

# Role of Hypothyroidism in Dyslipidaemia and Blood Glucose Regulation

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## ABSTRACT

### BACKGROUND

Hypothyroidism is associated with insulin resistance and hyperlipidaemia. Insulin resistance is the reason behind type 2 diabetes mellitus and is found in mild thyroid dysfunction with increased risk of dyslipidaemia. Prevalence of type 2 diabetes mellitus and cardiovascular risk is more common in hypothyroidism. Hence regular screening of blood glucose and lipid profile in hypothyroidism individuals may prevent dreaded complications. The aim of this study to evaluate the role of thyroid dysfunction on alteration of glucose and lipid metabolism leading to insulin resistance, an important risk factor for cardio vascular diseases.

### METHODS

In this study, we included 50 subjects, aged 25 to 35 years. This is a case control study conducted in the department of Biochemistry. Investigations like fasting and post prandial blood sugar, HbA1c and lipid profile (Cholesterol, Triglycerides, HDL, LDL & VLDL) were done. Blood pressure was measured. Body weight and height were measured, and BMI was calculated. All the parameters were analysed using XL 640 fully automated random-access analyser. Data was analysed using GraphPad QuickCalcs software.

### RESULTS

The cases were selected based on T4 and TSH concentrations whose values were significantly decreased and elevated respectively. The patients with hypothyroidism exhibited significant increase in concentration of total cholesterol, LDL, fasting blood glucose and HbA1c while HDL ( $p < 0.05$ ) showed a decrease in its concentration in comparison to controls. BMI and diastolic blood pressure showed significant elevation in hypothyroid individuals when compared to controls.

### CONCLUSIONS

It is evident from this study that insulin resistance may lead to T2DM in individuals with thyroid dysfunction. Disturbed lipid metabolism may eventually lead to cardiovascular complications in patients with thyroid dyscrasias.

### KEY WORDS

Hypothyroidism, Lipid Profile, Glycated Haemoglobin, Blood Pressure, BMI

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**BACKGROUND**

Decreased activity of thyroid gland is known as hypothyroidism. Reduced functioning of thyroid gland leads to decreased secretion of hormones like total thyroxine (T4) and triiodothyronine (T3). This decrease in T4 and T3 leads to secondary activation of pituitary gland to release increased levels of serum TSH. Hypothyroidism is contributing to one of the causes of metabolic syndrome which is a clinical syndrome due to slowing down of metabolic activity.<sup>1</sup> The prevalence of disease ranges from 2% to 15% of the population depending on the severity of disease. Women are affected more often than men and both sexes are affected more frequently with increasing age. Clinical symptoms include lethargy, fatigue and cold intolerance. It is associated with insulin resistance and hyperlipidaemia which is proven by different studies.<sup>2</sup> Thyroid hormones have effect on synthesis and distribution of lipids. In some studies, it was shown that 25% of the new onset cardiovascular disease (CVD) are due to metabolic syndrome.<sup>3</sup> Hyperlipidaemia and insulin resistance are the components of metabolic syndrome. Thyroid hormones have regulatory effect on blood pressure along with glucose and lipid metabolism which may be considered as the risk factors for cardiovascular morbidity in hypothyroidism.<sup>4</sup> Almost one-third of the people are in iodine deficiency state. The prevalence of goiter has gone up to 80 % in these endemic areas of iodine deficiency. The most commonly encountered thyroid disorders in these areas are autoimmune diseases like primary atrophic hypothyroidism, Hashimoto’s thyroiditis and Graves’ disease.<sup>5</sup> The role of thyroid hormones in glucose homeostasis has been established long back.<sup>6</sup> In 1927, Collier and Huggins had proved the association between hyperthyroidism and diabetes. This association has been proved experimentally in hyperthyroid patients with diabetes in whom glucose homeostasis has been restored after surgical removal of parts of thyroid gland.<sup>7</sup> Even morbid obesity is related to thyroid activity which is another component of metabolic syndrome.

