Serum total bilirubin and alanine transaminase levels in hyperthyroidism

Navikala K[1], Vasudha KC[2,*], Pramila Kalra[3], Radhika K[4]

[1]Assistant Professor, [2]Professor, Dept. of Biochemistry, [3]Professor, Dept. of Endocrinology, [4]Lecturer/ Statistician, Dept. of Community Medicine, Ramaiah Medical College, Bengaluru, Karnataka

***Corresponding Author:**
Email: vasudhrachokkanna@yahoo.co.in, navikalashri@gmail.com

Abstract

Thyroid hormones are essential for normal growth, development and function of all tissues of the body by regulating basal metabolic rate of all cells, including hepatocytes. The present study was taken up to show the correlation between hyperthyroidism and hepatic dysfunction by measuring ALT and total bilirubin so that it helps in diagnosing patients of hyperthyroidism presenting with liver dysfunction or liver dysfunction as a manifestation of antithyroid drug treatment. 21 newly diagnosed hyperthyroid patients, 21 patients who are on treatment and Twenty one controls in the age group of 20-50yrs participated in the study. Serum T3, T4, TSH were analyzed by electrochemiluminescence, total bilirubin by diazzonium ion (blanked) and ALT (Alanine transaminase) by IFCC without PLP method. Kruskal Wallis test was done to compare T3, T4, TSH, total bilrubin and ALT levels among three groups. Post Hoc test was done for multiple comparisons between two groups. A significant difference for T3, T4, TSH ($p < 0.001$) and total bilirubin values($p=0.012$) was observed among the different groups. Post Hoc test for multiple comparisons between two groups revealed that total bilirubin levels were significantly high in newly diagnosed hyperthyroid patients and patients who are on treatment compared to controls. Six out of twenty one newly diagnosed hyperthyroid patients (29%) and five out of twenty one patients on treatment (24%) had total bilirubin values more >1mg/dl. ALT levels did not show statistically significant increase compared to controls.

Conclusion: Assessing the liver function at the time of diagnosis and during treatment is necessary to monitor the hepatotoxic effects of hyperthyroidism so that an alternative treatment can be chosen for such patients.

Keywords: Hyperthyroidism, Total bilirubin, ALT (Alanine transaminase), Liver function, Hepatotoxicity.

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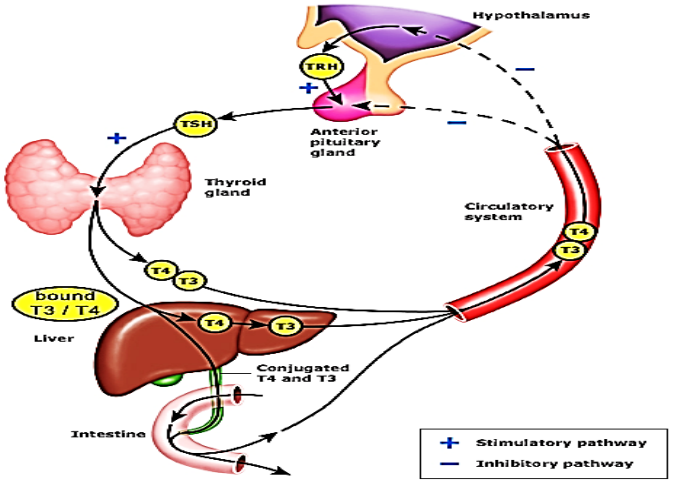
Introduction

Thyroid hormones are necessary for normal growth, development, function and regulation of the basal metabolic rate of all cells and therefore, its alteration will affect the metabolism.(1)

Thyroid hormones regulate the basal metabolic rate of hepatocytes.(1) The level of thyroid hormones is essential for normal hepatic function and bilirubin metabolism.(2,3) Hyperthyroidism is a common endocrinological disorder characterized by low TSH levels and increased level of thyroid hormones.

