RESEARCH ARTICLE

# Biochemical markers of liver function test (ALT, AST, ALP) in thyroid dysfunction (Hyperthyroidism and Hypothyroidism)

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**Thyroid hormone synthesis is vital for all body organs to develop, grow, and function healthily. All cells, including hepatocytes, have these hormones that control their resting metabolic rates. Between both the thyroid and the liver, there are complicated interactions. When thyroid dysfunction is treated and thyroid hormones return to normal, the body's metabolism changes. This temporary shift can affect liver function, potentially influencing liver test results and making them appear abnormal even if the liver itself is healthy. Thyroid dysfunction can sometimes lead to abnormal liver function, but treatment may not always be necessary for the liver, depending on the specific cause and severity. This study was done to assess the relationship between serum enzymes of liver functions and direct bilirubin in thyroid disorders. 90 subjects including 38 healthy controls, 27 hyperthyroidism patients, and 25 hypothyroidism patients were quickly tested for alkaline phosphatase (ALP), alanine transaminase (ALT), and aspartate transaminase (AST) using the calorimetric method and standard reagent kits. To measure the serum levels of T3, T4, and TSH, ELISA kits were employed. The results showed that serum AST, ALT, and ALP levels were 38, 50, and 150 U/L for hyperthyroid patient and 70, 78, and 110 U/L for hypothyroid patient compared to the control groups of 25, 28, and 95 U/L, respectively. On the other hand, serum T3, T4, and TSH were 3.2 ng/mL, 18.5 mg/dL, and 0.94 µIU/L for hyperthyroid patient. In a study comparing liver function in hypothyroid patients and healthy controls, AST, ALT, and ALP levels were 0.8, 4.9, and 25.7 U/L in the hypothyroid group compared to 1.1, 6.3, and 2.5 U/L in the control group. The findings of this study demonstrated that there was a correlation between the concentrations of ALP and AST in hypothyroid and hyperthyroid patients.**

**Keywords:** aspartate transaminase; alkaline phosphatase; alanine transaminase; thyroid hormone; thyroid stimulating hormone.

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## Introduction

The thyroid gland is one of the primary endocrine glands in human body and is in charge of the hormones triiodothyronine (T3) and thyroxine (T4). These hormones influence hepatic functions by regulating all cells' baseline metabolic rates, including hepatocytes. Therefore, any thyroid condition may impair liver function [1]. Reduced blood T3 level, which is brought on by a reduction in the deiodinase enzyme's activity that catalyzes the conversion of T4 to T3, is one of the harmful effects of liver dysfunctions on the thyroid. However, because the relevant enzyme's activity is unaltered, the effect is that liver diseases lower T3 by increasing reconstituted T3, which is an

inactive form of T3, and decreasing the activity of the enzyme that transforms T4 to T3. Reverse T3, the inactive form of thyroid hormone, increases while T3, the active form of thyroid hormone, decreases as a result of liver illness [2]. Depending on whether the T4 and T3 levels in blood are high or decreased, respectively, thyroid diseases are frequently categorized into two main categories as hyperthyroidism and hypothyroidism [3]. The thyroid hormone that is biologically active is T3. Nearly all tissues depend on these hormones for healthy growth, development, and operation [4]. The thyroid gland secretes two iodine-containing amine hormones, L T4 and L T3, from the amino acid tyrosine (T3). After entering all cells, a nuclear T3 receptor is connected to free T3 and T4 across the plasma membrane [5]. The principal function of the thyroid receptor is as a ligand-activated transcription factor that directly regulates the expression of target genes *via* DNA response elements (thyroid response elements, TREs) [6]. The thyroid gland secretes 110 nmol of thyroxine and 10 nmol of triiodothyronine daily in healthy individuals [7, 8]. Hypothyroidism can be the outcome of any factor that lessens the production of T3 and T4 hormones. Atypical lipid metabolism brought on by hypothyroidism may result in atherosclerosis and cardiovascular disease. Only diabetes mellitus follows thyroid problems as the most prevalent endocrine diseases [9]. The liver and thyroid are two of the most crucial organs because their physiological relationships are so intricately entwined in numerous biochemical processes that any problem with one of them may negatively impact the other. T4 and T3 can enter the cytoplasm and even the nucleus membranes due to the nature of thyroid hormones when combined with thyroid hormone receptors. The thyroid receptor binding region is described as the location on the DNA where the combined hormone-receptor complex binds [10]. Weight loss, a fast or irregular heartbeat, anxiety, irritability, difficulty falling asleep, and tremor in the hands and fingers, increased perspiration, increased heat sensitivity, weakness of the muscles, *etc.* are all signs of hyperthyroidism, while hypothyroidism can cause weight gain, an increased sensitivity to cold, muscle weakness, joint or muscle pain, sadness, weariness, pale, dry skin, a bloated face, a raspy voice, and other symptoms [11]. Thyroid hormones T4 and T3 production is raised in hyperthyroidism, which is a very common condition [12].

