Original Research Article

ASSESSMENT OF CARBIMAZOLE, PROPYLTHIOURACIL & L-THYROXINE FOR LIVER MARKERS IN THYROID PATIENTS FROM PUNJAB, PAKISTAN

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ABSTRACT

Hepatic functions dependency on thyroid hormones has been reported in many past studies. Momentous change in physiology and chemistry of thyroid gland not only affects the glandular function but also profoundly impinge working of liver markers causing hepatic dysfunction. Consequently, in order to give better response for thyroid diseases, the efficiency of thyroid drug is also calculated in persuading liver markers towards standard ranges which previously have been disturbed due to thyroid invasion. The current study was aimed with the intent to find effect of thyroid drugs on liver markers in Pakistani thyroid population from Mayo Hospital, Lahore, Punjab. Patients of hyper and hypothyroidism on thyroid drugs were recruited in the study and their thyroid and liver profiles were compared with controlled population. Carbimazole and propylthiouracil were administered to hyperthyroid patients and hypothyroid patients were given levothyroxine. The data was analyzed statistically based on p-values for parameters such as triiodothyronine, thyroxine, thyroid stimulating hormone, aspartate aminotransferase and alanine aminotransferase. Potential results were obtained for all parameters with carbimazole and propylthiouracil but only thyroxine and alanine aminotrasferase were stabilized with levothyroxine. So, we suggest use of adjunctive therapy with levothyroxine to be prescribed in hypothyroidism.

Keywords: Hepatic dysfunction, carbimazole, propylthiouracil, levothyroxine, thyroid hormones

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RUNNING TITLE: Thyroid Drugs and Secondary Liver Crisis

INTRODUCTION

Thyroid dysfunction has been found in perpetuating tasks of many vital organs of the body for instance liver, kidney, bones, brain etc. An imperative role of the liver is reputable in thyroid hormones metabolism since it is concerned with many biochemical courses of action including conjugation, biliary excretion, oxidative deamination and extra thyroidal deamination of

thyroxine (T4) to triiodothyronine (T3). In addition, the levels of thyroid hormones are crucial for regular functioning of hepatocytes and bilirubin metabolism. Accordingly, the disorders of these two organs would interrelate or influence the track of each other, therefore, while doing thyroid profiling, liver profile is also carried out in thyroid positive patients to see the extent of liver damage caused by thyroid disorders (Miau-Ju and Liaw, 1995) (Kristen Hull et al., 2007). For estimating proper functioning of liver, tool of liver function tests (LFT's) has occupied its unique place through performing group of blood tests to detect inflammation or damage to liver, and, in identifying exertion. Through these tests, certain enzymes and proteins are measured and they purely reveal overall health of hepatic system and sometimes indicate other diseases also such as malnutrition or bone disorders.

Under normal circumstances the hepatic enzymes reside in the hepatocytes, but when the liver is damaged these enzymes spill out into the bloodstream causing their elevation which points towards liver diseases. Measuring these enzymes in diseased state and comparing their values with the normal range can help us in diagnosing different disorders. Three hepatic enzymes (ALT, AST & ALP) are of great significance and are mostly measured in diseased states. Alanine aminotransferase (ALT or SGPT) and aspartate aminotransferase (AST or SGOT) are considered as the most sensitive liver enzymes and categorized as aminotransferases, and, in presence of any hepatic problem, these deviate from their standard ranges. Since, these enzymes are the biochemical hepatic markers in a myriad of diseases and are highly affected by the impediment of normal physiological functions, therefore, status of hyperthyroidism and hypothyroidism abhorrently distress the performance, likewise range of hepatic enzymes (Ayodeji F.Ajayi and Roland E.Akhigbe, 2012). The standard range of ALT in serum is 7 to 56 IU/L whereas of AST is 5 to 40 IU/L.

