CORRELATION BETWEEN PLASMA THYROID HORMONES AND LIVER ENZYMES LEVEL IN THYROTOXIC CASES AND CONTROLS IN HAZARA DIVISION

Tariq Mehmood Khan, Saqib Malik*, Inayat Ullah Diju**

Department of Physiology, *Medicine, Ayub Medical College, Abbottabad, **Department of Medicine, Abbottabad International Medical College, Abbottabad, Pakistan

Background: Thyrotoxicosis is defined as increased synthesis and secretion of thyroid hormones; when associated with defused goitre it is known as grave's disease. Hepatic changes in thyrotoxiosis are fatty changes, cirrhosis and centrilobular necrosis, resulting in elevated serum levels of liver specific enzymes ALT, AST and ALK. Objective of the study was to determine a correlation between plasma levels of 3 liver enzymes, and thyroid hormones in thyrotoxic cases, and matched controls in Hazara Division. **Methods:** This study was conducted at Ayub Teaching Hospital Abbottabad from 1st July 2004 to 30th June 2007. The controls were selected from staff and students of Ayub Medial College Abbottabad. Fifty cases of thyrotoxicosis and 50 controls were included in this study by convenience sampling. Their thyroid profile for T_3, T_4, TSH and liver enzymes profile for ALT, AST, ALK were determined and analysed for a correlation. **Results:** Mean T_3 of cases was 5.23±1.95 and of controls 1.95±0.35. Mean T_4 of case was 248.88±62.75, and of controls was 113.40±19.01. Mean TSH of cases was 0.07±0.25 and that of controls was 2.24±0.80. Mean ALT of cases was 38.78±4.96 while that of controls was 23.98±5.27. Mean AST of cases was 39.76±5.05 and of controls was 26.52±4.49. Mean ALK of cases was 299.68±22.32 and of controls was 155.10±37.07. **Conclusion:** Although liver enzymes levels were slightly elevated in many thyrotoxic cases, no significant correlation emerged between any of the thyroid hormones and any of the liver enzymes, either in cases or controls.

Keywords: Thyrotoxiosis, Liver enzymes, Grave's disease, Hyperthyroidism

INTRODUCTION

Thyrotoxicosis is one of the most common endocrine disorder characterised by increased secretion of thyroid hormones T_3 and T_4.[1] When associated with diffuse goitre and ocular signs it is known as Grave's disease. It accounts for 60–80% of all the thyrotoxic cases with the highest incidence in women between the ages of 20–40 years due to unknown aetiology. Grave's disease is almost always an autoimmune disease demonstrated with specific immnuoglobulins in the plasma of these patients. These immunoglobulins are autoantibodies known as long acting thyroid stimulators (LATS), having a potent and prolonged effect as compared to thyroid stimulating hormone.[2,3]

Thyroid hormones are essential for normal growth, development and function of all tissues of the body by regulating BMR of all cells, including hepatocytes. The liver in turn metabolises thyroid hormones and regulates their systemic endocrine effects. Therefore thyroid dysfunction may disturb liver functions and liver diseases modulate thyroid hormones metabolism.[4]

Thyrotoxicosis is associated with a variety of abnormalities of liver function. The pathogenesis of hepatic dysfunction in thyrotoxicosis is unknown, but has been attributed to mitochondrial dysfunction and hepatic tissue hypoxia. Increases in AST and ALT after starting anti-thyroid treatment for grave's disease is not due to the side effects of anti-thyroid drug but may be induced by changes in thyroid function.[5]

Liver has a key role in thyroid hormones metabolism and their serum level is very important for normal hepatic function and bilirubin metabolism. Besides the associations between thyroid and liver diseases of an autoimmune nature, such as primary biliary cirrhosis and thyrotoxiosis, thyroid diseases are frequently associated with liver injuries and biochemical test abnormalities, i.e., elevation of ALT, AST, and ALK. These thyroids liver associations may cause diagnostic confusions and neglect of these facts may result in over or under diagnosis of associated liver or thyroid diseases. Therefore it is suggested to measure free T_4 and TSH level to rule out coexistent possibility of thyroid dysfunction in any patient with unexplained liver biochemical test abnormalities.[6]

All the studies carried out reflect a strong relationship between thyroid and liver in health and disease. In spite of the fact that thyrotoxicosis is very common in the hilly areas of Hazara Division, no research was carried out and no data was available from the area. Therefore a study was conducted in Hazara Division to determine plasma levels of three liver enzymes ALT, AST, ALK in patients with grave's disease and compare them with controls and to determine correlation between plasma levels of three liver enzymes alanine amino transferase, aspaartate amino transferase and alkaline phosphatase

and thyroid hormones tri iodothyronin (T_3) and thyroxine (T_4) in confirmed cases of thyrotoxiosis and matched controls.

