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Original Article

Clinical Implication of Hepatic Phosphatases in Hyperthyroidism

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ABSTRACT

Thyroid hormones significantly affect the proper growth, development and functioning of liver. It has been seen that the drugs indicated for thyroid abnormalities also cause troubles in liver function. **Objective:** To check the effect of thyroid abnormality on liver function. **Methods:** Patients were recruited from Center of Nuclear Medicine and examined for their thyroid status and liver functions. **Results:** The results obtained through biochemical tests for potential biomarkers were further explored through statistical analysis which showed the strong correlation between disturbed function of thyroid gland and liver working. Any variation in thyroid function brings change in liver functioning. **Conclusions:** Therefore, while treating thyroid patients, combination therapy must be recommended to effectively treat the associated disorder and increasing the better social and psychological status of the patient. Furthermore, patients coming with thyroid dysfunction must also be examined for liver abnormalities so that culprit cause of this thyroid abnormality could be treated from the root if present.

INTRODUCTION

Hypothalamus is the part of brain which controls the production of thyroid hormones and also involved in the regulation of pituitary gland. Thyrotropin releasing hormone (TRH), produced by hypothalamus sends a signal to the pituitary gland that activates the thyroid stimulating hormone (TSH) which upon activation releases the thyroid hormones [1, 2]. Around 80% of the tetraiodothyronine (T4) is converted to its ten times more active form, triiodothyronine (T3) by peripheral organs. Thyroxine (T4) is synthesized by the protein of thyroid residue, thyroglobulin and follicular cells [3]. The susceptibility of thyroid disorder increases with the age and the women are seven times more prone to get thyroid diseases as compared to men [4]. Incidence and prevalence rate of thyroid disorders also depend on the genetic, geographical and environmental predisposition factors and also on the abundance or deficiency of available iodine. Overproduction and secretion of thyroid hormones manifests increased metabolic rate of the body and wide range of clinical signs [5]. Graves' disease, thyrotoxicosis, toxic multinodular goiter (TMNG) are some conditions with clinical depiction of hyperthyroidism. Certain medications also increase the risk of hyperactivity. Amiodarone is an example which is prescribed during cardiac issues, contains a large amount of iodine which ultimately leads to thyroid abnormalities. Hepatic variations in hyperthyroid patients have been studied widely. Sometimes these changes are linked with the use of anti-thyroid drugs [6-8]. Propylthiouracil (PTU), mostly used drug in hyperthyroidism, is not good for the liver as it has been reported with bad profiles of hepatic functions [9-11]. The other parameters which are reportedly associated with anti-thyroid drugs are anemia,

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tachycardia, hypercalcemia, granulocytosis and higher levels of alkaline phosphatases and transaminases [12]. Pakistan is that country in which the deficiency of iodine is common and mostly the occurrence is seen more in northern areas. Due to the hyperactivity of the thyroid gland almost every tissue is affected. The reported signs are anxiety, nervousness, thinning of skin, hand tremor, increased heart rate, increased perspiration, muscular weakness and disturbed bowl movements. Hyperthyroidism varies with the patient age, diet, excessive hormonal secretion and the duration of illness. The older patients exhibit some specific signs and symptoms which make the evaluation of hyperthyroidism even more difficult. Shen *et al.*, described a case of 24-year-old patient diagnosed with hyperthyroidism who later on developed liver failure due to treatment with thiamazole. Liver functions were not evaluated at the time of diagnosis [13]. Behroozi-Lak *et al.*, worked on a case of women of 89 years of age. The symptoms were constipation, weakness, fatigue, indigestion, and urinary leakage. Biochemical tests showed the increased levels of calcium, ALP and PTH, and the primary hyperthyroidism was diagnosed. After that they also see the higher levels of ALP which cause the renal complications. ALP involved in the alkaline hydrolysis of a large number of compounds which are naturally occurring and made synthetically [14]. ALP found in the cell membrane and all tissues of the body. In the intestinal epithelium, kidney tubules, bones, liver and placenta have higher values of ALP. ALP is also involved in the transportation of the lipid and as well as bone calcification. The activity of ALP is non-functional at the 56 °C but it is functional at low temperature. Serum ALK phosphatase should be measured in hepatobiliary and bone diseases. When tissues secrete bile it effects on the liver ALP that enhanced the serum enzyme action [15, 16]. In hepatobiliary disease enzyme is failed to secret the bile. In the condition of hepatobiliary disease, the liver synthesizes more ALP. The newly synthesized enzymes enter in the circulation and due to this the ALP level becomes high in the blood serum. Some drugs like chlorpromazine increases the level of ALP up to 2.5 times than the normal limit. Levels of ALP are also increased in infectious hepatitis. In osteomalcia the ALP is moderately higher which is usually decreased with vitamin D therapy. In Fanconni's syndrome the level of ALP is moderately elevated. The level of ALP is higher in primary and secondary hyperthyroidism due to the involvement of the skeleton. In osteogenic bone cancer the level of the ALP in highly elevated. In the children due to the bone growth the level of ALP is1.5 to 2.5 times higher than the normal adults. In first trimester 2 to 3 folds increase has been seen. Causes may be attributed to some complications in pregnancy like gestational hypertension and pre-eclempsia.

