Role of hypothyroidism in dyslipidemia and blood glucose regulation.

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ABSTRACT

Context: Overt hypothyroidism is an established risk factor for insulin resistance and hyperlipidemia

Aims: 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.

Setting and Design: In this study we included 50 subjects, aged 25 to 35 years. This is a case control study conducted in department of Biochemistry.

Materials & Methods: 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 analyzed using XL 640 fully automated random access analyzer.

Statistical analysis used: tudent t test was used using graph pad 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 bears an indispensable role in connecting T2DM and thyroid dysfunction. Cardiovascular events are the counter reflection of resurgence of heavily disturbed lipid metabolism due to thyroid dyscrasias.

Keywords: Hypothyroidism, lipid profile, glycated hemoglobin, blood pressure and BMI

Key Messages: Careful screening of patients with hypothyroidism is necessary to determine the lipid and diabetic status with the aim of timely treatment and prevention of the development of atherosclerosis and potential complications of atherosclerosis.

INTRODUCTION

Hypothyroidism is defined as a deficiency of thyroid activity. It results from reduced secretion of total thyroxine (T4) and triiodothyronin (T3). Hypothyroidism is a clinical syndrome due to deficiency of thyroid hormones which results in a generalized slowing down of metabolic process.[1]. Overt hypothyroidism is an established risk factor for insulin resistance and hyperlipidemia.[2]

Hyperlipidemia is one of the components of metabolic syndrome. In some studies, metabolic syndrome and its components (dyslipidemia) are responsible for 25%of the new onset cardiovascular disease (CVD).[3] Thyroid hormones have an important regulatory effect on glucose and lipid metabolism, and blood pressure control.[4]

In iodine-replete areas, most persons with thyroid disorders have autoimmune disease, ranging from primary atrophic hypothyroidism, Hashimoto's thyroiditis to thyrotoxicosis caused by Graves' disease.[5] Thyroid hormone action has long been recognized as an important determinant of glucose homeostasis.[6] The role of hyperthyroidism in diabetes was investigated in 1927, by Coller and Huggins proving the association of hyperthyroidism and worsening of diabetes. It was shown that surgical removal of parts of thyroid gland had an ameliorative effect on the restoration of glucose tolerance in hyperthyroid patients suffering from coexisting diabetes.[7]

There is recent trend in cardiovascular sciences towards assessment of thyroid function in cardiac conditions as there is relation in between thyroid function and lipid metabolism which is risk factor for cardiac disease.we try to confirm this relationship with biochemical assays.

Subjects and Methods:

The present study was conducted in the department of biochemistry. 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. Venous blood samples were collected to analyse the thyroid profile, fasting and post prandial blood glucose levels, glycated hemoglobin and lipid profile. The sample was collected after taking the consent both from cases and controls. Thyroid hormones were analyzed using Vidas. All the other parameters were analyzed using XL640 fully automated random access analyzer. 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:

CASE- ndividuals having hypothyroidism with an age group between 25-35 years.

CONTROL- Individuals with normal thyroid profile in the age group of 25-35 years.

EXCLUSION CRITERIA:

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

Biochemical analysis

All the parameters were analyzed using ERBA system pack reagents on Erba XL-640 fully automated analyzer. 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. Mean and SD values of analytes were calculated, they were used for calculation of p value by using student t- test. p value <0.05 is considered to be significant, denoting a significant change between two groups.

Table 1 demographic characters

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 2 Thyroid profile

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 3 Lipid profile

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 4 Fasting plasma glucose, post prandial plasma glucose and glycated hemoglobin

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 hemoglobin (HbA1C)	6.136 ± 0.76	5.312 ± 0.94	0.0001

Discussion:

In the present study, the majority of the cases and the controls were seen in the age group of 25-35 years. The mean serum TSH level in the case group and the control group was statistically significantly different The levels of 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, 87 (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.