MATERIAL AND METHODS

The study was conducted at Ayub Medical College and Hospital Complex Abbottabad. The cases were selected from the patients attending different units of Ayub Teaching Hospital and Institute of Nuclear Medicine, Oncology and Radiotherapy Abbottabad, whereas the controls were selected from the staff and students of Ayub Medical College Abbottabad.

It was a descriptive study and was completed in a period of three years from 1st Jul 2004 to 30th Jun 2007. One hundred subjects, 50 cases of confirmed thyrotoxicosis and 50 cases of matched controls (age, gender and BMI matched) were selected by convenience (non-probability) sampling belonging to various villages and urban areas of Hazara Division. Height (Cm), weight (Kg) and BMI of each subject were recorded. The subjects belonged to two groups. A group of 50 cases of thyrotoxicosis having elevated plasma T_3, T_4 and depressed TSH levels that had reports available with them and a group of 50 controls consisting of healthy individuals having no past history of any hepatic or other systemic diseases.

Subjects belonging to both groups were permanent residents of the research area and were between 20–60 years of age belonging to both sexes. Detailed medical history was taken on a pre-designed proforma. Laboratory investigations of the cases and controls were done and recorded, including plasma T_3, T_4, TSH, ALT, AST, ALK levels. Subjects using a drug affecting liver function, e.g., methyldopa, carbamezepine, cytotoxic drugs, ferrous sulphate, indomethacine, isoniazide, MAO inhibitors, paracetamol, phenothiazine, phenylbutazone, phenytoin, valproate etc. were not included in the study. Also none of the cases were previously or currently on anti-thyroid therapy. Verbal consent to participate in this study was obtained from each subject. Mean and standard deviation were calculated for ALT, AST, ALK, T_3, T_4 and TSH. The data was entered into SPSS-10 for statistical analysis. The mean values were compared between cases and controls using *t*-test at 5% level of significance. Pearson's correlation coefficients were calculated to determine correlation between the liver enzymes and thyroid hormones levels.

RESULTS

Three variables were measured for all the cases and controls, i.e., plasma level of liver specific enzymes ALT, AST and ALK. Reports of plasma levels of thyroid hormones T_3, T_4 and TSH were available with the cases; however, they were measured in the controls. The data were analysed to compare the mean values between cases and controls and to find out correlation between thyroid hormones profile and liver enzymes profile in the cases and controls.

Overall the cases and controls were in the age range of 21–60 years. As only 10 males and 40 female patients came into the sample by chance, the matching number of subjects was taken as controls. Hence, female to male ratio was 4:1 in both the groups. Mean age of males and females in cases was 41.16±6.40 and 41±6.50 years. The corresponding figures for controls were 43.20±7.84 and 43±6.35 years. The cases and controls did not differ significantly with respect to age and gender.

Table-1 shows thyroid profile of the cases, and Table-2 shows their mean values in cases and controls. Table-3 shows the liver enzymes profile of the cases and Table-4 shows the mean values of ALT, AST and ALK in cases and controls. The normal range of the plasma ALT level is up to 40 U/l in males and 35 U/l in females, AST level up to 35 U/l and 30 U/l, while ALK level is between 79 and 279 U/l in both genders. The mean levels of all the three enzymes were significantly greater in cases than in controls (p<0.001).

Table-5 show correlation and significance between liver enzyme and thyroid hormones profile in the cases as mean and standard deviation. Table-6 shows correlation between liver enzymes and thyroid hormones profiles in the controls with mean and standard deviation.

Table-1: Thyroid profile of the cases (µg/dl)

T_3	Cases	T_4	Cases	TSH	Cases
2.5–4.5	21 (42%)	160–200	13 (26%)	0.00	20 (40%)
4.6–6.5	20 (40%)	201–250	17 (34%)	0.01–0.05	20 (40%)
6.6–8.5	6 (12%)	251–300	12 (24%)	0.06–0.10	7 (14%)
8.6–10.5	2 (4%)	301–350	2 (4%)	0.11–0.15	3 (6%)
>10.5	1 (2%)	351–400	6 (12%)	>0.15	0 (0%)

Table-2: Mean thyroid profile of cases and controls

Test	Cases n=50	Controls n=50	*p*
T_3	5.23±1.96*	1.95±0.35	<0.001*
T_4	248.88±62.75*	113.40±19.01	<0.001*
TSH	0.07±0.25*	2.24±0.80	<0.001*

