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INSULIN RESISTANCE AND ITS CORRELATION WITH BMI AND TOTAL CHOLESTEROL IN PATIENTS WITH OVERT AND SUBCLINICAL HYPOTHYROIDISM

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ABSTRACT

Background: Subclinical hypothyroidism (SCH), though often considered a mild or asymptomatic condition, has been increasingly linked to fasting hyperinsulinemia and early metabolic dysfunction. Insulin resistance in hypothyroidism is closely associated with dyslipidaemia, characterized by increased LDL cholesterol, elevated triglycerides, and reduced HDL cholesterol. Given these metabolic consequences, the present study aims to explore the association between thyroid function, insulin resistance, and its impact on lipid profile abnormalities in hypothyroid patients.

Materials and Methods: The Prospective observational study was carried out for the period of March 2023 to November 2024 in the department of medicine and biochemistry, Sharda Hospital, Greater Noida. 20 clinical hypothyroidism, 20 subclinical hypothyroidism patients and 20 age and sex matched euthyroid healthy individuals as controls.

Results: In our study Serum TSH levels were more significantly positively correlated with serum insulin in overt hypothyroidism as compared to subclinical hypothyroidism. TSH levels were significantly positively correlated with HOMA-IR in both subclinical hypothyroidism and overt hypothyroidism. Serum TSH levels were positively correlated with total cholesterol triglycerides LDL while negatively correlated with HDL, VLDL in subclinical hypothyroidism. But serum TSH is positively correlated with total cholesterol, triglyceride, LDL, VLDL and negatively correlated with HDL in overt hypothyroidism.

Conclusion: In our study we found in overt and SCH is associated with higher insulin levels and insulin resistance which correlates positively with TSH levels. There is a risk of development of insulin resistance disorders such as metabolic syndrome, cardiovascular disorders in patients with SCH. Our study demonstrated that dyslipidaemia is associated with hypothyroidism and it may be recommended that patients having evidence of metabolic syndrome should be screened for the thyroid disorder.

Keywords: Hypothyroidism, Subclinical Hypothyroidism, Cholesterol, Insulin Resistance.

INTRODUCTION

Subclinical hypothyroidism (SCH) is a common thyroid dysfunction that often goes undiagnosed due to its mild or asymptomatic presentation. Epidemiological data suggest that SCH affects approximately 6–8% of women and 3% of men in the general population. The prevalence of SCH is higher in elderly populations, with studies reporting rates as high as 20% in individuals above the age of 70. Although SCH is considered a mild form of

thyroid dysfunction, it has been associated with increased cardiovascular risks, dyslipidaemia, and progression to overt hypothyroidism, necessitating careful monitoring and management.[1]

Subclinical hypothyroidism (SCH) is defined by elevated TSH levels with normal T3 and T4 levels, often presenting with mild or no symptoms. SCH has been identified as risk factors for insulin resistance, dyslipidaemia, hypercoagulability, and chronic low-grade inflammation, all of which contribute to metabolic and cardiovascular diseases.[2]

In hypothyroidism, reduced T3 levels impair GLUT-4 translocation, resulting in decreased glucose uptake, whereas hyperthyroidism may lead to enhanced hepatic glucose production and increased insulin clearance, potentially contributing to glucose dysregulation.[3] Thyroid hormones also have a direct influence on pancreatic beta-cell function and insulin secretion. Studies have detected thyroid hormone receptors in pancreatic beta cells, indicating that T3 and T4 play a role in the differentiation, growth, and functional maturation of insulin-secreting cells.[4] The presence of these receptors suggests that thyroid hormones are essential for maintaining normal insulin synthesis and secretion, ensuring proper glucose regulation. Hypothyroidism has been associated with reduced beta-cell responsiveness to glucose stimulation, leading to impaired insulin release and compensatory hyperinsulinemia, which further contributes to insulin resistance and metabolic dysfunction.[5]