Several factors are there which repulsively intrude the proper working of thyroid gland and answer for thyroid illness. These factors may be environmental or genetic. Besides these, sex and age are the other two factors which greatly affect gland performance. People at low or high iodine diet are also more prone to get thyroid disorders due to crucial role of iodine in normal thyroid functioning. Similarly persons with family history of thyroid disorders exhibit high chance of thyroid disorders (Friedman and Yu, 2007). Hypothyroidism is a condition in which a reduced amount of thyroid hormones are produced and the most common cause of this diminished amount is the iodine deficiency. In some other cases it may be autoimmune disarray in which body's own immune system overwhelms thyroid cells and cause destruction of the cells. Such type of condition is called Hashimoto's Thyroiditis; a type of hypothyroidism (White, 2010). In hyperthyroidism the level of triiodothyronine and thyroxine are increased which is an indication of thyroid over activity. The most frequent ground of hyperthyroidism is an autoimmune Graves' disease in which the antibodies stimulate the thyroid cells to produce excess thyroid hormones.

Both organs i.e., liver and thyroid gland show symbiotic relation where thyroid hormones assist in liver function by regulating the rate of metabolism of hepatocytes and on the other hand liver does the metabolism of two hormones so that they can efficiently do their endocrine functions. Defect in thyroid influences the execution capacity of the liver, and, liver malfunctioning destroys the metabolism of thyroid hormones. So a faulty working in either organ causes havoc in the other. This shows that whether it is a diseased state or healthy state both organs affect each other (R.Malik and H.Hodgson, 2002). Currently it is reported that excessive triiodothyronine induces apoptosis of liver cells and causes liver damage which results in liver dysfunction

(Upadhyay G et al., 2004). A case of fulminant hepatic failure was seen recently in patient of Grave's disease and, on thyroidectomy, liver dysfunction was markedly reversed and patient was discharged from hospital with normal liver and thyroid functions (Emad Kandil et al., 2011).

Thyroid profiling should also be included not only in ruling out specific liver diseases, but also in diagnosis of non-specific liver diseases (Aliye Soylu et al., in 2008). Thyrotoxicosis has also found to be associated with cholestasis but this condition is rare and might be severe too (G K. et al., in 2007) (Dilek Soysal et al., in 2008). Arora S. et al., in 2008 reported that biomarkers of kidney and liver functions were manipulated by thyroid dysfunction (Arora et al., 2009). They did a case-controlled follow up research in hypothyroid subjects from India and concluded that hypothyroidism results in reversible impairment of hepato-renal function. A strong correlation of hepato-cellular carcinoma with hypothyroidism was reported recently and it was recommended that hypothyroidism was more common in hepatocellular carcinoma patients with an unknown cause (Reddy A. et al., in 2007) (E. Tzemanakis et al., in 2000).

Studies done on monitoring therapy for hyperthyroidism have noted that betterment in a patient's thyroid function is escorted by stabilization of the liver panel. The mode of liver harm in sole hyperthyroid circumstances is not well documented (Saro Khemichian, Tse-Ling Fong, 2011). In cases where liver abnormality is lucidly due to thyroid dysfunction then, importantly, liver function tests return to normal once the primary thyroid pathology is recognized and treated (Bayraktar M and Van Thiel DH, 1997).

For the management of thyroid disorders antithyroid thyroid drugs are given and in many cases surgery becomes essential. Antithyroid drugs generally prescribed to cope with thyroid ailments include; Levothyroxine (L-T4), Methimazole (MMi), Propylthiouracil (PTU) and Carbimazole. Levothyroxine is used to treat hypothyroid patients and is the form of thyroxine which is converted into active triiodothyronine by the action of the enzymes deiodinases. Carbimazole is another potential antithyroid drug for the treatment of hyperthyroid condition. It is a pro-drug converted into methimazole after absorption and demonstrates its action by serving as a substrate for thyroid peroxidase and decreases incorporation of iodide into tyrosine molecules by inhibiting thyroid peroxidase. It also inhibits coupling of mono-iodinated and di-iodinated residues to form thyroxine and triiodothyronine. Propylthiouracil is a thiourea antithyroid drug used for controlling the conditions of hyperthyroidism and works by inhibiting thyroid peroxidase and thus inhibits production of thyroid hormones (Papich, 2011).