The regular metabolic operation of body cells, including those in the liver, depends on thyroid hormones. Once more, the liver is where thyroid hormone metabolism happens. As a result, hyperthyroidism can modify the quantity of hepatic enzymes and harm liver cells. Hepatocyte metabolism is regulated by thyroid hormones, which also control hepatic function. [13]. It makes sense that the diseases of these two organs would interact or have an impact on one another. Numerous clinical and laboratory studies have connected thyroid and liver issues. Liver damage can be brought on by subclinical physiological effects on liver function, direct toxic effects, or systemic consequences of excessive thyroid hormone. Some people with chronic liver diseases may also have thyroiditis, hyperthyroidism, or hypothyroidism due to autoimmune factors. Thyroid or other hormonal imbalances may cause changes in thyroid hormone metabolism or testing because of liver illness and thyroid or liver-related conditions [14]. A healthy liver is necessary for the metabolism of thyroid hormones, which is vital for thyroid hormone health. A healthy thyroid and enough thyroid hormone production are also necessary for a healthy liver [15]. The neurological, cardiovascular, and gastrointestinal systems are among those affected by hyperthyroidism with the liver being a significant organ in the latter [1]. The liver function test is one of the most often prescribed screening blood tests for liver function tests (LFT). Whether these tests are performed to investigate potential liver illness, monitor the condition's development, or merely perform "normal" blood studies, they can provide a wealth of information on a range of disease processes [16]. However, the term "liver function tests" is rather misleading since only the bilirubin and albumin values were tested. At its

most basic, a patient's underlying disease can be identified as hepatitis or cholestatic based on the analysis of their liver enzymes [17]. Knowing the ratios of the enzymes and recognizing patterns, between 15% and 79% of patients with untreated hyperthyroidism have liver biochemical dysfunctions with some having significant liver failure and reduced synthetic function [13]. The transfer of an amino group is catalyzed by the cytoplasmic enzyme, alanine transaminase (ALT). Liver is the main location of ALT. In contrast to other tissues, including the kidney, pancreas, brain, skeletal muscle, and heart, the liver has a very high concentration of it. Viral hepatitis, ischemic liver injury, and toxicity-induced liver injury are all connected to elevated alkaline phosphatase ALT levels [18, 19]. Phospho-monoesters that hydrolyze phosphate esters are referred to as Alanine Aminotransferase (ALP). Most human bodily tissues including kidney, liver, bone, gut, and placenta contain ALP enzymes. Raised serum ALP levels are seen in bile duct obstruction, metastatic liver disease, cholestasis, viral hepatitis, and bone disease [20]. Hyperthyroid patients have higher serum levels of ALT and ALP [21]. The best technique to assess liver function is liver function tests (LFT), which include direct bilirubin (DBIL), alkaline phosphatase (ALP), aspartate amino transferase (AST), and alanine amino transferase (ALT) [22]. The thyroid hormones are then processed by the liver, which also controls their systemic endocrine impact [23, 24]. When treating a patient whose liver function tests are abnormal, the practitioner must take thyroid function tests into account [25, 26]. On the other hand, normal liver function and bilirubin metabolism also depend on thyroid hormone levels [27]. Anomalies in the liver's biochemical tests have been connected to hyperthyroidism include abnormalities in AST, ALT, gamma-glutamyl transferase (yGT), ALP, as well as increased bromsulphalein retention, decreased albumin, and increased bilirubin. ALP elevation is the most common finding with a reported prevalence range of 15–76% [12], and can be related to fatigue, myalgia’s, changes in mental status, weakness, dyspnea with exertion, muscle cramps, and edema [28]. Hypothyroidism may also share other symptoms with liver illnesses. Additionally, untreated hypothyroidism may be linked to slightly elevated serum levels of the enzymes gamma glutamyl transferase (GGT) and alanine aminotransferase (ALT), which may be related to the possibility of hepatic steatosis and impaired lipid metabolism in hypothyroidism [29]. Due to the bilirubin UDP's diminished action of transferase of glucuronic that results in a delayed emptying of the biliary tract, hypothyroidism may have a pathogenic role in gallstone development [30]. It is advised to check for thyroid dysfunction in all individuals with common bile duct stones [31]. If the dosage is right, levothyroxine, the preferred treatment for hypothyroidism, is a safe medicine [32]. Levothyroxine hypersensitivity reactions have been linked to moderate jaundice and an elevation in liver enzymes [33]. The myopathy brought on by hypothyroidism may be linked to an increase in the enzymes lactate dehydrogenase (LDH) and aspartate aminotransferase (AST) [34].

