 64 hypothyroid patients were found to have TG/HDL ratio ≥ 3, that is considered closely correlated to insulin resistance [5]. A total 10 (32%) out of 31 hyperthyroid patients were found to have TG/HDL ratio ≥ 3. (Figure 2)

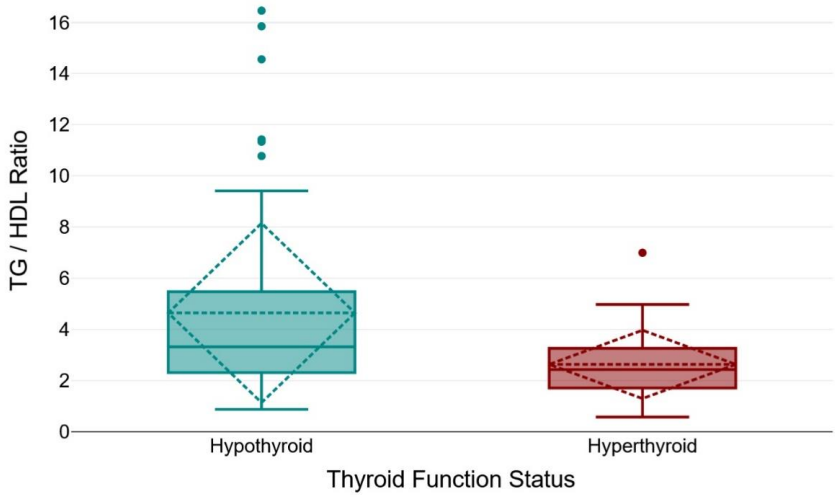

Figure 2: TG/HDL ratio in hypothyroid and hyperthyroid patients

Results of the Pearson correlation analysis indicated that T3, T4, TSH have no significant correlation with lipid profile and glycaemic parameters. One notable exception was that a significant medium positive relationship was observed between T4 and HbA1c, ($r(28) = 0.415$, $p = 0.023$) in hyperthyroid patients (Figure 3).

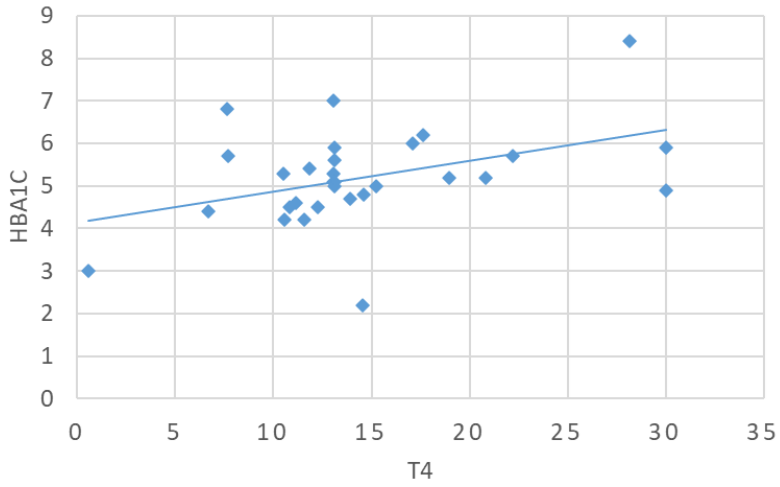

Figure 3: Correlation plot betweenT4 and HbA1c in hyperthyroid patients

Discussion:

In our cross-sectional observational study, thyroid dysfunction was found to more prevalent in females as compared to males. This was true for both the hypothyroid and hyperthyroid patients and consistent with previous reports. Lipid and carbohydrate metabolism in thyroid dysfunction are altered and manifested as dyslipidemia, disturbed glycaemic parameters and insulin resistance in such patients [11]. These aberrations in lipid and insulin resistance are of major concern, as these pose a significant risk for development of cardiovascular disease [12]. Thus, current study was aimed at mining the prevalence of dyslipidemia, altered glycaemic parameters and insulin resistance in thyroid dysfunction viz., hypothyroid and hyperthyroid patients.

