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Influence of Thyroid Hormones on Metabolic Profile Before and After Therapy in Primary Hypothyroidism

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ABSTRACT

Background: *Thyroid hormones play an important role in human metabolism. Hypothyroidism is diagnosed by elevated thyroid stimulating hormone (TSH) and decreased serum levels of T_4 or T_3, and is associated with a wide range of metabolic abnormalities.*

Aims and objectives: *To estimate serum lipid profile, serum creatinine, uric acid, haemoglobin levels in newly diagnosed hypothyroid patients and to evaluate the efficacy of the L-thyroxine treatment on the same in Shivamogga population.*

Materials and methods: *We measured serum lipid profile [Total cholesterol (TC), Triglyceride (TG), HDL-Cholesterol (HDL-C), LDL-Cholesterol (LDL-C), VLDL-Cholesterol (VLDL-C)] serum creatinine, uric acid and haemoglobin (Hb) levels in 100 newly diagnosed primary hypothyroid patients. The same patients were revaluated after treatment with L-thyroxine at the end of six months. Fasting venous sample was used for analyzing the parameters. Statistical analysis was done using student's unpaired't' test. Pearson's correlation coefficient test was done to establish the relationships between the parameters.*

Results: *The serum creatinine, uric acid, TC, TG, LDL-Cholesterol, VLDL-Cholesterol were significantly elevated ($p<0.001$) and HDL-Cholesterol and Hb levels were significantly decreased ($p<0.001$) in primary hypothyroid cases. After six months of L-thyroxine treatment, haemoglobin and HDL-cholesterol showed a significant increase ($p<0.001$), serum TC, TG, LDL-Cholesterol, VLDL-Cholesterol, serum creatinine and serum uric acid levels showed a significant decrease ($p<0.001$).*

Conclusion: *Thyroid dysfunction induces varied effects on metabolic parameters and early intervention with thyroid replacement therapy resulted in reversible change in the metabolic parameters.*

KEYWORDS : Hypothyroidism, lipid profile, creatinine, uric acid, anaemia, L-thyroxine.

Introduction:

Thyroid is one of the larger endocrine glands located immediately below the larynx on either side of the trachea[1]. The principal hormones of thyroid gland are tetra-iodo-thyronine or thyroxine (T_4) and tri-iodo-thyronine (T_3). Thyroid stimulating hormone (TSH) is the anterior pituitary hormone regulating thyroid functions [2]. Thyroid hormones and TSH have physiological variations according to age[3], sex[4], nutrition[5] and race. Hypothyroidism is a clinical syndrome resulting from deficiency of thyroid hormones, leading to generalized slowing of all metabolic processes[6]. Hypothyroidism in infants and children results in growth and mental development retardation[7]. Prevalence of hypothyroidism has been showed to be varied from 2-5% depending on the study, increasing to 15% by the age of 75 years, with a higher incidence in females[7]. In iodine deficient areas like India the incidence can reach as high as 10-20 times more than non iodine areas like U.S.A[8-10].

Metabolic abnormalities associated with hypothyroidism include hyperlipidemia, reversible increase in creatinine, dilution hyponatremia and anaemia. Thyroid hormones are known to play a role in the synthesis, metabolism and mobilization of lipids. By affecting the metabolism of lipids, thyroid hormones accelerate the process of atherogenesis and it increases the cardiovascular risk[11]. Thyroid dysfunction causes significant changes in kidney function and the most common kidney derangements associated with hypothyroidism is elevation of serum creatinine levels, reduction in GFR and renal plasma flow[12]. Anaemia is prevalent in 20-60% of the patients with hypothyroidism. The most frequently encountered anaemia type is normochromic normocytic anaemia. This is due to the bone marrow repression because of the thyroid hormone deficiency as well as lack of erythropoietin production arising from the reduction in need of O_2. Thyroid hormones also increase 2-3 DPG (diphosphoglycerate) levels assisting in the transmission of oxygen into the tissues[13]. Long standing hypothyroidism increases the risk of coronary artery disease and can also cause a significant reversible change in renal function such as decrease in sodium reabsorption in proximal tubules, decrease in renal blood flow and glomerular filtration rate. The present study was carried out to determine the changes produced by thyroid hormone deficiency on metabolic parameters and efficacy of drug treatment on the same.

Materials and methods:

With the approval of the Institutional ethics committee and the informed consent of the participants, 100 newly diagnosed hypothyroid patients of 30-65 years of age were chosen and metabolic parameters like total cholesterol, triglycerides, HDL-Cholesterol, LDL-Cholesterol, VLDL-Cholesterol, serum creatinine, uric acid and haemoglobin were measured. The patients were then treated with the required dose of L-thyroxine and at the end of six months same parameters were measured. All the study participants were free of any confirmed renal, hepatic or cardiovascular disease and diabetes mellitus. All female patients were asked about their menstrual period duration, frequency, and amount of bleeding. Patients with a menstrual period lasting for more than 5 days or more than usual amount of bleeding were excluded from study.