**METHODS**

The present study is a case control study conducted in the department of biochemistry. Institutional ethical committee clearance was taken. The total size of the sample is 75 out of which 50 cases and 25 controls where their age and sex were matched and compared. The sample size was small as it was done over a week time during the endocrinologist consultation days. The control sample size though small the results were comparable; hence a smaller group was taken as control group. Venous blood samples were collected to analyse the thyroid profile, fasting and post prandial blood glucose levels, glycated haemoglobin and lipid profile. The sample was collected after taking the consent both from cases and controls. Thyroid hormones were analysed using Vidas. All the other parameters were analysed using XL640 fully automated random-access analyser. Height and weight were measured, and BMI was calculated. Blood pressure was measured for both cases and controls. History of the current illness, medication, alcohol consumption and cigarettes smoking were noted.

**Inclusion Criteria**

Individuals having hypothyroidism diagnosed based on thyroid profile and clinical features with an age group between 25-35 years were taken as cases. Individuals with normal thyroid profile in the age group of 25-35 years were taken as controls.

**Exclusion Criteria**

Persons with any acute or chronic illness like diabetes, hypertension, familial hyperlipidaemia.

**Biochemical Analysis**

All the parameters were analysed using ERBA system pack reagents on Erba XL-640 fully automated analyser. Glucose was determined by using GOD-POD method, Cholesterol by CHOD-PAP method, Triglycerides by GPO method & HDL by PVS/PEGME precipitation method and HbA1c by immunoturbidimetry. Thyroid profile was determined by using Fluorescent Immuno Assay on VIDAS.

**Statistical Analysis**

Data were computer analyzed using GraphPad QuickCalcs software. The independent sample t-test procedure was used to compare different continuous variables between the two groups separated based on thyroid profile. Descriptive data was presented as mean ± standard deviation. For all statistical analysis, p<0.05 was considered as statistically significant.

**RESULTS**

The demographic characteristics of study population and the results were shown as follows.

Parameter	Cases (Mean±SD)	Controls (Mean±SD)	p Value
Age	31.10±6.49	29.84±8.22	0.4713
BMI	28.16±4.26	25.74±4.31	0.0241
Systolic blood pressure	127.60±10.67	126.72±10.47	0.7357
Diastolic blood pressure	94.00±4.92	79.04±6.82	0.0001

**Table 1. Showing Demographic Characters**

Table 1 shows BMI and diastolic blood pressure are significantly higher in cases when compared to controls.

Parameter	Cases (Mean±SD)	Controls (Mean±SD)	p Value
Triiodothyronine (T3)	2.25±2.54	1.83±0.59	0.402
Thyroxine (T4)	72.30±38.01	101.00±25.32	0.0011
Thyroid Stimulating Hormone	21.10±26.91	2.52±1.17	0.0010

**Table 2. Showing Thyroid Profile**

From table 2 it is seen that total T4 is significantly lower and TSH is significantly higher in cases compared to controls indicating hypothyroidism.

Parameter	Cases (Mean±SD)	Controls (Mean±SD)	p Value
Total cholesterol	224.04±29.86	166.64±21.03	0.0001
LDL Cholesterol	155.24±30.73	96.04±21.03	0.0001
Triglycerides	166.00±24.31	160.00±19.66	0.2880
HDL Cholesterol	33.86±2.62	39.04±3.05	0.0001

**Table 3. Showing Lipid Profile**

From table 3 it is shown that total cholesterol and LDL cholesterol are higher in cases when compared to controls whereas HDL cholesterol is significantly lower in cases when compared to controls indicating hypothyroidism has its effect on lipid profile.

Parameter	Cases (Mean±SD)	Controls (Mean±SD)	p Value
Fasting plasma glucose	105.40±20.42	92.68±4.85	0.0031
Post prandial plasma glucose	141.90±20.69	143.40±16.09	0.7519
Glycated haemoglobin (HbA1c)	6.136±0.76	5.312±0.94	0.0001

**Table 4. Showing Fasting Plasma Glucose, Post Prandial Plasma Glucose and Glycated Haemoglobin**

Table 4 shows that fasting plasma glucose and HbA1c are significantly higher in cases when compared to controls.

