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ORIGINAL ARTICLE

BIOCHEMICAL MARKERS OF LIVER AND KIDNEY FUNCTION ARE INFLUENCED BY THYROID FUNCTION- A CASE-CONTROLLED FOLLOW UP STUDY IN INDIAN HYPOTHYROID SUBJECTS

Sarika Arora, Ranjna Chawla, Devika Tayal, Vinod K Gupta, Jagdeep S Sohi and V Mallika

Department of Biochemistry, G. B. Pant Hospital, New Delhi, India.

ABSTRACT

Thyroid hormones regulate the renal hemodynamics and basal metabolic rate of most cells. This hospital-based case-control study was done to evaluate the changes in biochemical markers of liver and kidney function in hypothyroid subjects before and after treatment. The study included 176 subjects randomly selected from Thyroid clinics. Serum T_3, T_4, TSH, Liver and Kidney Function tests were analysed using standard kits. Forty-six hypothyroid patients were re-evaluated 6 weeks after thyroxine substitution therapy. Hypothyroid subjects (n=80) showed significantly raised serum creatinine and uric acid levels as compared to euthyroid subjects (n=96). After 6 weeks of thyroxine replacement, serum creatinine and uric acid decreased significantly and were comparable to euthyroid group. A positive correlation of ALT, AST, uric acid, protein and albumin with TSH levels ($p<0.05$) and negative correlation of serum T_4 levels with ALT, AST, proteins ($p<0.05$) was observed in the hypothyroid group. Hypothyroidism results in reversible impairment of hepatorenal function.

KEY WORDS

Hypothyroidism, Bilirubin, Liver enzymes, Creatinine, Uric Acid

INTRODUCTION

The thyroid gland synthesizes and releases triiodothyronine (T_3) and thyroxine (T_4), which represent the only iodine containing hormones in the vertebrates. T_3 is the biologically active thyroid hormone (1). These hormones are required for the normal growth, development and function of nearly all tissues, with major effects on oxygen consumption and metabolic rate (2). Thyroid hormone synthesis and secretion is regulated by a negative feedback system that involves the hypothalamus, pituitary, and the thyroid gland (3).

Thyroid hormones regulate the basal metabolic rate of all cells including hepatocytes, and hence, modulate hepatic function; the liver in turn metabolizes the thyroid hormones and regulates their systemic endocrine effects (4). Normal circulating levels of thyroid hormone are required for both normal hepatic circulation and normal bilirubin metabolism (5). Thyroid dysfunction may perturb liver function and vice-versa (4). In experimental animals, surgical or drug-induced hypothyroidism of a few weeks' duration has been shown to result in a decrease in GFR (6, 7). However, clinical studies on hypothyroid subjects are very few and not much data is available on how hypothyroidism influences renal function in human beings.

This study was, therefore, planned in human subjects referred to Thyroid Clinic, with a view to evaluate the changes in liver and kidney function in hypothyroid subjects, before and after treatment and to correlate these values with thyroid profile of the patient.

MATERIALS AND METHODS

The study was conducted on subjects of age group 15 to 55 years referred to thyroid clinic in a tertiary care hospital of a

Address for Correspondence :

Dr Sarika Arora
Department of Biochemistry
G.B. Pant Hospital, New Delhi-110002
Tel: 91- 9811266400.
E-mail: sarikaarora08@rediffmail.com

developing country. For this, 563 ambulatory patients, presenting to thyroid clinic for the first time were screened. Brief clinical history and examination was done to rule out diabetes mellitus, renal disorders, liver disorder, or any other inflammatory and medical condition, which would have influenced the parameters under study. Only 176 subjects fulfilled the required inclusion criteria and were enrolled after a written and informed consent.

After overnight fasting, 6ml venous blood sample was collected. Serum obtained after centrifugation was divided into 2 aliquots- one for liver function tests (LFT) and kidney function tests (KFT) and second for thyroid function tests. Sample for LFT and KFT was analyzed immediately. Aliquots for thyroid function tests were stored at -70ºC until batch analysed.