Dyslipidemia is commonly observed in thyroid dysfunction patients. Hypothyroidism is associated with hypometabolic state resulting in low resting energy expenditure and triglyceride accumulation causing obesity. Uptake and β oxidation of free fatty acid by liver is decreased [13]. Our findings correlate with previous studies, as mean triglyceride levels were found to be significantly higher in hypothyroid patients as compared to hyperthyroid patients [14]. Further cholesterol clearance is decreased in patients with hypothyroidism [15]. This is reflected in our findings as mean total cholesterol was also found to be higher among hypothyroid patients as compared to hyperthyroid patients with nearly significant difference. Further, HDL-C which has protective role against cardiovascular disease, was found to lower in hypothyroid patients with a nearly significant difference [16]. Interestingly, LDL- C, that is directly associated with risk of cardiovascular disease, was not found to be significantly different between hypothyroid and hyperthyroid patients, but majority (76.56%) hypothyroid patients had LDL- C in above normal range [17]. Thus, in our study dyslipidemia was found to more pronounced in hypothyroid patients indicating higher risk for cardiovascular disease as compared to hyperthyroid patients.

Present study showed that levels of fasting blood glucose was higher in hypothyroid patients as compared to hyperthyroid patients, but the difference was not statistically significant. Similarly glycated hemoglobin was also found to be higher in hypothyroid patients. Findings indicate towards hypometabolic state resulting in dysglycemia in hypothyroid patients. This dysglycemia is further worsened by concurrent development of insulin resistance is these patients. Insulin Resistance (IR) is a pathological state, in which insulin dependent cells i.e, skeletal muscle and adipocytes are incapable of responding to normal circulatory levels of insulin due to decreased expression of GLUT4 transporters in cell membranes [18]. Insulin resistance is a significant finding observed in hypothyroid patients which leads to impaired disposal of glucose in peripheral tissues [19]. Insulin resistance is considered as an important biological marker for many metabolic disorders, such as obesity, dyslipidemia, prediabetes and cardiovascular disease. Further, a significant medium positive relationship observed between T4 and HbA1c, in hyperthyroid patients, indicates to the propensity towards poor glycaemic control in these patients. Hyperthyroidism has long been known to lead to hyperglycaemia, observed as a positive correlation between T4 and HbA1c in our study [20].

Hyperinsulinemic euglycemic clamp is considered as a gold standard method for measuring insulin resistance, but not commonly used due to complex procedure and high cost [21].

Currently HOMA-IR is the most commonly used but has its own limitations [22]. In several studies it has been observed that serum TG levels are increased and HDL-C levels are decreased in patients with insulin resistance. Thus TG / HDL ratio can be used as an easy and low-cost alternative tool to predict insulin resistance based on routine lipid profile parameters [23, 24]. TG / HDL ratio ≥3 has been reported previously as closely correlated to insulin resistance [5]. Our findings also concord with previous studies as higher prevalence of insulin resistance was observed in hypothyroid patients. Similarly, values of insulin resistance measured as TG / HDL ratio was found to significantly higher in hypothyroid patients as compared to hyperthyroid patients. This indicates towards higher risk of development of diabetes mellitus and cardiovascular disease in hypothyroid patients as compared to hyperthyroid patients.

Conclusion:

Thereby, we conclude that hypothyroidism poses higher risk of development of dyslipidemia and insulin resistance as compared to hyperthyroid patients. Considering the hypometabolic state prevalent in hypothyroid patients contrary to hypermetabolic state in hyperthyroid patients, metabolism of lipids and carbohydrates gets hampered. It leads to higher triglyceride and total cholesterol levels in hypothyroid patients. HDL-C and LDL-C levels are also affected in hypothyroid patients towards abnormal ranges. Further studies may be designed to deduce the complex interplay of various components of triglyceride and cholesterol metabolism in Indian hypothyroid patients. Findings of our study on indigenous population of Chhattisgarh, India, correlate with similar studies on other populations worldwide. Further studies with larger sample size may be designed to validate the findings.

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