Table-3: Liver enzyme profile of the cases

ALT (U/L)	No. (%)	AST(U/L)	No. (%)	ALK (U/L)	No. (%)
31–35	13 (26%)	31–35	12 (24%)	250–300	32 (64%)
36–40	14 (28%)	36–40	14 (28%)	301–350	17 (34%)
4145	17 (34%)	41–45	16 (32%)	351–400	1 (2%)
4650	6 (12%)	46–50	8 (16%)	>400	0 (0%)

Table-4: Comparison of mean liver profile of the cases and controls

Variable	Cases n=50	Controls n=50	*p*
ALT (U/L)	38.78±4.96*	23.98±5.27	<0.001*
AST (U/L)	39.76±5.05*	26.52±4.49	<0.001*
ALK (U/L)	299.68±22.32*	155.10±37.07	<0.001*

Table-5: Correlation between liver enzymes and thyroid hormones profiles of the cases (n=50)

LE\TP	ALT Correlation γ	AST Correlation γ	ALK Correlation γ
T_3	0.414	0.333	0.339
T_4	0.316	0.265	0.296
TSH	-0.034	-0.010	-0.066

Table-6: Correlation between liver enzymes and thyroid hormones profiles of the controls (n=50)

LE\TP	ALT Correlation γ	AST Correlation γ	ALK Correlation γ
T_3	-0.132	-0.315	0.280
T_4	0.205	0.180	0.108
TSH	-0.075	-0.125	0.025

DISCUSSION

Liver enzymes profile had been proved valuable as diagnostic and prognostic guideline both in clinical practice and occupational medicine; reflecting the status, size, structure and functions of liver affected by age, sex, environmental factors, various diseases and drugs. In Pakistan, prevalence of hyperthyroidism is 5.1% with higher prevalence in females than in ales.[7] Thyrotoxicosis is quite common problem in hilly Hazara Division with highest frequency in young females due to unknown aetiology. Its incidence decreases in old age due to difference in life style and aging factors. In majority of the cases diagnosis is usually straightforward on clinical grounds. However, various diagnosic tests are performed for confirmation of the disease, i.e., plasma T_3, T_4 and TSH levels.[1]

It is well known that liver biochemical abnormalities have been shown in untreated patients with thyrotoxicosis.[8,9]

In the present study 50 thyrotoxic cases and 50 matched controls were selected and examined for their serum levels of enzymes AST, ALT and ALK. The serum reports of thyroid hormones T_3, T_4 and TSH were already available with the cases, while these tests were performed for the controls. Since no previous data was available from the area under study, the observed liver enzymes profile was compared with normal standard and correlated with thyroid hormones profile in cases and controls. Results of the study from the Hazara Division did not differ significantly from other studies and have been found in conformity with previous works carried out by various scientists. Therefore these results can be generalized for whole of the Pakistan. Therefore, results of the study from Hazara Division project an unexplained relationship between plasma thyroid hormones and liver enzymes level in grave's disease.

Malik and Hodgson reviewing the relationship between thyroid gland and liver in hyperthyroidism[4] mentioned that thyroid hormones T_3 and T_4 are essential for the growth, development and function of all organs of the body. They regulate BMR of all cells of the body including the hepatocytes and thereby modulate hepatic function. The liver in turn metabolises thyroid hormones and regulates their systemic endocrine effects. Therefore thyroid dysfunction may disturb liver function and liver disease affects thyroid hormone metabolism and a variety of systemic diseases affect both organs. It highlights a close relationship between thyroid and liver in health and disease. The clinical features of liver injury caused by thyrotoxicosis are relatively common and can be conveniently divided into hepatic and cholestatic types. In hepatic injury an increase in levels of AST and ALT was reported in 27% and 37% of the patients respectively, although majority of them showed no other clinical or biochemical features of liver impairment. The mechanism of injury appears to be relative hypoxia in periventricular regions of the liver, due to an increase in hepatic oxygen demand without an appropriate increase in blood flow.

A study conducted by Huang and Liaw[6] in Taiwan on clinical associations between thyroid and liver diseases revealed that liver has a key role in thyroid hormones metabolism. Their serum level is very important for normal hepatic function and bilirubin metabolism. Besides the associations between thyroid and liver diseases of an autoimmune nature, e.g., between primary biliary cirrhosis and thyrotoxicosis, thyroid diseases are frequently associated with liver injuries and biochemical test abnormalities, e.g., elevation of liver enzymes, ALT, AST and ALK. These thyroid-liver associations may cause diagnostic confusions and neglect of these facts may result in over or under diagnosis of associated liver and thyroid diseases and errors in patient care. Therefore it is suggested to measure plasma free thyroxin (FT_4) and TSH levels to rule out coexistent possibility of thyroid dysfunctions in any patient with unexplained liver biochemical tests abnormalities.