Sample collection:

After an overnight fast of 10-12 hours, 4 ml of venous blood was collected in EDTA and plain vacutainer [BD Biosciences] from antecubital vein from each patient. Serum creatinine was estimated by Jaffe's method[14], uric acid by modified Trinder method[15], serum lipid profile was estimated by the enzymatic CHOD -POD method[16] for TC, GPO-Peroxidase method[17] for Triglycerides, CHOD, CHER-POD method[18] for HDL-Cholesterol, by using Erba Mannheim reagent kits obtained from Transasia Bio-Medicals and all the parameters were estimated by using fully automated analyser – Erba Mannheim (EM 100). LDL-Cholesterol concentrations were calculated by Friedewald's formula[19]. EDTA anti coagulated blood samples were processed in Haematology Analyser (cell counter) Erba – Sysmax (XP-100) for determination of Haemoglobin (Hb).

Estimation of thyroid profile was done by Lilac kit by using a Chemiluminescence method. The following three parameters were estimated under thyroid profile: Tri-iodo-L-thyronine (T_3), Tetra-iodo-L-thyronine (T_4), Thyroid stimulating hormone (TSH).

Diagnosis of Hypothyroidism was established based on clinical signs and symptoms and the T_3, T_4 and TSH estimations.

Statistical Analysis:
Data obtained was entered into Microsoft Excel sheet and statistical analysis was performed. Results were analysed and presented as numbers and mean ± standard deviation (SD). Kruskal Wallis test, Mann Whitney –U test , Fisher test and student's unpaired 't' test were applied for the descriptive analysis and the correlation was done by the Pearson's correlation coefficient. A *p*-value of <0.001 was considered as statistically significant.

Results:
The mean age of hypothyroid patients was 51.15±9.56 years.

Table-1 shows the serum TSH and thyroid hormone levels in newly diagnosed primary hypothyroid patients before and after treatment with L-thyroxine. Mean TSH level was significantly higher with lower T_3 and T_4 values in the hypothyroid group. Significant difference was observed in levels of TSH, T_3 and T_4 in subjects before and after treatment with L-thyroxine.

Table-2 illustrates significant dyslipidemia in the hypothyroid pool with an increase in TC, TG, LDL-Cholesterol and VLDL-Cholesterol levels and decreased HDL-Cholesterol levels. The mean TC, TG, LDL-Cholesterol, VLDL-Cholesterol and HDL-Cholesterol levels were 245.82±18.06, 214.76±21.16, 163.79±19.48, 42.95±4.23 and 39.08±1.94 respectively. Serum creatinine and uric acid concentrations were significantly increased and Haemoglobin concentration was decreased in the hypothyroid cases. The mean values of serum creatinine, serum uric acid and Haemoglobin were 1.40±0.06, 7.13±0.33 and 8.57±0.61 respectively. These patients were treated with L-thyroxine and the same patients were evaluated at the end of six months. The changes in the metabolic parameters were found to be reversible after thyroxine replacement therapy. In the present study, there was a decrease in the mean TC levels from 245.82±18.06 to 224.11±18.88, mean TG levels from 214.76±21.16 to 206.79±18.57, mean LDL-Cholesterol levels from 163.79±19.48 to 142.31±19.51, mean VLDL-Cholesterol levels from 42.95±4.23 to 41.36±3.71, mean serum creatinine levels from 1.40±0.06 to 1.21±0.06, mean uric acid levels from 7.13±0.33 to 6.13±0.39 which was statistically significant (p<0.001). Haemoglobin showed a mean increase from 8.57±0.61 to 10.09±0.53 and HDL-Cholesterol from 39.08±1.94 to 40.44±1.77 which was statistically significant (P<0.001).

Discussion:
Deficiency of thyroid hormones in hypothyroidism causes an elevation of the LDL-cholesterol synthesis due to an increase in the cholesterol synthesis and absorption, a decrease in the hepatic lipase and the lipoprotein lipase activities, defects in the receptor- mediated catabolism of LDL-cholesterol[11, 20], an increase in the oxidation of plasma cholesterol (mainly TC and LDL-cholesterol), reduced activity of HMG-Co A reductase and a decrease in the HDL receptors on the hepatocytes. Decrease in Lipoprotein lipase activity causes a decrease in clearance of triglyceride rich lipoproteins.

In the hypothyroid pool which was diagnosed, based on the raised TSH and the lower T3 and T4 levels, the triglycerides were found to be significantly elevated, along with TC, LDL-Cholesterol and there was a significant decrease in serum HDL-Cholesterol level [Table-2]. Mild thyroid hormone deficiency per se is responsible for reversible endothelial dysfunction and reduced nitric oxide availability, which act as promoters of atherosclerosis. Evidence is available, to say that not only TC and LDL-cholesterol, but that the triglycerides were also independent risk factors for Coronary Heart Disease (CHD), cerebrovascular disease, and peripheral artery disease[21,22] . The findings in relation to the lipid status point to the high susceptibility of the hypothyroid subjects to the development of cardio vascular diseases.