Hypothyroidism is a common disorder with a prevalence rate of up to 20%.[8] Whether a deficit in resting energy expenditure (REE) plays a role in the development of weight gain leading to obesity in hypothyroidism is a matter of debate, but thyroid function, which affects energy expenditure, is generally normal in obesity.[9] The recent discovery of leptin, a peptidic hormone produced by adipose tissue, has led to a renewed interest in the pathophysiology of obesity; some studies have focused on the relationship between leptin and energy expenditure as well as thyroid function. As far as thyroid function is concerned, hypothyroid patients have been reported to have higher levels of leptin than healthy subjects matched for body mass index (BMI). [10] A deficit of REE may be one of the factors leading to the development of obesity; [11–13] a possible impairment of REE due to a reduced peripheral effect of thyroid hormones. 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 hormone stimulates the hepatic *de novo* cholesterol synthesis by inducing the enzyme HMG CoA reductase, which catalyzes the conversion of HMG CoA to mevalonate. This results in an enhanced synthesis of cholesterol in hyperthyroidism and a decreased one in hypothyroidism. However, serum cholesterol levels are conversely decreased in hyperthyroidism, or increased in hypothyroidism because thyroid hormone may simultaneously affect the synthesis and degradation of LDL cholesterol.[14] Additionally, approximately 3% of thyroxine (T4) is bound to lipoproteins, mainly to HDL (92%) and less to LDL (6.7%).[15] The T4-LDL complex is recognized by the LDL receptor, and constitutes a credible mechanism of T4 entry into the cells.[16] Finally, thyroid hormone activates the LDL receptor leading to an increased fractional catabolic rate of apoB without influencing its synthetic rate.[17] Plasma HDL concentrations have been reported as normal or decreased in hyperthyroidism, and normal or even elevated in severe hypothyroidism.[18] These conflicting results are partly because of the recently reported regulation of CETP and HL activity by thyroid hormone .[19] CETP transports cholesteryl esters from HDL2 to VLDL, IDL and remnants, and inversely triglyceride to HDL2. [20] The latter are consequently hydrolyzed and converted to HDL3 by HL. Thus, HL is the main responsible lipolytic enzyme for the conversion of IDL to LDL and HDL2 to HDL3. CEPT 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 .[21]

Thyroid hormones up regulate the expression of genes for GLUT-4 and phosphoglycerate kinase, involved in glucose transport and glycolysis respectively, thus acting synergistically with insulin in facilitating glucose disposal and utilization in peripheral tissue.[22] In hypothyroidism because of altered metabolism of lipid and insulin, binding of insulin to insulin receptor decreases.[23] Impaired translocation of GLUT-4 glucose transporters on plasma membrane occurs, resulting in decreased glucose uptake in muscles and adipose tissue occurs. 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.

The American Diabetes Association (ADA) have approved the use of HbA1c for the screening and the diagnosis of diabetes.[24] The HbA1c concentration not only depends on prevailing glycaemia but also the life span of the erythrocytes and so, the conditions which affect the erythrocyte turnover or survival may lead to falsely elevate or lower the HbA1C levels.[25] Recent studies have shown its spurious elevation in hypothyroidism in the absence of diabetes.26 Hypothyroidism is mainly complicated by normocytic normochromic anaemia which may be early iron deficiency anaemia due to nutritional deficiency or it may be secondary to hypothyroidism itself.[27] The aetiology of anaemia in hypothyroidism can be related to the nutritional iron deficiency or to the endocrine disorder itself where the lowered thyroid hormone levels represses the bone marrow often resulting in decreased erythrocyte production which may affect the life span of erythrocytes. Altered erythrocyte life span may be partially responsible for spurious elevation in HbA1C levels.[28-30] 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 cutoff 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 hemoglobin 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. In Kuwaiti a study done by Al-Sayed A et al, on women to investigate the correlation between Subclinical hypothyroidism and insulin resistance, they found that the insulin levels were significantly higher in the Subclinical hypothyroidism group comparable to the normal control.[31]

Long-standing hypothyroidism is associated with several pathologic cardiovascular manifestations such as decreased intravascular volume, increased systemic vascular resistance, and hypertension.[32] Most often, the alterations of cardiac performance are because of changes in the peripheral circulation. Hypertension is common in hypothyroidism and more specifically, diastolic hypertension may be present in 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..[33] The coexistence of hypertension and lipid disorders in thyroid failure may accelerate the process of atherosclerosis. It is noteworthy that it has been demonstrated that thyroid hormone replacement therapy leads to a significant improvement of cardiovascular performance. [34] The decrease in blood pressure requires an optimum hormone replacement therapy and it might occur over a prolonged time course. [35]

Conclusion

Thyroid hormone regulates the metabolism of lipids. Thyroid disease may lead to lipid abnormalities that are associated with endothelium dysfunction, diastolic hypertension, and cardiovascular disease .Insulin resistance is a cardinal feature of type 2 diabetes mellitus and is relatively frequently found in mild thyroid dysfunction with increased risk of dyslipidemia. In recent times tremendous interest has been raised in the influence of thyroid hormone action on insulin levels. The development of insulin resistance leads to many metabolic abnormalities

Clinical significance

Thyroid dysfunction leads to altered glucose and lipid metabolism leading to insulin resistance, which is an important risk factor for cardio vascular diseases. Early detection of insulin resistance and prompt intervention for it in hypothyroid patients will be helpful to decrease cardiovascular morbidity and mortality. Only treatment of diabetes will not be that effective to resolve insulin resistance completely. Along with diabetes treatment, if we check and treat hypothyroidism even in subclinical stage then it will take care of its contribution to total insulin resistance.

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