Insulin resistance (IR) is a metabolic condition in which cells fail to respond effectively to insulin, leading to reduced glucose uptake, hyperinsulinemia, and an increased risk of type 2 diabetes mellitus (T2DM). Several studies suggest that insulin sensitivity in the fasting state, as assessed by HOMA-IR, may be either normal or decreased in hypothyroid individuals.[6] Some researchers have found that patients with overt hypothyroidism (OH) exhibit significantly higher HOMA-IR values, indicating increased insulin resistance, while others report that insulin action remains relatively normal, particularly in mild or subclinical cases. The discrepancy in findings may be attributed to variations in patient populations, TSH levels, genetic predisposition, and differences in study methodologies.[6] Despite these inconsistencies, it is widely accepted that thyroid hormones play a crucial role in insulin signalling and glucose metabolism, and any dysfunction in thyroid status can contribute to metabolic disturbances.

Subclinical hypothyroidism (SCH), though often considered a mild or asymptomatic condition, has been increasingly linked to fasting hyperinsulinemia and early metabolic dysfunction.[7] Studies have reported that patients with SCH exhibit higher fasting insulin levels, suggesting that even mild thyroid dysfunction can contribute to insulin resistance and altered glucose homeostasis.[8] Furthermore, insulin resistance in hypothyroidism is closely associated with dyslipidaemia, characterized by increased LDL cholesterol, elevated triglycerides, and reduced HDL cholesterol, all of which contribute to an increased risk of atherosclerosis and cardiovascular disease. Given these metabolic consequences, the present study aims to explore the association between thyroid function, insulin resistance, and its impact on lipid profile abnormalities in hypothyroid patients, emphasizing the need for early detection and intervention to prevent long-term complications.[8]

MATERIALS AND METHODS

The Prospective observational study was carried out for the period of March 2023 to November 2024 in the department of medicine and biochemistry, Sharda Hospital, Greater Noida after obtaining ethical clearance from institutional ethic committee. The study had a total of 60 subjects, willing to participate in the study with informed consent and were selected as per the selection criteria.

20 clinical hypothyroidism, 20 subclinical hypothyroidism patients and 20 age and sex matched euthyroid healthy individuals as controls were selected based on inclusion and exclusion criteria

Inclusion Criteria

Cases-newly diagnosed, clinically proved cases of hypothyroidism in the age group of 18-70 years.

1. Patients with signs and symptoms of goitre and myxoedema.
2. Clinical overt hypothyroidism patients
3. Subclinical hypothyroidism patients
4. Controls-will include healthy euthyroid age and sex matched individuals without any major illness and not on any medications.

Exclusion Criteria

1. Diabetes, hypertension.
2. Patients on thyroxine treatment, hypolipidemias, anti-epileptic drugs, women on oral contraceptives.
3. Pregnant women, previous thyroid surgeries, and other systemic illness like liver disorders and kidney disorders.

Methodology

- Overt Hypothyroidism (OH): Overt hypothyroidism is defined as elevated serum TSH levels with low serum T3 and T4 concentrations, accompanied by clinical symptoms such as fatigue, weight gain, cold intolerance, and bradycardia.[9]
- Subclinical Hypothyroidism (SCH): Subclinical hypothyroidism is characterized by elevated serum TSH levels with normal T3 and T4 concentrations, often presenting with mild or no symptoms but linked to metabolic disturbances like dyslipidaemia and insulin resistance.[9]

- Under all aseptic precautions about 4ml of venous blood was collected in a sterile bulb after overnight fasting of 12 hours.
- 2 ml will be collected in plain vial (for serum), it was subjected to centrifugation, serum and plasma will be separated and T3, T4, TSH, insulin, and cholesterol will be estimated from serum and fasting glucose from plasma (In fluoride vial)

a) Estimation of serumT3, T4, and TSH by immune-enzymometric assay (chem-luminescence immunoassay).
b) Estimation of serum fasting insulin by solid phase two-site enzyme immunoassay.[10]
c) Estimation of fasting plasma glucose by Glucose oxidase-peroxidase method10
d) Calculation of insulin resistance by HOMA & HOMA2 model11 **Formula:** HOMA-IR = [fasting plasma glucose (mmol/l) x fasting insulin(mU/l)] / 22.5 HOMA2 is the updated computer model of HOMA
e) Estimation of total cholesterol by cholesterol oxidase/phenol amino antipyrine method,[12]
f) Calculation of body mass index(BMI),[13]

Statistical Analysis

All data will be entered in the proforma and analysed using SPSS(statistical package for social sciences)v 22 operating on window.[11] One-way ANOVA will be used for multiple groups comparison and student 't' test for group wise comparison.