METHODS

From the CENUM (Center for Nuclear Medicine) Mayo Hospital Lahore, 115 patients of both sexes, ranging in age from 40 to 60 years, were selected as freshly referred patients for thyroid evaluation. According to the referring doctor's advice, these patients underwent clinical evaluation, thyroid scanning, and FT4 and TSH concentration determination. The skilled doctor carefully recorded the patient's medical history. The thyroid gland was physically inspected, and a clinical evaluation of its functioning status was performed. Name, age, gender, medication use, surgery, prior instances of thyroid dysfunction, use of iodized salt, the presence of a goitre and its size, and family history of thyroid problems were all part of the patient's medical history. There were additional symptoms and signs of thyroid dysfunction observed. Serum was isolated from blood by low-speed centrifugation (2000 g) for five minutes at room temperature. Until analysis, serum samples were kept at -20°C. For FT4, ALK, and TSH, serum samples were examined. Using commercial kits from Immunotech Inc., FT4 and ALK were determined using radioimmunoassay (RIA), while TSH was determined using IRMA methods (Beckman, Czech Republic). ELISA was used to measure the serum TPO-Ab titer in a subset of patients using a commercial kit from IMMCO Diagnostics, Inc. in New York, USA.

RESULTS

Figure 1 showed mean, standard deviation and standard error of mean of control and hyperthyroid population for free tetraiodothyronine 4 were 16.901, 2.10205 and + 0.28344; 38.8593, 13.23540 and + 1.72310 respectively. The standard deviation and standard error of mean were found to be highly changed among controlled and diseased population. Statistical values of this parameter for both study groups i.e., control and diseased, showed high difference. Significance or non-significance of data was estimated using analysis of variance test among study population for all designed study parameters. p- values more than 0.01 were set to be non- significant and below 0.01 were considered significant. All study parameters i.e., free tetraiodothyronine 4, thyroid stimulating hormone and alkaline phosphatase appeared highly significant. The results appeared with statistical analysis show that there is a strong correlation between disturbed function of thyroid gland and liver function. A variation in thyroid function brings change in liver function.

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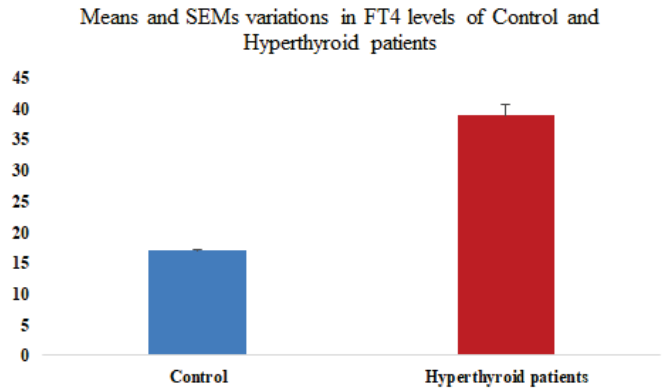

Figure 1: FT4 level in control and hyperthyroid patients

The mean, standard deviation and standard error of mean of control and hyperthyroid population for thyroid stimulating hormone were 1.5195, 0.69794 and + 0.09411; 0.0500, 0.00000 and + 0.00000 respectively (Figure 2).

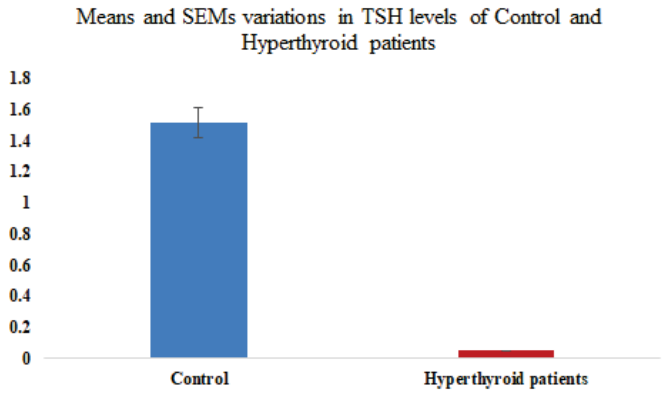

Figure 2: TSH level in control and hyperthyroid patients

The mean, standard deviation and standard error of mean of control and hyperthyroid population for alkaline phosphatase were 220.5091, 137.16250 and + 18.49499; 396.7966, 186.05235 and + 24.22195 respectively (Figure 3).