Since, carbimazole and propylthiouracil are the drugs of choice for the management of hyperthyroidism and their dosage depends upon age, gender, and concomitant therapy so careful monitoring of drug dosage is required to achieve euthyroid status (Andres Pinto and Michael Glick, 2002). The merit of thyroid drugs should also be distinguished in their effectiveness for secondary hepatic disorders due to thyroid agitation. So, this study was aimed to check the expediency of anti thyroid drugs (ATD's) in quashing anomalous liver markers on account of primary thyroid disease.

METHODOLOGY

In our case control study, a total of 70 cases of thyroid disorders were enrolled from Centre of Nuclear Medicine, Mayo Hospital Lahore, Pakistan. Out of 70 cases, 20 were hypothyroid patients and 50 were experiencing hyperthyroidism. 20 cases participated as healthy control for

comparison. Patients who visited Center for Nuclear Medicine (CENUM) laboratories, Mayo Hospital Lahore for the evaluation of their hormonal status were selected after taking their complete history and medical as well as physical examination were also done. Hypothyroid patients were taking levothyroxine with dosage of 50-100 micrograms once daily, while in hyperthyroid group 40 patients were taking 15-40 mg/ day dose of carbimazole and 10 patients were on 200-400 mg/ day dose of propylthiouracil. Patients with concomitant disorders and/ or on multidrug therapy were proscribed form the study and informed consents were signed by all patients. All participants were undergone for their thyroid and liver profiling and results were compared with data of healthy controlled population. Thyroid profiling was done by using ELISA technique and for this ELISA kits were purchased from Generic Assay GmbH Company, and, renal parameters were estimated through spectrophotometric analysis by using reagents of Crescent Company (Jeddah 21423, KSA). Analysis of variance (ANOVA) test was applied to statistically analyze all parameters and means and standard error of means were identified. Confidence interval was 0.95 and p- value above 0.05 was taken as non-significant while value below 0.05 was considered significant.

RESULTS

Table 1. Values of means (M) and standard error of means (SEM's) of fT4, fT3, TSH, ALT and AST in Control and Hypothyroid groups

S. No.	Parameters	Healthy Control N= 20 Means ± SEMs	Hypothyroid on Levothyroxine Patients N= 20 Means ± SEMs	P-Values
1.	fT4	16.62 ± 0.72	14.16 ± 2.34	0.333
2.	fT3	4.73 ± 0.15	2.81 ± 0.5	0.002
3.	TSH	3.07 ± 0.18	16.65 ± 6.06	0.043
4.	ALT	32.5 ± 2.24	26.79 ± 2.51	0.103
5.	AST	42.25 ± 1.84	62.79 ± 7.87	0.006

Table 2. Values of means (M) and standard error of means (SEM's) of fT4, fT3, TSH, ALT and AST in Control and Hyperthyroid groups

S. No.	Parameters	Healthy Control N= 20 Means ± SEMs	Hyperthyroid Patients on Carbimazole therapy N = 40 Means ± SEMs	Hyperthyroid patients on Propylthiouracil therapy N= 10 Means ± SEMs	P-Values
1.	fT4	16.62 ± 0.72	39.61 ± 19.52	27.45 ± 9.96	0.708
2.	fT3	4.73 ± 0.15	7.21 ± 0.94	9.53 ± 4.97	0.136
3.	TSH	3.07 ± 0.18	6.26 ± 2.20	1.99 ± 0.67	0.520
4.	ALT	32.5 ± 2.24	22.79 ± 3.14	16.5 ± 4.25	0.078
5.	AST	42.25 ± 1.84	47.64 ± 5.35	32 ± 4.81	0.504

