Journal of
Clinical and Experimental Pharmacology

Ajay Kumar, Clin Exp Pharmacol 2013, 3:3
DOI: 10.4172/2161-1459.1000128

Research Article Open Access

The Effect of L – Thyroxine on Metabolic Parameters in Newly Diagnosed Primary Hypothyroidism

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Abstract

Objective: Thyroid hormones regulate the basal metabolic rates of most of the cell. This hospital based study was done to evaluate the metabolic changes induced in newly diagnosed hypothyroid patients and the benefits of early intervention in the same.

Methodology: The study included 30 patients randomly selected from the department of endocrinology. Serum T3, T4, TSH, kidney function, total cholesterol levels were measured using standard kits. The same patients were revaluated after treatment with L-Thyroxine at the end of 6 months.

Results: Hypothyroid patients showed decreases in Hb, increase in total cholesterol, serum uric acid and creatinine level compared to euthyroid patients. After 6 months of thyroxine treatment, Hb showed a significant increase ($p<0.005$), serum cholesterol ($p<0.001$), and serum uric acid level($p<0.001$) showed a significant decrease, where as the serum creatinine level showed no significance($p<0.350$).

Conclusion: This shows that early intervention with thyroid replacement therapy resulted in reversible change in the metabolic parameters

Keywords: Hypothyroidism; Anemia; Levothyroxine; Bilirubin; Creatinine; Uric acids

Introduction

Gull first described hypothyroidism in the year 1874 under the name of myxedema. The active principle of thyroid extract, thyroxin was isolated by Kendall in 1914. Hypothyroidism is a clinical syndrome characterized by the clinical and biochemical manifestation of thyroid hormone deficiency in the target tissue, leading to generalized slowing of all metabolic processes.

The thyroid gland synthesizes and release T3 and T4. The Biological active hormones T3 [1] and T4 Play a significant role in the growth, development and function of all major tissues. Thyroid hormones regulate the basal metabolic rate of all cells, which also include hepatocytes. Liver in turn metabolizes the thyroid hormones and in turn regulates their endocrine effects [2]. Normal circulating levels of the thyroid hormone are required for hepatic circulation and normal bilirubin metabolism [3]. Thyroid hormone synthesis and secretion is regulated by the negative feedback system that involves the hypothalamus, pituitary and the thyroid gland [4]. Thyroid dysfunction may perturb the liver function and vice versa.

Various animal experiments or drug induced hypothyroidism have shown to decrease GFR on long standing [5,6].

Primary hypothyroidism is due to abnormality in thyroid gland itself, secondary hypothyroidism may be due deficiency of TSH. In central hypothyroidism, the TSH secretions are not sufficient to stimulate the thyroid gland. Basal TSH values in central hypothyroidism are low, normal or slightly elevated. The incidence of hypothyroidism depends on different environmental and various geographic factors, they include dietary iodine deficiency (most common), genetic variation in population. Iodine deficiency remains the main cause of hypothyroidism throughout the world. Autoimmune disorders remain the other cause.

Hypothyroidism is the most common hormonal deficiency, the diagnosis can be made quickly, confirmed or excluded and the treatment is straight ward with excellent prognosis. Thyroid hormone deficiency affects virtually every tissue in the body. The clinical finding is slowing of physical and mental activity. Pathologically, there is accumulation of glycosaminoglycans, which is related to loss of inhibitory effects of thyroid hormones on the synthesis of hyaluronate, fibronectin and collagen by fibroblasts.

Long-standing hypothyroidism can cause reversible changes in the metabolic parameters such as increase in serum uric acid, serum creatinine levels, abnormal lipid profile and low levels of Hb%.

The present study was carried out to determine the changes produced by thyroid hormone deficiency on metabolic parameters and the efficacy of drug treatment on the same.

Materials and Methods

It was a open label, single centre, randomized prospective study carried out in the Outpatient Department of Endocrinology, Govt. Rajaji Hospital, Madurai, for a period of 6 months (July-December 2011) after obtaining approval from the Institutional Ethical Committee, Ref no:6087/E4/3/2011

Collaborating epartments

- Institute of Pharmacology
- Department of Endocrinology
- Department of Biochemistry

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Received April 28, 2013; **Accepted** June 01 2013; **Published** June 04, 2013

Citation: Ajay Kumar N (2013) The Effect of L–Thyroxine on Metabolic Parameters in Newly Diagnosed Primary Hypothyroidism. Clin Exp Pharmacol 3: 128. doi:10.4172/2161-1459.1000128

Selection of cases

30 Patients (male & female) who fulfilled the following inclusion criteria were enrolled for the study.

Inclusion criteria:

1. Newly Diagnosed Hypothyroid patients with elevated TSH.
2. Both male and females above 18yrs.

Exclusion criteria: Pregnant, Breast feeding women and Patients with other chronic ailments like Chronic Arterial Disease (CAD), Deep Venous Thrombosis(DVT) etc, were excluded from study.