## DISCUSSION

In the present study, the majority of the cases and the controls were seen in the age group of 25-35 years. Serum TSH and T4 were significantly higher in the case group ( $p = 0.001$ ) compared with the control group. But the T3 do not show significant difference between the two groups. The study also showed female predominance with 82% (41 out of 50) versus male, 26 (13 out of 100) of total participants. There was no statistically significant difference between the case group and the control group with regard to age and sex. So, we can say that the levels of lipid profile and other parameters in both the groups were not affected by age or sex. The prevalence of hypothyroidism is around 20%.<sup>8</sup> The relationship between hypothyroidism and obesity was not established clearly so far.<sup>9</sup> Few studies have attributed the obesity in hypothyroidism to be due to the deficit in resting energy expenditure. But some other studies have found that thyroid function is normal in most of the obese individuals. It's a known fact that leptin, a peptide hormone produced by adipose tissue, has a role in the pathophysiology of obesity. It was found that hypothyroid individuals have higher leptin levels when compared to euthyroid subjects with same body mass index (BMI)<sup>10</sup> but still some studies show that deficit in resting energy expenditure may be one of the causes for obesity in hypothyroid patients. The reduced Resting Energy Expenditure is due to reduced peripheral effect of thyroid hormones.<sup>(11-13)</sup> This can be evidenced from this study with significant ( $p = 0.021$ ) elevation in BMI in hypothyroid individuals when compared to controls.

The study also shows that the subjects with hypothyroidism showed significant ( $p > 0.0001$ ) elevation in the concentrations of total cholesterol, LDL cholesterol and decrease in HDL cholesterol but there is no significant difference in triglyceride levels when compared to controls. Thyroid hormones induce HMG CoA reductase which is the rate limiting enzyme of cholesterol synthesis. This results in decreased synthesis of cholesterol in hypothyroidism. However, serum cholesterol levels are conversely increased in hypothyroidism. This is because thyroid hormone may simultaneously affect metabolism of LDL cholesterol.<sup>14</sup> Approximately 3% of thyroxine (T4) is bound to lipoproteins, 92 % to HDL and 6.7% to LDL.<sup>15</sup> The LDL bound T4 is engulfed by the LDL receptor and helps in its degradation.<sup>16</sup> This results in predominant catabolism without any effect on synthesis of LDL.<sup>17</sup> Plasma HDL concentrations have been reported to be either normal or even elevated in severe hypothyroidism.<sup>18</sup> These conflicting results arising because thyroid hormones regulate the activity of CETP and HL.<sup>19</sup> Cholesterol esters are transferred from HDL2 to VLDL, IDL, and inversely from triglyceride to HDL2 by CETP.<sup>20</sup> HDL2 is then converted to HDL3 by HL. CETP and more specifically HL seem to be dependent on the status of thyroid function, and they are

decreased in hypothyroidism.<sup>21</sup> Thyroid hormones help in regulation of glucose levels. They have a role in development of insulin resistance by effecting circulating insulin levels, counter regulatory hormones, intestinal absorption, hepatic production and uptake of glucose by peripheral tissues. Thyroid hormones act differently on different tissues of insulin action like liver, skeletal muscles and adipose tissue. Thyroid hormones regulate the expression of genes for GLUT-4 involved in glucose transport and enzymes like phosphoglycerate kinase involved in glycolysis. This action of thyroid is synergistic with insulin in facilitating glucose transport and utilization by peripheral tissue.<sup>22</sup> In hypothyroidism, because of altered metabolism of lipid in adipose tissue as seen in obesity, binding of insulin to insulin receptor decreases.<sup>23</sup> There is also Impaired translocation of GLUT-4 glucose transporters on plasma membrane resulting in decreased glucose uptake in muscles and adipose tissue. But the results from our study showed only significant (0.003) elevation in fasting blood glucose in cases when compared to controls while the post prandial blood glucose do not significant (0.75) difference between the two groups. Even the fasting plasma glucose though elevated when compared to controls the mean value (105) has just crossed the upper normal limit. This indicates an impaired state with a chance of development of diabetes in future as the value is significantly high compared to controls.