Our study shows significant increase in creatinine levels in hypothyroid patients (Table-2)**.** Similar changes in serum creatinine with hypothyroidism have been reported in support of our study [23-26]. The increase in serum uric acid may be either due to increased production or decreased renal clearance of uric acid. With thyroxine replacement therapy, significant decrease in serum creatinine and uric acid levels was observed. Histological changes in nephrons, especially basement membrane thickening have been demonstrated in hypothyroid rats and humans[27].Decreased renal blood flow and glomerular filtration rate (GFR) is believed to be due to the generalized hypo dynamic state of the circulatory system in hypothyroid patients. Thyroid hormones have a role in the maturation of the Renin Angiotensin Aldosterone system (RAAS) system[28, 29]. Our study confirms the association of hypothyroidism with elevated uric acid and creatinine which may be due to a decrease in GFR levels and alteration in the RAAS. Thyroid hormones induce relaxation of blood vessels resulting in a reduction in vascular resistance and in increase in serum levels of Renin activity and angiotensin concentration thereby increase in GFR. In another study done by Md. Aminul Haque Khan on 80 hypothyroid patients, serum creatinine and uric acid level was found to be significantly higher in hypothyroid patients [30-32]. Iglesias study on thyroid dysfunction and kidney disease shows elevation of serum creatinine levels due to de- creased GFR and due to decreased renal plasma flow[12].

Thyroid diseases are frequently associated with erythrocyte abnormalities[33]. Anaemia of hypothyroidism has been ascribed to a physiological compensation for the diminished need of tissues for oxygen. It is thought that thyroid hormones affect haematopoiesis through an increase in erythropoietin production or haematopoietic factors by non erythroid cells[34]. The low plasma erythropoietin levels found in hypothyroid anaemia is in accordance with this hypothesis[35]. Patients with hypothyroidism have a decreased erythrocyte mass due to reduction of plasma volume and may be undetectable by routine measurement such as haemoglobin concentration[36]. The determination made by Christ-Crain and colleagues indicated that erythropoietin values were increased as result of Levothyroxine treatment in women with subclinical hypothyroidism [37]. In our study also there was increase in haemoglobin concentration on treatment with L-thyroxine.

Conclusion:
Our study concluded that there is a significant increase in the serum TC, TG, LDL-Cholesterol, VLDL- Cholesterol, Serum creatinine and uric acid levels and decrease in HDL-Cholesterol and Hb levels in hypothyroid patients. Thyroid dysfunction alters the lipid status and increases the risk of myocardial Infarction or stroke. Thyroid dysfunction causes significant changes in kidney function and the most common kidney derangements associated with hypothyroidism is elevation of serum creatinine levels, reduction in GFR and renal plasma flow. Hence hypothyroidism should also be considered in patients presenting with the biochemical abnormalities of chronic kidney diseases. There was significant decrease in TC, TG, LDL-Cholesterol, VLDL-Cholesterol, Serum creatinine, serum uric acid levels and increase in HDL-Cholesterol and haemoglobin levels on treatment with Levothyroxine. The findings in the current study help us to understand the complex interaction between the thyroid gland and major organ systems. It also denotes the importance of early intervention of hypothyroidism which will help in the prevention of long term complications like CAD, CVD and decrease in mortality rate. We suggest those people with thyroid disorder should have routine screening of haematological, biochemical and hormonal profile assay and simultaneously proper management of this metabolic disease should be provided based on American endocrinologist guidelines. Hence a multisystem approach is required to treat patients suffering from hypothyroidism.

TABEL 1: THYROID STATUS OF STUDY GROUPS

TESTS	HYPOTHYROID	TREATED **HYPOTHYROID**	**p-value**
T3 (ng/ml)	0.28±0.09	0.56±0.06	<0.001*
T4 (µg/dl)	2.43±0.68	4.45±0.54	<0.001*
TSH (µ IU/ml)	54.81±7.09	28.34±6.06	<0.001*

TABLE 2: METABOLIC PARAMETERS OF STUDY GROUPS

TESTS	HYPOTHYROID	TREATED HYPOTHYROID	p-value
TC (mg/dl)	245.82±18.06	224.11±18.88	<0.001*
TG (mg/dl)	214.76±21.16	206.79±18.57	<0.001*
HDL (mg/dl)	39.08±1.94	40.44±1.77	<0.001*
LDL (mg/dl)	163.79±19.48	142.31±19.51	<0.001*
VLDL (mg/dl)	42.95±4.23	41.36±3.71	<0.001*
CREATININE (mg/dl)	1.40±0.06	1.21±0.06	<0.001*
URIC ACID (mg/dl)	7.13±0.33	6.13±0.39	<0.001*
Hb% (gm/dl)	8.57±0.61	10.09±0.53	<0.001*

***Statistically significant**

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