Methodology

Institutional review board approval was obtained prior to the initiation of the study. The study group, consisting of 30 patients, who satisfied the inclusion and exclusion criteria, was selected from the outpatient department of Endocrinology in Tertiary care teaching hospital.

They were informed verbally and in writing by the investigator about the nature, significance, implication and risks of the study prior to enrollment. All terms were explained by the investigator in a language and in terms that were easy to understand by the patient. Informed consent was obtained from all patients personally and signed by both the patient and the investigator. The details of the investigator (name, phone number, and contact address) were given to each patient, to enable them to contact for any ailments at anytime during the study period. Newly diagnosed hypothyroid patients with elevated TSH were selected for the study. The impact of hypothyroidism on various metabolic parameters such as Hb%, lipids, serum uric acid level, serum creatinine were measured at the beginning of the study. The patients were then treated with the requird dose of l-Thyroxine in the outpatient clinic for a period of six months. At the end of six months the same parameters were measured,tabulated compared and analysed statistically using one way anova test.

Results

The study population is of 30 newly diagnosed patients with primary hypothyroidism from the out patients departments of the hospital. All patients included were screened for T3, T4, TSH, Hb , total cholesterol, serum uric acid and serum creatinine level (Figures 1-4). A significant difference was observed in levels of TSH, T 3 and T4 in euthyroid and the hypothyroid patients. This study shows an increase in serum creatinine with a mean of 1.119 , increase in serum uric acid with a mean of 7. 358 and increase in serum cholesterol with a mean of levels 226.19 along with decrease in Hb levels with a mean of 9.503. 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 the Hb showed a mean increase from 9.503 to 10.823 and statistically significant ($p<0.005$), the mean serum cholesterol levels decreased from 226.19 to 186.71 ($p<0.001$) statistically highly significant , the mean uric acid levels decreased from 7.358 to 5.797 ($p< 0.001$) statistically highly significant and the serum creatinine decreased 1.119 to 0. 948 ($p< 0.350$) not statistically significant.

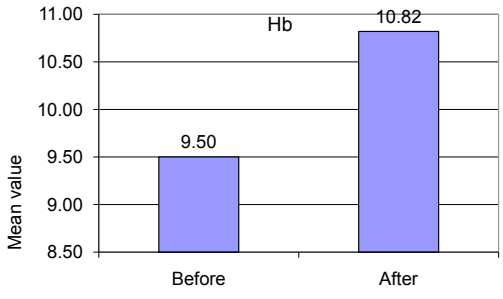

Figure 1: Total Hemoglobin.

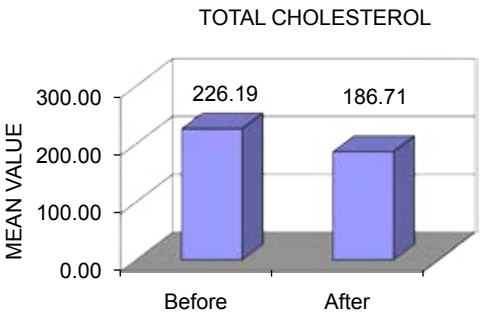

Figure 2: Total Cholesterol.

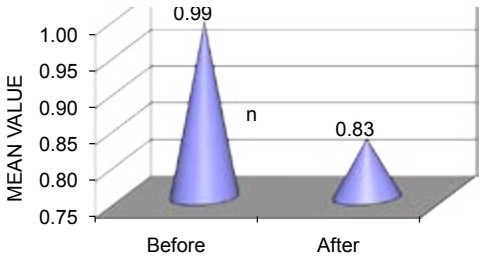

Figure 3: Serum Creatinine.

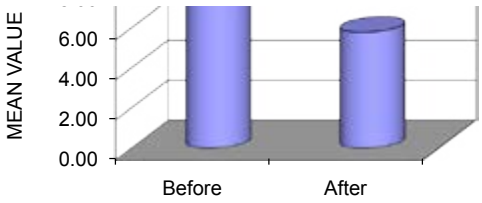

Figure 4: Serum Uric.

Discussion

Hypothyroidism is a clinical syndrome resulting from deficiency of thyroid hormones, leading to generalized slowing of all metabolic process [6]. Hypothyroidism in infants and children results in

growth and mental development retardation [7]. The prevalence of hypothyroidism varies in different part of the region but generally higher among females [8]. The metabolic disturbance associated with hypothyroidism includes anemia, hyperlipidemia, increases in serum creatinine and uric acid levels. Thyroid hormones are involved in haemoglobin synthesis in the adults and maturation of haemoglobin in the fetus [9] and by affecting hematopoietic process, hypothyroidism results in anemia through slowing the oxygen metabolism [10]. The anemia in patients with hypothyroidism varies between 20-65% [11] indicating a high correlation between hypothyroidism and anemia. The current study showed that all the patients had a significant improvement in the mean values of Hb ($p<0.005$) after treatment with l-thyroxine. Besides the incidence of anemia was found to be greater in women than men, this higher association may be linked to menorrhagia [12]. The standard administration of levothyroxine is able to reduce TSH level as well as improve the anemic status.