As shown in a study by Thompson[10] where a patient with primary biliary cirrhosis and jaundice had a dramatic deterioration in liver function over two months as a result of development of grave's disease. Clinical examination, radiological and cardiovascular investigations excluded heart failure and biliary obstruction as the cause of this deterioration. The patient's jaundice entirely reversed with treatment of hyperthyroidism, with bilirubin levels decreasing from 244 to 16 mol/L (14.35–0.94 mg/dl).

In another study clinical records of 30 cases of Grave's disease were analysed to identify the spectrum of abnormal results of liver function tests. The values for ALK, AST, ALT,GGT and bilirubin were examined. Frequencies of increased levels in their study group were similar but somewhat lower than those reported in previous studies. Out of the 30 patients, 11 (37%) had at least one abnormal result of a liver function test. These findings indicate that abnormal results of liver function tests are common in patients with hyperthyroidism and

make the diagnosis of concomitant unrelated liver disease difficult until the euthyroid state has been established.[8]

Mean plasma levels of liver enzymes ALT, AST and ALK were considerably elevated in response to increased plasma levels of T_3 and T_4. The mean values of the plasma liver enzymes AST, ALT and ALK were also higher in thyrotoxic cases with T_3 level more than 3 μg/dl, T_4 level more than 300 μg/dl and TSH level of almost zero μg/dl as compared to less higher levels. Therefore results of the present study along with the earlier reports are suggestive of the fact that more the plasma thyroid hormones level is elevated the higher is plasma liver enzyme level. Thus showing a positive relationship between T_3, T_4 and ALT, AST ALK levels, that is in accordance with the values reported in the previous studies.

The relationship between thyroid hormones and liver enzyme levels has been well documented, though its importance as hepatotoxic is still controversial. Findings of the present study are consistent with the previous work regarding elevated plasma liver enzyme levels in thyrotoxicoosis. But contrary to the expectations, the correlation between thyroid and liver enzyme profile was found to be non significant which is in agreement with previous studies. Regardless of the reasons, significant increase in plasma level of liver enzymes in thyrotoxicosis was not seen in enough individuals to make us feel comfortable in using it as a reliable tool for diagnosis and prognosis of the diseases.

CONCLUSION

Based on the results and the comparison with contemporary studies it is concluded that thyrotoxicosis has a significant effect on liver that is reflected in increased level of liver specific enzymes i.e. AST, ALT and ALK. But no significant correlation was found between the liver enzyme profile and level of plasma thyroid hormones either in cases and controls.

RECOMMENDATIONS

The elevated plasma level of the liver specific enzymes in humans can be used as a diagnostic tool for predicting the presence of clinically significant hepatic changes in patients with thyrotoxicosis. Furthermore the technique being very simple, reliable, specific and non invasive can be easily performed in central and peripheral hospitals for the study of prognosis of thyrotoxicosis but does not replace other valuable tests.

REFERENCES

1. Cooper DS. Hyperthyroidism. Lancet 2003;362:459–68.
2. Weetam AP, McGregor AM. Autoimmune thyroid disease: Developements in our understanding. Endocr Rev 1984;5:309–55.
3. Botazzo GF, Doniach D. Autoimmune thyroid disease. Annu Rev Med 1986;37:353–9.
4. Malik R, Hodgson H. The relationship between the thyroid gland and the liver. QJM 2002;95:559–69.
5. Kubota S, Amino N, Matsumoto Y, Ikeda N, Morita S, Kudo T, *et al*. Serial changes in liver function tests in patients with thyrotoxicosis induced by Grave's disease and painless thyroiditis. Thyroid 2008;18:283–7.
6. Huang MJ, Liaw YF. Clinical associations between thyroid and liver diseases. J Gastroenterol Hepatol 1995;10:344–50.
7. Khan A, Khan M M A, Ahktar S. Thyroid disorders, Etiology and Pevelance. J Med Sci 2002;2(2):89–94.
8. Biscoveanu M, Helsinki S. Abnormal results of liver function tests in patients with Grave's disease. Endocr Pract 2000;6(5):367–9.
9. Bayraktar M, Van Thiel DH. Abnormalities in measures of liver function and injury in thyroid disorders. Hepatogastroenterology 1997;44:1614–8.
10. Thompson NP, Leader S, Jamieson CP, Burnham WR, Burroughs AK. Reversible jaundice in PBC due to hyperthyroidism. Gastroenterology 1994;106(5):1342–3.

Address for Correspondence:

Dr. Tariq Mehmood Khan, Department of Physiology, Ayub Medical College, Abbottabad-22040, Pakistan. **Cell:** +92-314-5020033