Serum TSH, T_4 and T_3 were assayed using ELISA kits obtained from Ranbaxy, India. Serum T_3 and T_4 were performed using competitive ELISA technique (8) and serum ultra sensitive TSH was performed using sandwich ELISA technique (9). The normal ranges for TSH, T_4 and T_3 values were 0.39-6.16 μIU/ml, 4.4-10.8μg/ml, and 0.52-1.85ng/ml respectively. The intra- and inter-assay coefficients of variation (CV) for TSH, T_4 and T_3 were 5 and 6, 3 and 3.7, 5.4 and 6 respectively. The spectrophotometric analysis of thyroid hormones was done on ELISA reader (Tecan Austria, GmbH, Austria Europe).

Liver Function Tests (Serum Bilirubin, Alanine Transaminases (ALT), Aspartate Transaminases (AST), Alkaline Phosphatase, Total Proteins and Albumin), Kidney Function Tests (Serum Urea, creatinine and Uric Acid) were estimated on fully automated Olympus AU 400 Analyzer (Olympus Diagnostics GmbH, Germany) using standard reagent kits from Randox Laboratories (Crumlin , United Kingdom).

Based on TSH levels, these subjects were classified as hypothyroid (TSH > 6 μIU/ml) or euthyroid (TSH ≤ 6 μIU/ml) for statistical evaluation. Forty-six overtly hypothyroid patients were re-evaluated 6 weeks after starting thyroxine replacement therapy.

Statistical analysis: Continuous variables were expressed as mean ± Standard Error of Mean. Normality of the sample distribution of each continuous variable was tested with the Kolmogorov–Smirnov test. The Student's 't' or Mann–Whitney U test, depending on the shape of the distribution curves, was used for evaluation of differences in continuous variables. Chi-Square tests were used for categorical variables. For paired samples, Wilcoxon- signed rank test was used. Spearman's rank correlation was applied to test for association between continuous variables. A two-tailed p value<0.05 was considered statistically significant and those less than 0.1 were considered marginally significant. A stepwise method of multiple regressions ($p < 0.05$ as entrance and $p > 0.1$ as removal criterion) was applied in order to select variables exerting an independent effect on studied parameters of liver and kidney function in hypothyroid subjects out of those correlated in univariate analysis. Statistical analysis was carried out using SPSS for windows 12.0 software (SPSS Inc., Chicago, IL, USA).

RESULTS

In our study population, 80 patients were found to be hypothyroid and 96 were euthyroid. Both the groups were age and sex-matched. Mean age group of hypothyroid subjects was 46.55 ± 1.8 years and that of euthyroid subjects was 45.72 ± 2.1 years. Hypothyroid group consisted of 72.5% women whereas the euthyroid group had 68.75% women. A highly significant difference was observed in Serum TSH, T_4, T_3, creatinine and uric acid levels between the study group and the control Group (Table 1). Hypothyroid subjects had significantly higher levels of serum TSH, creatinine and serum uric acid as compared to euthyroid subjects (p<0.001). All the patients with moderate (TSH> 10.5 μIU/ml) and overt hypothyroidism (TSH >20 μIU/ml) had hyperuricemia (Uric acid levels > 7 mg/dl). The levels of serum creatinine in hypothyroid subjects were within normal range (< 1.4 mg/dl) but significantly higher than in the euthyroid subjects (p<0.001).

Table 1: Comparison between the laboratory values obtained in euthyroid and hypothyroid subjects

	Euthyroid (n=96)	Hypothyroid (n=80)	p-Value
TSH (μIU/ml)	2.57 ± 1.35	36.44 ± 15.48	<0.001
T_4 (μg/dL)	8.75 ± 0.59	4.95 ± 2.01	<0.001
T_3 (ng/ml)	1.07 ± 0.07	0.68 ± 0.27	<0.00
Urea (mg/dl)	23.85 ± 8.1	24.01 ± 8.6	0.900
Creatinine (mg/dl)	0.71 ± 0.27	0.85 ± 0.29	0.001
Uric Acid (mg/dl)	5.86 ± 1.72	6.76 ± 1.49	<0.00
Total Bilirubin (mg/dl)	1.05 ± 0.55	1.14 ± 0.59	0.30
ALT (U/L)	24.53 ± 2.36	24.13 ± 1.99	0.89
AST (U/L)	30.8 ± 3.70	32.59 ± 2.43	0.70
ALP (U/L)	85.68 ±3.25	86.58 ± 4.19	0.86
Total Proteins (g/dl)	7.36 ± 0.61	7.48 ± 0.51	0.06
Albumin (g/dl)	4.35 ± 0.38	4.32 ± 0.29	0.56