The liver metabolizes the thyroid hormones and regulates their systemic endocrine effects. The liver is the manufacturer of proteins that bind thyroid hormone, such as thyroxine binding globulin, pre albumin and albumin.(1) It is the major site of thyroid hormone peripheral metabolism and is involved in its conjugation, biliary excretion, oxidative deamination and the extrathyroidal deiodination of thyroxine to triiodothyronine.(2,3)



Thyroid hormones maintain the metabolism of bilirubin by playing a role in the enzymatic activity of glucuronyltransferase and by regulating the level of ligandin, a major organic anion-binding protein. bilirubin.[4]

Liver injury can also be caused due to hyperthyroidsim associated autoimmnune conditions and heart failure.

The amino transferases are the important liver enzymes which are affected adversely following hyperthyroidism. The cause of hepatocyte injury may be due to direct toxic effects of thyroid hormones or due to hepatic ischemia, secondary to peripheral vasodilatation leading to mismatch between demand and supply.[5]

Alanine transaminase and Aspartate transaminase(AST) are two of the most reliable markers of hepatocellular injury or necrosis. Their levels can be elevated in various types of hepatic disorders. Of the two, ALT is thought to be more specific for hepatic injury because it is present mainly in the cytoplasm of the liver whereas AST is present both in mitochondria and cytosol of various tissues.[6]

Hyperthyroidism can cause elevation of hepatic enzymes and serum total bilirubin. Therefore the present study has been taken up to show the correlation between hyperthyroidism and hepatic dysfunction by measuring serum total bilirubin and Alanine transaminase so that it helps in diagnosing patients of hyperthyroidism who are presenting with liver dysfunction or liver dysfunction caused due to antithyroid drug toxicity.

Materials and Method

This study was conducted in department of Biochemistry, M. S. Ramaiah Medical College. Patients attending outpatient department of Endocrinology M. S. Ramaiah Hospitals for evaluation of their thyroid status were enrolled in the study.

This was a case control study which included:

Group 1: 21 newly diagnosed hyperthyroid patients suffering from Graves disease and multinodular goitre.

Group 2: 21 patients who have achieved euthyroid state during treatment for atleast 3 months.

Group 3: 21 Age and sex matched controls.

All individuals were in the age group of 20-50years. Written informed consent was taken from both cases and controls. Study protocol was approved by Ethical committee of the Institute.

About 2 ml of venous blood was collected. Serum was separated by centrifugation and stored at -20°C until the estimation of biochemical parameters.

Serum T3, T4 and TSH were analyzed by electrochemiluminescence.[6-9]

Serum ALT by IFCC without PLP method and Serum total bilirubin by Diazzonium ion (blanked) method on Roche cobas analyzer.[10,11,12]

Exclusion Criteria

1. History of patients with positive viral markers, alcoholism.
2. Patients on treatment with long term hepatotoxic drugs like oral contraceptives, warfarin, phenytoin, clopidogril.
3. Existence of comorbid conditions like diabetes mellitus, hypertension.

Results

The results of all variables were expressed as median values as our data did not follow normal Gaussian distribution. Kruskal wallis test was done to compare T3, T4, TSH, serum total bilirubin and ALT levels among three groups. Post Hoc test was done for multiple comparisons between two groups. Results were computed using SPSS (Statistical Package for the Social Sciences) software version 20.

Median values for T3 and T4 in newly diagnosed hyperthyroid patients were increased when compared to controls and patients on treatment in the euthyroid state. Patients on treatment achieved T3 and T4 levels which is almost normal.

TSH values in newly diagnosed hyperthyroid patients were low compared to controls and patients on treatment (p=0.001).