The problem that we see while conducting pathological analysis of thyroid hormones is whether it is considered an indicator related to the concentrations of liver enzymes. The aim of this research was to prove the existence of a relationship between concentrations of thyroid hormones and concentrations of liver enzymes.

## Materials and Methods

### Patient selection and blood sample collection

A total of 90 people including 38 healthy people, 27 hyperthyroidism patients, and 25 hypothyroidism patient between October and December 2022 were included in this study, where there were 23 males and 15 females with the ages from 16-50 years old in healthy group, 18 males and 9 females with the ages from 25-45 years old in hyperthyroidism group, and 10 males and 15 females with ages from 18 to 40 years old in hypothyroidism group. The people who had a history of liver disease, active or recent

**Table 1.** Correlated serum T3, T4, and TSH levels in hypothyroid, hyperthyroid, and control groups.

| Parameter | Hyperthyroidism | Hypothyroidism | Control | Normal range |
|---|---|---|---|---|
| T3 (ng/mL) | 3.2 ± 1.9 | 0.8 ± 1.2 | 1.1 ± 0.36 | 0.5-1.5 |
| T4 (mg/dL) | 18.5 ± 12.2 | 4.9 ± 8.4 | 6.3 ± 2.4 | 4.5-12 |
| TSH (mIU/mL) | 0.94 ± 0.25 | 25.7 ± 33.1 | 2.5 ± 0.5 | 0.5-5 |

infections, chronic alcoholism, hypertension, cardiac disease, pancreatic disease, pregnancy, diabetes, cancer, and drug use were excluded from this study. The thyroid cases were selected regardless of disease duration or treatment. Healthy adults are considered as control. All procedures in this study were approved by Research Ethics Committee of University of Babylon (Babylon, Iraq) (Approval No. DSM-dna-302). A total of 5 mL venous blood was taken from each participant. The blood samples were centrifuged at 3,000 rpm for 15 minutes and then divided into two parts with one for thyroid function tests and the other for liver function tests.

**Detection of biochemical markers**

The calorimetric method was applied for liver ALT, AST, BIL, and ALP measurements utilizing enzymatic reactions coupled with chromophores to produce a detectable color change. The intensity of the color formed was directly proportional to the enzyme activity, allowing quantification of the enzyme levels in the serum sample. Serum samples were diluted with the ARCHITECT® kit (Abbott Diagnostics, West Chicago, Illinois, USA) provided sample diluent according to the kit instructions. PerkinElmer Lambda 25 UV/Vis spectrometer (Thermo Fisher Scientific, Waltham, Massachusetts, USA) was used to measure the absorbance of the reaction mixture of each enzyme assay. The enzyme-linked immunosorbent assay (ELISA) kits (Abbott, Inc, North Chicago, Illinois, USA) were used to assess serum T3, T4, and TSH levels. ELISA plates were pre-coated with antibodies specific to either T3, T4, or TSH before serum samples and T3, T4, or TSH standards of known concentrations were added to the respective wells. The intensity of the color developed was directly proportional to the amount of T3, T4, or TSH presented in the sample according to manufacturer instructions. The absorbance of the ELISA reaction was measured using PerkinElmer Lambda 25 UV/Vis spectrometer.