Correlation analysis will be done to assess any relationship between insulin resistance, serum cholesterol, and BMI with hypothyroidism.

RESULTS

The study population was divided into three groups as: 20 Controls, 20 Subclinical Hypothyroid and 20 Overt hypothyroid on the basis of T3, T4 and TSH levels in serum.

Table 1: Base line characteristic and biochemical parameters of different study groups

Parameters	Euthyroid (n=20) M-7;F-13 (MEAN±SD)	Subclinical(n=20) M-5, F-15 (MEAN±SD)	overt(n=20) M-5, F-15 (MEAN±SD)	P value
BMI	20.9±0.92	26.19±2.79	25.42±2.62	0.000***
TSH	3±1.1	13.9±4.1	52.6±24.6	0.000***
T3	102.5±18.4	102.7±24.8	58.8±13	0.000***
T4	7.06±1.8	6.8±1.21	3.62±1.01	0.000***
FBS	87±8	93±8	94±8	0.020*
INSULIN	5.44±1.4	13.4±5.15	19.17±6.66	0.000***
HOMA-IR	1.41±1.13	3.21±1.29	4.3±1.86	0.000***
CHOLESTEROL	136±25	195±40	219±37	0.000***
TG	119±15	153±51	242±38	0.000***
HDL	40±4	39±11	31±6	0.001**
LDL	38±12	123±31	140±34	0.000***
VLDL	33±8	36±11	40±14	0.163

Mean ± SD values of different parameters in the two groups of cases p>0.05: Not Significant, *p: <0.05: Significant, ** p: <0.01: Highly significant, *** p: <0.001: Very highly significant. BMI: Body mass index; FBS: Fasting blood sugar; TSH: Thyroid stimulating hormone; HOMA-IR: Homeostatic model assessment insulin resistance; TG: Triglycerides; HDL: High density lipoprotein levels LDL: Low density lipoprotein; VLDL: very low density lipoprotein.

Table 2

CORRELATION BETWEEN DIFFERENT PARAMETERS AMONG SUBCLINICAL AND OVERT HYPOTHYROID PATIENTS

PARAMETERS	SUBCLINICAL HYPOTHYROIDISM SPEARMAN CORRELATION COEFFICIENT	P VALUE	OVERT HYPOTHYROIDISM SPEARMAN CORRELATION COEFFICIENT	P VALUE
TSH Vs				
INSULIN	0.678	0.001	0.985	0.000
HOMA - IR	0.743	0.000	0.835	0.000
CHOLESTEROL	0.778	0.000	0.991	0.000
TRIGLYCERIDE	0.654	0.002	0.994	0.000
HDL	-0.414	0.069	-0.969	0.000
LDL	0.800	0.000	0.983	0.000
VLDL	-0.002	0.994	0.272	0.247
INSULIN Vs.				
HOMA - IR	0.967	0.000	0.840	0.000
CHOLESTEROL	0.791	0.000	0.986	0.000
TRIGLYCERIDE	0.781	0.000	0.985	0.000
HDL	-0.377	0.101	-0.965	0.000
LDL	0.618	0.004	0.971	0.000
VLDL	0.191	0.419	0.269	0.252
HOMA - IR Vs.				
CHOLESTEROL	0.800	0.000	0.824	0.000
TRIGLYCERIDE	0.83	0.000	0.845	0.000
HDL	-0.495	0.027	-0.798	0.000
LDL	0.649	0.002	0.764	0.000
VLDL	0.262	0.264	0.331	0.154

p>0.05: Not Significant, p: <0.05: Significant, p: <0.01: Highly significant, p: <0.001: Very highly significant. TSH: Thyroid stimulating hormone; HOMA-IR: Homeostatic model assessment insulin resistance; TG: Triglycerides; HDL: High density lipoprotein levels LDL: Low density lipoprotein; VLDL: very low density lipoprotein.