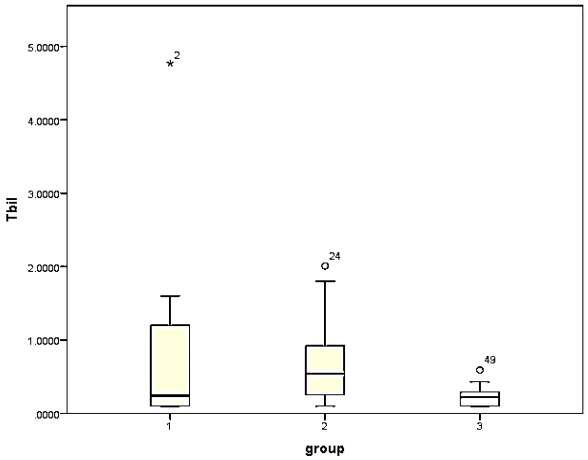
Total bilirubin levels were significantly high in newly diagnosed hyperthyroid patients and patients who are on treatment compared to controls. Six out of twenty one newly diagnosed hyperthyroid patients (29%) and five out of twenty one patients on treatment (24%) had total bilirubin values more >1.

There was no significant difference in ALT values among the three groups.

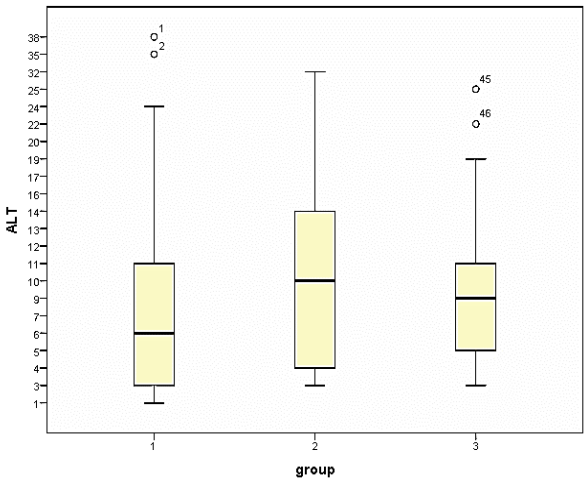
Comparison of median values of different variables among 3 groups

	Group 1	Group 2	Group 3	P value
T3	4.35(2.77-5.53)	2.12(1.38-3.05)	1.74(1.59-1.90)	<0.001
T4	205.8(154.2-292.1)	115.83(92.87-172.7)	102.6(94.33-111.6)	<0.001
TSH	0.005(0.005-0.011)	0.075(0.005-1.50)	1.90(1.22-3.08)	<0.001
Total Bilirubin	0.24(0.1-1.2)	0.54(0.23-0.98)	0.22(0.10-0.29)	0.012
ALT	6(3-12.5)	10(3.5-15)	9(4.5-12.5)	0.475

Total bilirubin: Median values



ALT: Median values



Post HOC Test for Multiple Comparisons

Dependent Variable	Group	Group	Mean Difference	Std. Error	Sig.
Tbil	1	2	-.0004762	.2155505	0.998
		3	.4776190*	.2155505	0.031
	2	3	.4780952*	.2155505	0.030
ALT	1	2	-.905	2.625	0.732
		3	.619	2.625	0.814
	2	3	1.524	2.625	0.564

Total bilirubin: There is significant difference between newly diagnosed hyperthyroid patients and controls indicating total bilirubin values are comparatively high in newly diagnosed hyperthyroid patients even before starting treatment.

There is also a significant difference between patients who are on treatment and controls indicating total bilirubin values are comparatively high due to hepatotoxic side effects of antithyroid drug therapy.

There is no significant difference between newly diagnosed hyperthyroid patients and patients who are on treatment suggesting the cause of hepatic dysfunction in hyperthyroidism may be due to hyperthyroidism per se or due to antithyroid drug treatment of hyperthyroidism.

Dependent Variable	Group	Group	Mean Difference	Std. Error	Sig.
T3	1	2	1.8013810*	.5502065	0.002
		3	2.7495238*	.5502065	0.001
	2	3	.9481429	.5502065	0.090
T4	1	2	91.2933333*	21.53274	0.001
		3	123.3671429*	21.53274	0.001
	2	3	32.0738095	21.53274	0.142
TSH	1	2	-.71176*	.31886	.029
		3	-1.94324*	.31886	.001
	2	3	-1.23148*	.31886	.001

T3 and T4: A significant difference was observed in T3 and T4 levels between newly diagnosed hyperthyroid patients and controls and also between newly diagnosed hyperthyroid and patients who are euthyroid during treatment. There was no significant difference in T3 and T4 levels between controls and patients who are euthyroid during treatment indicating the patients have attained T3 and T4 levels which is almost normal.