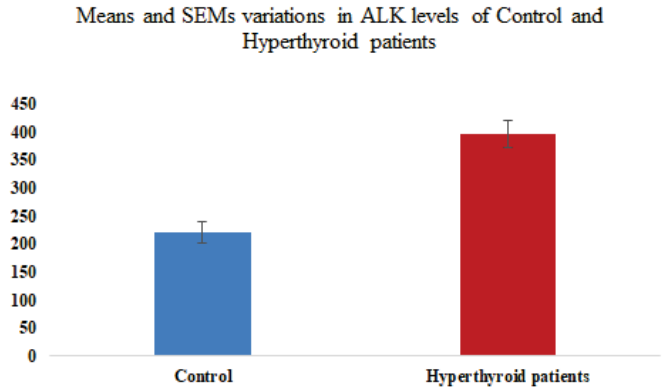

Figure 3: ALK level in control and hyperthyroid patients

DISCUSSION

Hyperthyroidism is a clinical condition that is characterized by the overproduction and secretion of thyroid hormones, leading to an increased metabolic rate and a wide range of clinical signs. The thyroid hormones are regulated by the hypothalamus-pituitary-thyroid axis, and any disruption in this axis can lead to the development of hyperthyroidism. The clinical manifestations of hyperthyroidism can vary depending on the age of the patient, diet, excessive hormonal secretion, and the duration of the illness [17]. In patients with hyperthyroidism, liver function tests may reveal increased levels of alkaline phosphatases (ALP). ALP is a group of enzymes that are present in various tissues, including the liver, bone, and intestine. ALP is produced by osteoblasts in bone and cholangiocytes in the liver, and it plays an important role in bone mineralization and the transport of bile acids. In hyperthyroidism, the increased metabolic rate leads to an increase in bone turnover, which in turn increases the production of ALP. Additionally, hyperthyroidism can lead to an increase in the size of the liver, which can also contribute to an increase in ALP levels. Several studies have reported an association between hyperthyroidism and elevated levels of ALP. Boulanger *et al.*, measured the levels of ALP in two groups of hyperthyroid patients, one group receiving treatment and the other group not receiving treatment [18]. They found that the total, liver, and bone ALP activities were significantly higher in the untreated hyperthyroid group than in the treated hyperthyroid group. They also found that bone ALP was higher than intestinal and liver ALP. Einollahi *et al.*, reported a case of a 36-year-old woman with hyperthyroidism who was prescribed Diazepam for anxiety and palpitations. She experienced skin pigmentation and weight loss and was subsequently prescribed Carbimazole. After a month of therapy, clinical improvements were observed, and it was concluded that thyroxin acts as an inducer for different enzymes, including ALP, which triggers osteoblastic activity [19]. Shen *et al.*, reported a case of a 24-year-old patient diagnosed with hyperthyroidism who later developed liver failure due to treatment with thiamazole [13]. During the course of treatment, high levels of ALP were seen, and liver biopsy showed intrahepatic cholestasis, mild inflammatory infiltrates, and a high degree of fibrosis. The authors suggested that regular liver function monitoring during thiamazole therapy is imperative in such patients [20]. In conclusion, elevated levels of ALP are commonly seen in hyperthyroidism, and it is important to monitor liver function in patients receiving treatment for hyperthyroidism. While the increase in ALP may be due to the increased metabolic rate and bone turnover associated with hyperthyroidism, drug-induced liver injury is also a potential complication of treatment. Therefore, regular liver function monitoring is essential to ensure early detection and management of any hepatic dysfunction.

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CONCLUSIONS

While treating thyroid patients, liver markers must be assessed, and, in case of any parallel liver abnormality combination therapy must be recommended to effectively treat the associated disorder. Furthermore, during the course of ongoing thyroid therapy, patients must also be re-evaluated for other potential biochemical markers so that culprit cause of this thyroid abnormality could be treated from the root if present.

Conflicts of Interest

The authors declare no conflict of interest.

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