Table 2 Depicts correlation between different parameters in Subclinical and overt hypothyroidism

The spearman's correlation coefficient was for relationship between serum TSH, insulin and HOMA-IR with different parameters in subclinical and overt hypothyroidism are shown in table 2

As observed in our study Serum TSH levels were more significantly positively correlated with serum insulin in overt hypothyroidism (r =0.985, p =0.00) as compared to subclinical hypothyroidism. (r = 0.678, p =0.001).

TSH levels were significantly positively correlated with HOMA-IR in both subclinical hypothyroidism (r =0.743, p =0.00) and overt hypothyroidism (r =0.835, p =0.00)

Serum TSH levels were also compared with different lipid parameters. It was found that serum TSH levels were positively correlated with total cholesterol (r = 0.778, p =0.00), triglycerides (r = 0.654, p = 0.002), LDL (r = 0.800, p = 0.00) while negatively correlated with HDL (r= -0.414, p -0.069), VLDL (r = -0.002, p=0.994) in subclinical hypothyroidism. But serum TSH is positively correlated with total cholesterol (r = 0.991, p = 0.00), triglyceride (r = 0.994, p = 0.00), LDL (r = 0.983, p =0.00), VLDL (r =0.272, p = 0.247) and negatively correlated with HDL (r = 0.969, p =0.00) in overt hypothyroidism.

In subclinical hypothyroidism the serum insulin levels were significantly positively correlated with HOMA-IR (r = 0.967, P = 0.00), and positively correlated total cholesterol(r =0.791 , P =0.00), LDL(r = 0.618 , P = 0.004), triglycerides(r =0.781 , P =0.00) and VLDL (r = levels while negatively correlated with HDL levels (r = -0.377 , P = 0.101), while in overt hypothyroidism also the serum insulin levels were significantly positively correlated with HOMA-IR (r = 0.840, P = 0.00), and positively correlated total cholesterol(r =0.986 , P =0.00), LDL(r = 0.0.971 , P = 0.000), triglycerides(r =0.985 , P =0.00) and VLDL (r = 0.269, p = 0.252)levels while negatively correlated with HDL levels (r = -0.965 , P = 0.00).

When HOMA-IR compared in subclinical hypothyroidism, it was found that HOMA-IR was positively correlated with cholesterol (r = 0.800, p = 0.00), triglyceride (r =0.83, p = 0.00), LDL (r = 0.649, p = 0.027) and VLDL (r = 0.262, p =0.264) and negatively correlated with HDL (r=-0.495, p=0.027).

When HOMA-IR compared in overt hypothyroidism it was found that HOMA-IR was positively correlated with cholesterol (r = 0.824, p = 0.00), triglyceride (r =0.845, p = 0.00), LDL (r = 0.764, p = 0.00) and VLDL (r = 0.331, p =0.154) and negatively correlated with HDL (r = -0.798, p = 0.00).

DISCUSSION

In the present study conducted we have tried to address the possible linkage between TSH, insulin resistance, and serum concentrations of lipids in subclinical hypothyroidism and overt hypothyroidism. Thyroid disorders are one of the most common endocrine disorders. It is more common in female as compare to male, also its prevalence increases with age.[14] For early detection of hypothyroidism increased TSH is a key laboratory finding.

Recently many studies are carried out to study the influence of thyroid hormone on level of insulin. Many of the metabolic abnormalities are developed because of insulin resistance. Insulin resistance has been attributed to main pathological basis for alteration in glucose homeostasis, dyslipidaemia, abdominal obesity and hypertension.[15,16] Insulin resistance is a feature of type 2 diabetes mellitus but alteration in thyroid function is also attributed to insulin resistance and dyslipidaemia.