TSH: A significant difference was observed in TSH values between newly diagnosed hyperthyroid patients and controls and also between newly diagnosed hyperthyroid patients and patients who are euthyroid during treatment.

A moderate significant difference between controls and patients who are euthyroid during treatment was observed which indicates TSH values are increasingly tending towards normal.

Discussion

Hyperthyroidism is an endocrinological disorder that exhibits low serum TSH levels and elevated levels of the thyroid hormones. Graves disease is an autoimmune thyroid disease in which anti TSH receptor autoantibodies cause hyperthyroidism.[13]

Thyrotoxicosis may cause a defect in bilirubin metabolism by decreasing bilirubin UDP glucoronyl transferase activity. With the presence of substrate build up, hyperbilirubinemia ensues due to decreased conjugation.[4]

The hypermetabolic state in hyperthyroidism will increase the hepatic oxygen consumption without increasing the hepatic blood flow, thus lowering the oxygen tension in the pericentral parts of hepatic acini and interfering with bile transport, resulting in cholestasis.[14]

In our study total bilirubin levels were high in newly diagnosed hyperthyroid patients and patients who are on treatment compared to controls. 6 out of twenty one newly diagnosed hyperthyroid patients (29%) and 5 out of twenty one patients on treatment (24%) had total bilirubin values more >1mg/dl.

The cause of hepatic dysfunction in hyperthyroidism may be multiple, occurring as a result of hyperthyroidism per se, antithyroid treatment of hyperthyroidism, conditions associated with autoimmune thyroid disease.[15]

Hepatic parenchymal enzymes rise earlier than bilirubin levels by convention when the liver function is deranged. In this study ALT levels are not affected but total bilirubin has significantly risen in 29% of newly diagnosed hyperthyroid patients. This may be due to anemia because of simultaneous increase in plasma volume, shorter erythrocyte life span, abnormal iron utilization, or deficiency of iron, vitamin B12, or folate.[16,17] Well-known autoimmune processes leading to anemia in Graves' disease are pernicious anemia, celiac disease (causing iron deficiency), and autoimmune hemolytic anemia.[18]

This finding suggests that baseline screening for liver function before therapeutic intervention is imperative. A rise in the Total bilirubin levels before treatment contraindicates the use of hepatotoxic antithyroid drugs as otherwise the already compromised liver function may further worsen. In such instances the mode of treatment which could be radioactive ablation or thyroidectomy can be justifiably chosen immediately on diagnosis without wasting much time on conventional antithyroid drug therapy.

In a study by Thompson et al, altered liver function tests and in particular elevation of bilirubin were reported in hyperthyroidism.[19]

The use of the antithyroid medications (propylthiouracil, methimazole, and carbimazole), in a hyperthyroid patient causes hepatic injury. The liver injury associated with the use of antithyroid drugs is drug specific, with propylthiouracil predominantly causing toxic hepatitis and methimazole or carbimazole predominantly causing a cholestatic pattern.[20] In this study 24% of the population in the group that was treated and was in euthyroid state were found to show a significant rise in serum total bilirubin. Since this is a cross sectional study it is not certain if these patients also had raised serum total bilirubin initially during diagnosis. However, in such individuals the rise may be explained on the basis of antithyroid hepatic drug toxicity as well. Perhaps, regular monitoring of liver function tests in hyperthyroid cases during treatment will aid in changing the therapeutic modality in time

before a permanent structural damage to the liver sets in.

Various other studies have demonstrated increase in enzymes like ALT, AST, ALP and GGT in hyperthyroidism.[21,22]

Conclusion

Hepatic dysfunction in hyperthyroidism is not uncommon. Assessing the liver function initially when diagnosis is made and during treatment is essential to decide on the therapeutic approach or to change the course of treatment respectively in hyperthyroidism.

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