Serum TSH levels showed a significant positive correlation with ALT, AST, total Protein and albumin levels, whereas T_4 levels had a significant negative correlation with all these parameters. Uric acid levels were significantly negatively correlated only with T_3 levels (Table 2). Forty-six moderate and overtly hypothyroid patients were re-evaluated after 6 weeks of uninterrupted thyroxine replacement therapy. A significant decrease was observed in serum Creatinine, uric acid, albumin after 6 weeks of thyroxine replacement therapy (Table 3). After 6 weeks of thyroxine replacement, the values of various parameters except albumin were comparable to euthyroid group.

Table 2 : Correlation (r- values) of liver and kidney function tests with thyroid function in hypothyroid subjects

	TSH levels	T_4 levels	T_3 levels
Urea	-0.009	0.017	0.014
Creatinine	0.076	-0.08	-0.11
Uric Acid	0.21	-0.16	-0.26*
Total Bilirubin	-0.012	0.07	0.07
ALT	0.29**	-0.27*	-0.20
AST	0.37**	-0.35**	-0.25*
ALP	-0.018	0.06	0.08
Total Proteins	0.27*	-0.25*	-0.16
Albumin	0.45**	-0.46**	-0.36**

* P<0.05 ; ** P< 0.01

Table 3: Comparison between the laboratory values obtained in hypothyroid subjects before and after treatment

	Pre-treatment values (n=46)	After thyroxine replacement (n=46)	p-Value	Reference values of the laboratory
TSH (μIU/ml)	39.42 ± 2.03	3.45 ± 2.18	<0.001	0.39 - 6.16
T_4 (μg/dL)	4.08 ± 0.29	8.61 ± 0.87	<0.001	4.4 - 10.8
T_3 (ng/ml)	0.58 ± 0.05	1.06 ± 0.06	<0.001	0.8 – 1.52
Urea (mg/dl)	24.17 ± 1.32	25.39 ± 6.32	0.52	20 -40
Creatinine (mg/dl)	0.85 ± 0.05	0.69 ± 017	0.005	0.4 -1.4
Uric Acid (mg/dl)	6.9 ± 0.21	5.6 ± 1.14	<0.001	3.0 – 7.5
Total Bilirubin	1.21 ± 0.09	1.01 ± 0.49	0.095	0.2 -1.2
ALT (U/L)	27.02 ± 3.27	20.41 ± 1.64	0.074	10 – 35
AST (U/L)	35.52 ± 4.01	28.33 ± 2.03	0.113	10 -40
ALP (U/L)	84.9 ± 4.41	75.3 ± 3.8	0.103	<117
Total Proteins (g/dl)	7.53 ± 0.08	7.48 ± 0.10	0.630	6.0 – 8.0
Albumin (g/dl)	4.36 ± 0.0 5	4.13 ± 0.05	0.001	3.5 - 5.0

DISCUSSION

Thyroid hormone influences the function of all body organs and cells. The data presented here clearly indicates how biochemical markers of two major organ systems of the body (liver and kidney) may be affected by alteration in the level of thyroid hormones in the body. The hypothyroid cases in the present study were mainly the referral cases from different out patient departments of the hospital. A significant difference was observed in TSH, T_3 and T_4 levels of euthyroid and hypothyroid patients. On evaluation, it was observed that 37.5% of the patients were overtly hypothyroid (TSH> 20 μIU/ml) and another 27% were moderately hypothyroid at the time of first presentation to thyroid clinic.