Although the association between hypothyroidism and dyslipidemia is still lacking, most reports have documented relationship between hypothyroidism and reversible dyslipidemia. Hypothyroid patients have increased levels of Total Cholesterol and Low Density Lipoprotein C [13]. Indeed, hypothyroidism is a common cause of secondary dyslipidemia [14,15]. Although decreased thyroid function is accompanied by reduced activity of HMG-CoA reductase, TC and LDL-C levels are increased in patients with overt hypothyroidism [16]. This is due to the decreased LDL-receptor activity, resulting in decreased catabolism of LDL and IDL [17,18]. Moreover, a decrease in LPL activity is found in overt hypothyroidism, decreasing the clearance of TG-rich lipoproteins [19]. Therefore, overt hypothyroid patients may also present with elevated TG levels associated with increased levels of VLDL and occasionally fasting chylomicronemia [20].

Hypothyroid patients have increased lipoprotein (a) [21] levels, which are associated with increased CVD risk [22]. In addition, an increase in Carotid Intima Media Thickness (CIMT) has been observed in hypothyroid patients [23]. Administration of substitution therapy with L-thyroxine significantly improves lipid metabolism abnormalities. A period of 4-6 weeks of thyroxin replacement therapy is usually needed to correct dyslipidemia in overt hypothyroidism. A study in newly-diagnosed hypothyroid patients (n=60) showed a decrease in serum TC and LDL-C levels after thyroxine treatment A more dramatic reduction of TC levels has been observed in hypothyroid patients with higher baseline TSH levels [24].

Thyroid failure is associated with increased levels of Creatinine Kinase (CK) [25]. Statin therapy may substantially increase levels of CK. A study examined the effects of accidentally starting statin therapy in patients with undiagnosed hypothyroidism (n=9) [26]. These patients had significantly higher CK levels (1095 U/L) compared with untreated hypothyroid patients matched for free T4 levels (n=18; CK=395; $p<0.05$) [27]. Therefore, it is imperative to firstly correct thyroid dysfunction with thyroxine substitution therapy and then treat the underlying dyslipidemia with statins.

Mild thyroid hormone deficiency *per se* is responsible for reversible endothelial dysfunction and reduced nitric oxide availability, which act as promoters of atherosclerosis [28]. Accordingly, Mizuma et al. recently described the presence of an iodothyronine deiodinase in human Vascular Smooth Muscle (VSM) cells [29]. Although the target genes for T3 action in VSM cells remain unknown, it could be speculated that, as described in cardiac myocytes, they are involved in the modulation of sarcoplasmic reticulum and sarcolemmal ion flux and VSM contractility. Indeed, the presence of an iodothyronine deiodinase suggests that VSM cells, which are in physiologic cross-talk with endothelium, may be a target for thyroid hormone action and lends support to the hypothesis of a direct involvement of thyroid hormone deficiency in IMT thickening. The fact that L-T4 replacement therapy was able to improve both the atherogenic lipoprotein profile and intima-media thickening suggests that lipid infiltration of arterial wall may represent a major mechanism underlying IMT increase in this selected subset of patients.

Long standing hypothyroidism can also cause a significant reversible change in renal function such as a decrease in sodium resorption in the proximal tubules, impairment in the concentrating and diluting capacities of the distal tubules, a decrease in urinary urate excreation , and a decrease in the renal blood flow and the glomerular filtration rate. The increase in uric acid concentration in hypothyroid state may be either due to increased in production or due to decrease in renal clearance of uric acid. Though the observed decrease in renal function was not so severe in this study , a recent case report illustrated how hypothyroid induced renal dysfunction may lead to adverse clinical consequences in patients taking medications cleared by the kidneys. With thyroxine replacement therapy, a significant decrease in serum uric level was observed to that of serum creatinine levels. Other scattered studies and case reports also demonstrate an improvement in the renal status of patients with treatment of hypothyroidism. Histological changes in nephrons, especially basement membrane thickening have been demonstrated in hypothyroid rats and humans [30]. Some of these functions include decrease in GFR and renal blood flow. The cause of the decrease in renal blood flow and GFR is believed to be due to the generalized hypodynamic state of the circulatory system in hypothyroid patients. This decrement in GFR is readily reversible upon correction of thyroid hormone deficiency [31].

Thyroid hormones have a role in the maturation of the RAAS system. Plasma level of renin is low in hypothyroidism in contrast to hyperthyroidism. The study confirms association of hypothyroidism with elevated uric acid and creatinine, which may be due to a decrease in GFR levels and alteration in the RAAS system. Thyroid hormones induce relaxation of blood vessels resulting in a reduction in vascular resistance and in increase in serum; levels of rennin activity and angiotensin concentration thereby increase in GFR. The study concluded that there is a significant decrease in the total cholesterol levels ($p<0.001$) and the serum uric acid levels ($p<0.001$) where as there is a significant increase in the Hb level ($p<0.005$), the decrease in the serum creatinine level though was not statistically significant ($p<0.350$).

All 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 complication like CVD and decrease in mortality. Hence, a multi system approach is indeed needed to treat patients suffering from hypothyroidism.

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