In our study, the body mass index (BMI) of the subjects in both the OH and SCH group were significantly more than those in the control group. Serum TSH levels are increased in SCH and further increased in Overt Hypothyroidism when compared to controls. Serum T3 decreased in SCH and OH when compared to controls. Serum T4 is decreased more in OH as compared to SCH and controls. Though Insulin levels were higher in the SCH, in OH it was significantly higher as compared to the SCH and the EU group. Mean HOMA-IR was highest in OH followed by SCH as compared to controls. Our study demonstrated that hypothyroidism whether SCH or OH, in course of disease develop a state of insulin resistance. Our results were in agreement with those of Kapadia et al,[17] and Abdel-Gayoum AA,[18] who noted "significantly increased fasting serum insulin level with lower insulin sensitivity in the hypothyroid patients." Explanation for this can be found in previous studies, which states that "hypothyroidism is associates with disorders of glucose and insulin metabolism, involving defective insulin secretion in response to glucose, hyperinsulinemia, altered peripheral glucose disposal and insulin resistance".[19] A study conducted by Maratou et al17 concluded that "insulin resistance is associated with hypothyroidism with comparable HOMA IR values in OH and SCH". However in study carried out in our institute OH patient had significantly higher serum insulin and HOMA-IR values as compared to SCH patients.

Higher total cholesterol, TG and LDL were found in OH and SCH as compared to controls. If compared between OH and SCH both cholesterol, TG and LDL were significantly higher in OH as compared

to SCH. The HDL levels were also comparable. HDL levels were significantly low in OH and SCH as compared to control with lowest values seen in OH. The VLDL levels when compared in three groups were lowest in control and highest in OH but no significant difference was found in their values. Alteration in normal thyroid function as in hypothyroidism and effect of thyroid hormone on LDL receptor expression and activity of lipoprotein lipase is responsible for elevation of total cholesterol, TG and LDL. And this dyslipidaemia occurring in hypothyroidism has important role in atherogenesis and cardiovascular risk arising from it.[20] Activity of HMG CoA reductase is increased by thyroid hormone which leads to synthesis of cholesterol. So decreased cholesterol levels should be manifestation of hypothyroidism, but levels of serum total cholesterol are high in hypothyroidism. The reason for this is decreased clearance of cholesterol by liver due to decreased cholesterol receptors on liver cells in hypothyroidism. So, the overall effect is raised total cholesterol levels, though its production in decreased.

Some investigators suggested along with reduction in hepatic LDL receptors, decrease in catabolism of hepatic cholesterol because of T3-regulated cholesterol 7-α-hydroxylase enzyme is also responsible for decrease in clearance of LDL particles from circulation.[21] Demidova and Galieva based on their study reported that "abnormally high level of TSH may be a component of metabolic syndrome".[22]

Many Studies have shown the correlation of OH with insulin resistance and alteration in lipid metabolism,[23,24,25] but the studies correlating with SCH with insulin resistance and alteration in lipid metabolism are lacking. In our study we have studied correlation of both OH and SCH with insulin resistance and dyslipidaemia. In current study Serum TSH levels were positively correlated with serum insulin and HOMA-IR in OH and SCH. These results show that fasting serum insulin and insulin resistance are strongly influenced by serum TSH levels. In current study there was a significant difference between insulin resistance in OH and SCH which may suggest that TSH and thyroid hormone levels may have contribution in development of insulin resistance and dyslipidaemia.

Explanation for insulin resistance in OH and SCH is found in action of thyroid hormone on liver, skeletal muscle and adipose tissue, where thyroid hormone acts differently. Thyroid hormone has role in up regulation of expression of gene for GLUT4 which is involved in glucose transport. Thyroid hormone also up regulates phosphoglycerate kinase, an enzyme of glycolytic pathway. So thyroid hormone works synergistically with insulin in turn facilitates glucose disposal and peripheral utilization of glucose. So in hypothyroidism there is impaired translocation of GLUT-4 glucose transporters on plasma membrane, which leads to reduced glucose uptake in muscle and adipose tissue. Lekakis et.al,[26] in his study stated that "flow mediated endothelial vasodilatation is impaired in hypothyroidism which leads to insulin resistance."