HbA1c is one of the accepted investigation for diagnosis and monitoring of diabetes according to American Diabetes Association (ADA).<sup>24</sup> The HbA1c concentration gives the blood glucose concentration over a period of time rather than at a particular point of time as HbA1c concentration is dependent on the life span of the erythrocytes. Hence HbA1c levels may vary with alteration in the turnover of erythrocytes though blood glucose levels may not be altered.<sup>25</sup> so there may be possibility of false high or low values in spite of normal glucose levels. Recent studies have shown that there is a false elevation of HbA1c levels in hypothyroidism.<sup>26</sup> Normocytic normochromic anaemia commonly seen in hypothyroidism may be simply an iron deficiency anaemia due to nutritional deficiency or it may be secondary to hypothyroidism itself.<sup>27</sup> This is because reduced thyroid hormone levels repress the bone marrow resulting in decreased erythrocyte production. This reduced erythrocyte life span may be responsible for false elevation in HbA1c levels.<sup>28-30</sup> The value of HbA1c in the present study showed significant (0.0001) elevation in the cases when compared to controls but the value (6.1) does not cross the cut-off value of diagnosing diabetes. Even the value is not corresponding to the blood glucose values. It is inconclusive from this study whether to attribute the elevated HbA1c to impending diabetes or it is a spurious elevation as haemoglobin values were not evaluated to compare. Instead of HbA1c, we might have taken insulin levels which would be a more reliable parameter to assess glucose status. This finding has been elaborated by a study done by Al-Sayed A et al, in which they found that the insulin levels were significantly higher in the Subclinical hypothyroidism group comparable to the normal control.<sup>31</sup> But in this study insulin levels could not be evaluated which is a drawback for this study.

Long-standing hypothyroidism is associated with several cardiovascular manifestations. Such as it may cause decreased intravascular volume, increased systemic vascular resistance, and thereby hypertension.<sup>32</sup> Altered cardiac performance is

most probably due to changes in the peripheral circulation. Hypertension especially diastolic hypertension is more common in hypothyroidism which may contribute to approximately 20% of hypothyroid patients as seen in this study where there is a significant (0.0001) elevation in diastolic blood pressure in cases when compared to controls while there is no (0.73) significant difference in systolic blood pressure between the two groups.<sup>33</sup> Hypertension and dyslipidaemia in thyroid failure together may accelerate the process of atherosclerosis. It has been demonstrated that thyroid hormone replacement therapy in these individuals lead to a significant improvement of cardiovascular performance.<sup>34</sup> Optimum hormone replacement over a prolonged time course may help in decrease of hypertension.<sup>35</sup>

### CONCLUSIONS

Hypothyroidism results in dyslipidaemia. This dyslipidaemia may in turn affect the endothelium function. It may ultimately result in diastolic hypertension and cardiovascular disease. Insulin resistance which is the pathophysiological process of type 2 diabetes mellitus, is frequently found in thyroid dysfunction. The development of insulin resistance leads to many metabolic abnormalities apart from diabetes. Hence nowadays there is more focus on the influence of thyroid hormones on insulin levels. Thyroid dysfunction leads to alteration in glucose and lipid homeostasis which may in turn lead to insulin resistance. Insulin resistance is an important risk factor for cardiovascular diseases. Early detection of insulin resistance and prompt intervention in hypothyroid patients will be helpful in decreasing cardiovascular morbidity and mortality. Treatment of diabetes alone will not be able to resolve insulin resistance completely in hypothyroid individuals. Treatment of hypothyroidism along with diabetes will only take care of total insulin resistance in those diabetic individuals with hypothyroidism.

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