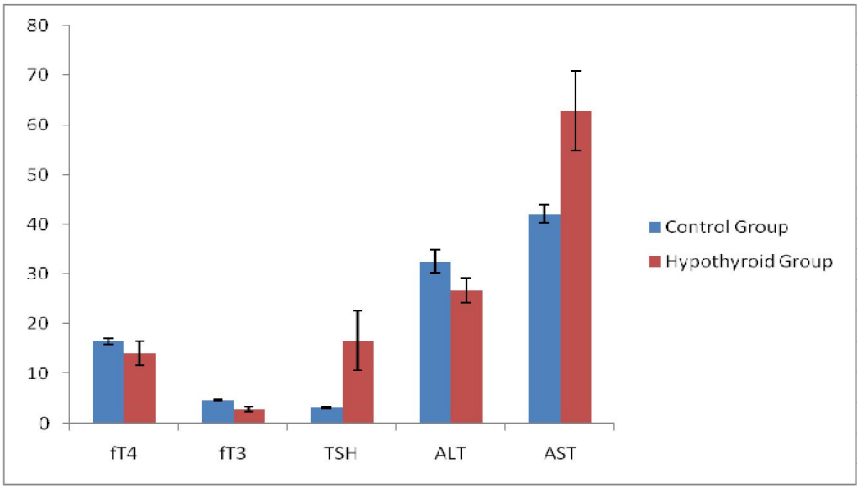

Figure 1. Bar chart representation of Mean values and Standard Error of Means (SEMs) of Liver Markers in Control and Hypo-medicated groups

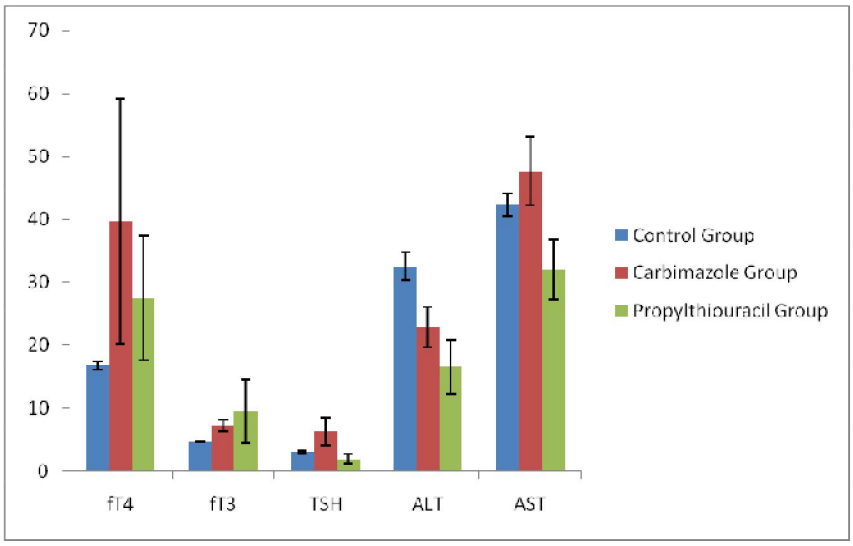

Figure 2. Bar chart representation of Mean values and Standard Error of Means (SEMs) of Liver Markers in Control and Hyper-medicated groups

DISCUSSION

Thyroid hormones are essential for proper functioning of body cells and in condition of hypothyroidism the levels of triiodothyronine and thyroxine are decreased also affecting liver cells along with other systems of body. Levothyroxine is given to treat hypothyroidism, which control the levels of thyroid hormone in patients and also decrease augmented levels of liver aminotransferases (Christ-Crain Mirjam et al., in 2004).

In our study the patients of hypothyroidism were given levothyroxine and their thyroid and liver profiles were compared with healthy control. The means and standard error of means of control and hypothyroid patients for fT4 were 16.62 ± 0.72 and 14.16 ± 2.34; for fT3: 4.73 ± 0.15 and 2.81 ± 0.5; for TSH: 3.07 ± 0.18 and 16.65 ± 6.06; for ALT: 32.5 ± 2.24 and 26.79 ± 2.51; and for AST: 42.25 ± 1.84 and 62.79 ± 7.87 respectively.