Some of the findings of our study are not consistent with previous studies which reported that "insulin resistance was similar in patients with OH and SCH.".[27,28] Some studies indicates that "even small rise in TSH level can affect the insulin secretion"29 and "rise in TSH may cause insulin resistance and metabolic syndrome".30 So as compensation to insulin resistance higher fasting serum insulin levels are found. Maratou et al in their study concluded that "hypothyroid patients have decrease in glucose transporter GLUT4 leading to reduced glucose uptake which promotes insulin resistance".[29]

Many investigators has related insulin resistance to obesity,[31] and same results were observed in our study as higher level of BMI was found in OH and SCH patients as compare to OH.

Serum TSH, serum insulin and HOMA-IR levels were positively correlated with total cholesterol, triglycerides, LDL in OH and SCH with correlation being much higher in OH than in SCH. Serum TSH, serum insulin and HOMA-IR levels were negatively correlated with serum HDL level in OH and SCH. Which means, as serum TSH or serum insulin increases consequently total cholesterol, TG, LDL also rises and HDL decreases. While there was no significant correlation found between VLDL levels and serum TSH, serum insulin and HOMA-IR. From above facts it can be concluded that with increasing severity of hypothyroidism, the problem of dyslipidaemia and atherogenic risk arising from it also worsens in turn increasing the cardiovascular risk in hypothyroid patients.

The study's findings are similar to those of Kapadia et al. and Abdel-Gayoum AA, who observed significantly increased fasting serum insulin levels and lower insulin sensitivity in hypothyroid patients.18 It also aligns with Maratou et al., who concluded that insulin resistance is associated with hypothyroidism, with comparable HOMA-IR values in overt hypothyroidism (OH) and subclinical hypothyroidism. Additionally, studies by Demidova and Galieva suggest that high TSH levels may be linked to metabolic syndrome.[19]

Some of the study's findings are inconsistent with previous studies, such as those that reported no significant difference in insulin resistance between OH and SCH patients. Specifically, the study contradicts findings from some researchers who suggested that insulin resistance was similar in both OH and SCH patients. Additionally, Ujwal Upadya et al. found that insulin was positively correlated with cholesterol but showed no correlation with other lipid profile parameters, whereas the current study did observe correlations with other lipid parameters.[32]

CONCLUSION

In our study we found in overt and SCH is associated with higher insulin levels and insulin resistance which correlates positively with TSH levels. There is a risk of development of insulin resistance disorders such as metabolic syndrome, cardiovascular disorders in patients with SCH. SCH is diagnosed either on routine TSH screening or when nonspecific symptoms are evaluated. Hence regular screening by TSH should be done and thyroid treatment should be started at an early stage. Frequent monitoring with glucose and insulin should be done in order to ward off the adverse cardiovascular effects.

Our study confirms that hypercholesterolemia and insulin resistance correlate positively with hypothyroidism status. Hence it will be good practice to screen people for presence of Sub Clinical Hypothyroidism and insulin resistance, so that early detection and prompt intervention can prevent or prolong the appearance of various fatal complications associated with insulin resistance in hypothyroidism

Our study demonstrated that dyslipidaemia is associated with hypothyroidism and it may be recommended that patients having evidence of metabolic syndrome should be screened for the thyroid disorder

There is need to closely monitor rise in serum TSH levels as SCH and OH with raised TSH has higher risk of developing dyslipidaemia and cardiovascular complications related to dyslipidaemia.

Limitation of Study

- Small Sample Size – The study had a small sample size, which may affect the generalizability of the findings.
- Lack of Follow-Up Data – The study did not include follow-up data to assess the long-term effects of hormone replacement therapy on insulin resistance in SCH and OH patients.
- Need for Larger Population-Based Studies – The study suggests that larger, population-based studies are required to validate the findings in a broader perspective.

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