This study shows that there is significant increase in creatinine and uric acid levels in hypothyroid patients as compared to euthyroid subjects. The changes in biochemical markers of renal function were found to be reversible after thyroxine replacement therapy in the 46 patients who were administered thyroxine replacement. Similar changes in serum creatinine with hypothyroidism and improvement with treatment have been reported in a few scattered studies and case reports (10-13). In the present study, a decrease in serum creatinine was observed in 95.65% and a decrease in uric acid was observed in 91.30% of paired values before and after treatment for hypothyroidism. These changes in kidney function tests did not show significant correlations with thyroid hormones except uric acid, which showed a negative correlation with T_3 levels. This finding indicates that uric acid levels are negatively regulated by thyroid hormones, especially T_3 and therefore tend to increase in overt hypothyroid cases when T_3 levels are low. Histological changes in nephrons, especially basement membrane thickening have been demonstrated in both hypothyroid rats (6) and humans (14). These changes may result in physiological effects including alterations in renal hemodynamics (14, 15), decrements in renal blood flow and glomerular filtration rate (GFR) and hence reduced clearance of creatinine and uric acid. Another recent study also indicates a mutual relationship between kidneys and thyroid status where TSH >2.5mIU/L were associated with decreased estimated glomerular filtration rate (e-GFR) (16).

In the present study, no significant difference was seen in liver function tests when all subjects in hypothyroid group were compared with euthyroid subjects. The lack of significance observed in this case may be due to the presence of 34 cases of sub-clinical hypothyroidism present in this group. However, when sub-group of moderate to severe hypothyroid subjects (n=46) subjects were compared to euthyroid subjects, serum

bilirubin and liver enzymes showed an increase in hypothyroid subjects, but there is no statistical significance. In these patients the levels of bilirubin and liver enzymes (ALT, AST and ALP) decreased after 6 weeks of thyroxine replacement therapy. Earlier studies utilizing experimental models of hypothyroidism have also provided an evidence that hypothyroidism may directly affect liver structure or function (4). Hypothyroidism has been associated in a few case reports with cholestatic jaundice attributed to reduced bilirubin and bile excretion. The increased bilirubin levels observed in the hypothyroid group in the present study might be explained by the findings from earlier observational studies, which proposed that the activity of bilirubin UDP-glucuronyltransferase is decreased, resulting in a reduction in bilirubin excretion (4). Aspartate transaminase (AST) elevation may be attributed to myopathies, which are usually associated with hypothyroidism (4). Few experimental studies in the past have shown that the hepatic abnormalities associated with hypothyroidism can be reversible over a matter of weeks with thyroxine replacement, with no residual liver damage (17, 18) The liver enzymes (ALT and AST) showed a significant positive correlation with serum TSH levels and a negative correlation with serum T_4 levels. AST levels also showed a negative correlation with T_3 levels. Similar results have been observed in a retrospective study of 10,292 outpatients where similar correlations were seen with Gamma Glutamyl Transferase and ALT (19).

Serum protein and albumin demonstrated a significant positive correlation with TSH levels and a significant negative correlation with T_4 levels. Albumin also demonstrated a significant negative correlation with T_3 levels. After thyroxine replacement in hypothyroid subjects, a significant decrease was observed in the albumin levels whereas a non-significant decrease was seen in total protein levels. Even mild degrees of hypothyroidism are known to be associated with low-grade inflammation (20). The resultant increase in inflammatory proteins and immunoglobulins may account for marginally raised serum proteins observed in hypothyroid subjects in the present study. The liver synthesizes a number of plasma proteins that bind the lipophilic thyroid hormones. A compensatory increased synthesis of Thyroid binding globulin (TBG) by liver to bind the exogenously administered thyroid hormone, might explain the observed decrease in serum albumin with achievement of euthyroid state in previously hypothyroid subjects.

All the findings of the present study are helpful in understanding the complex interactions between the thyroid gland and major organ systems like liver and kidney. Although clinically a severe impairment of either liver or renal function was not observed in most hypothyroid cases but it should be stressed that most of these abnormalities improve after administration of thyroid hormone. The findings of this study have a lot of clinical relevance since, a multisystem approach to treating patients with diseases affecting either of these organs (thyroid, liver or kidney) would prove vital to avoid missing subtle but clinically relevant abnormalities.

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