The p-values with use of levothyroxine for fT4, fT3, TSH, ALT and AST were 0.333, 0.002, 0.043, 0.103 and 0.006 respectively. P-values less than 0.05 were taken significant while values above 0.05 were considered non-significant. fT3, TSH and AST were proved to be significant and only fT4 and ALT were found non-significant. Raised levels of AST reveal that altered thyroid state in hypothyroidism causes liver dysfunction, so, liver function tests should be monitored in thyroid dysfunction, more considerably in hypothyroidism (Ajayi AF and Akhigbe RE, 2012). The insignificancy of fT4 and ALT provide evidence of efficacy of levothyroxine only for fT4 and ALT in our population. Moreover, reversal of abnormal ALT can readily be seen during normalization of altered fT4.

Increased levels of thyroid hormones perturb the levels of liver enzymes as observed in many studies. Michaela Biscoveanu and Hasinski S. in 2000 conducted a study to find out the frequency of liver dysfunction in patients with hyperthyroidism. They concluded that abnormal LFT's in hyperthyroid patients is common and this makes the diagnosis of liver disease hard until euthyroid state has achieved (Michaela Biscoveanu and Hasinski S. 2000). By employing anti-thyroid drugs thyroid hormones come to their standard levels and sometime surgery

becomes obligatory. Two drugs were exploited in our study i.e., carbimazole and propylthiouracil for restoring thyroid hormones.

The means and standard error of means for control population for fT4 were: 16.62 ± 0.72; for fT3: 4.73 ± 0.15; for TSH: 3.07 ± 0.18; for ALT: 32.5 ± 2.24, and, for AST: 42.25 ± 1.84 respectively. In study group of hyperthyroid patients on carbimazole therapy the means and standard error of means of parameters i.e., fT4, fT3, TSH, ALT and AST were 39.61 ± 19.52, 7.21 ± 0.94, 6.26 ± 2.20, 22.79 ± 3.14 and 47.64 ± 5.35 respectively; while with propylthiouracil therapy, these values were 27.45 ± 9.96, 9.53 ± 4.97, 1.99 ± 0.67, 16.5 ± 4.25 and 32 ± 4.81 respectively.

All parameters were found non- significant in hyperthyroidism with both drugs when statistically analyzed with control group. Same results were reported in district Hazara, Khyber Pakhtunkhwa, Pakistan by Khan T.M et al., in 2010 where insignificant relation was found between plasma thyroid hormones and liver enzymes (Khan T.M et al., 2010). In our study, the p-values for fT4, fT3, TSH, ALT and AST were 0.708, 0.136, 0.520, 0.078 and 0.504 respectively. This statistical analysis suggests that the antithyroid drugs i.e. carbimazole and propylthiouracil have a strong effect in normalizing raised levels of thyroid hormones as well as blatantly reverse abnormal levels of ALT and AST (Hitoshi Ichikawa et al., 2009). Previous studies have proved the capability of antithyroid drugs in restoring euthyroid status and normalizing abnormal thyroid levels. A case study was conducted by E. Tzemanakis et al in 2000 in which a patient suffering from hyperthyroidism developed acute icteric hepatitis. The patient showed an increased level of ALT and AST and all the conditions of hepatitis were reversed as far as antithyroid drug was started (E. Tzemanakis et al., 2000). Similarly, a study was conducted by Leeuwenburgh et al., 2001 in which a 15-year-old boy was brought with hyperthyroidism with associated biological and histological hepatic aberrations. He was undergone with antithyroid therapy and after therapy with antithyroid agents not only the hyperthyroidism reversed but also the hepatic profile were stabilized (Leeuwenburgh et al., 2001).

CONCLUSION

Carbimazole and propylthiouracil successfully normalize the biochemical parameters fT4, fT3, TSH, ALT and AST while levothyroxine fail to normalize the levels of fT3, TSH and AST. So, we recommend the use of combinational therapy along with levothyroxine in hypothyroid patients in order to control disturbed levels of thyroid hormones and better performance of the liver. Furthermore, liver function tests should also performed in thyroid patients in order to check any abnormality in liver function as a result of thyroid disorder.

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