**Statistical analysis**

SPSS (IBM Corporation, Armonk, New York, USA) software was employed for the statistical analysis of this study. All data were analyzed using the LSD test, T-test, and one way ANOVA test.

## Results

**Blood thyroid hormone levels**

The average T3, T4, and TSH values of hypothyroid group were 0.8 ng/mL, 4.9 mg/dL, and 25.7 µIU/L comparing to control group values of 1.1 ng/mL, 6.3 mg/dL, and 2.5 µIU/L, respectively. The mean values of T3, T4, and TSH in hyperthyroid patients' group were 3.2 ng/mL, 18.5 mg/dL, and 0.94 µIU/L, respectively (Table 1). Reduced serum T3 levels were one of the negative effects of liver dysfunctions on the thyroid, which was caused by decreased deiodinase enzyme activity that catalyzed the conversion of T4 to T3. Nevertheless, reverse T3 levels were unaffected since the activity of the enzyme responsible for this biochemical reaction was unaffected.

**Blood liver enzyme levels**

The serum AST, ALT, and ALP levels of the hyperthyroid patients' group were 38, 50, and 150 U/L compared to the control group values of 25, 28.4, and 95 U/L, and 70, 78, and 110 U/L in hypothyroid patients' group, respectively (Table 2). There were no significant difference among the levels of ALT, ALP, and AST ($P > 0.05$). The

**Table 2.** Correlated serum ALT, ALP, AST levels in hypothyroid, hyperthyroid, and control groups.

| Parameter | Hyperthyroidism | Hypothyroidism | Control | Normal range |
|---|---|---|---|---|
| ALT (IU/L) | 50 ± 6.5 | 78 ± 7.5 | 28.4 ± 8.2 | 5-40 |
| ALP (IU/L) | 150 ± 6.5 | 110 ± 7.4 | 95 ± 5.7 | 30-120 |
| AST (IU/L) | 38 ± 7.5 | 70 ± 4.5 | 25 ± 4.5 | 10-40 |

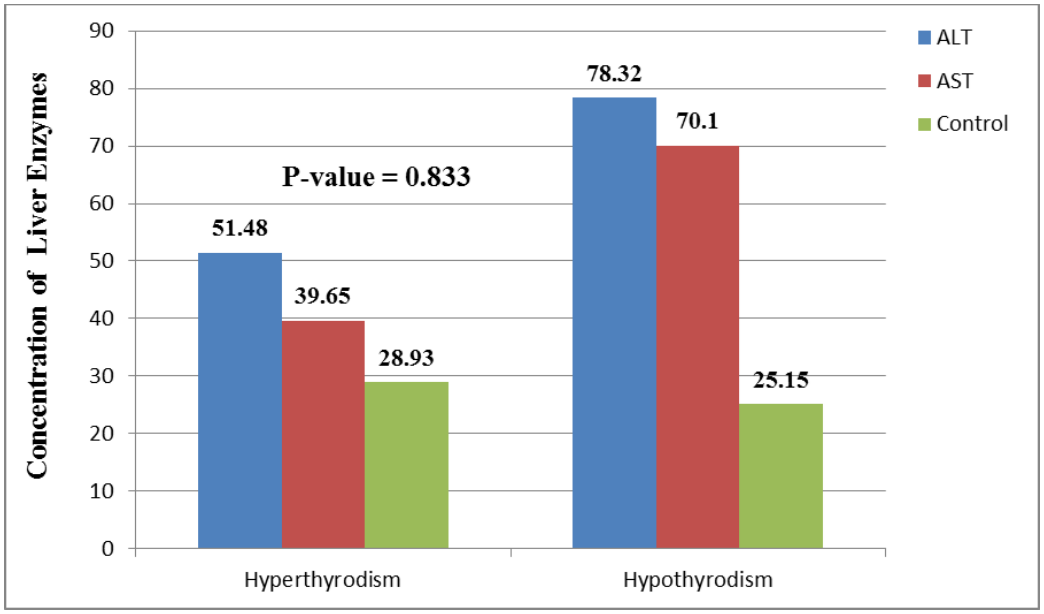


**Figure 1.** Correlation of ALT and AST between hyperthyroidism and hypothyroidism patients. (units: IU/L).

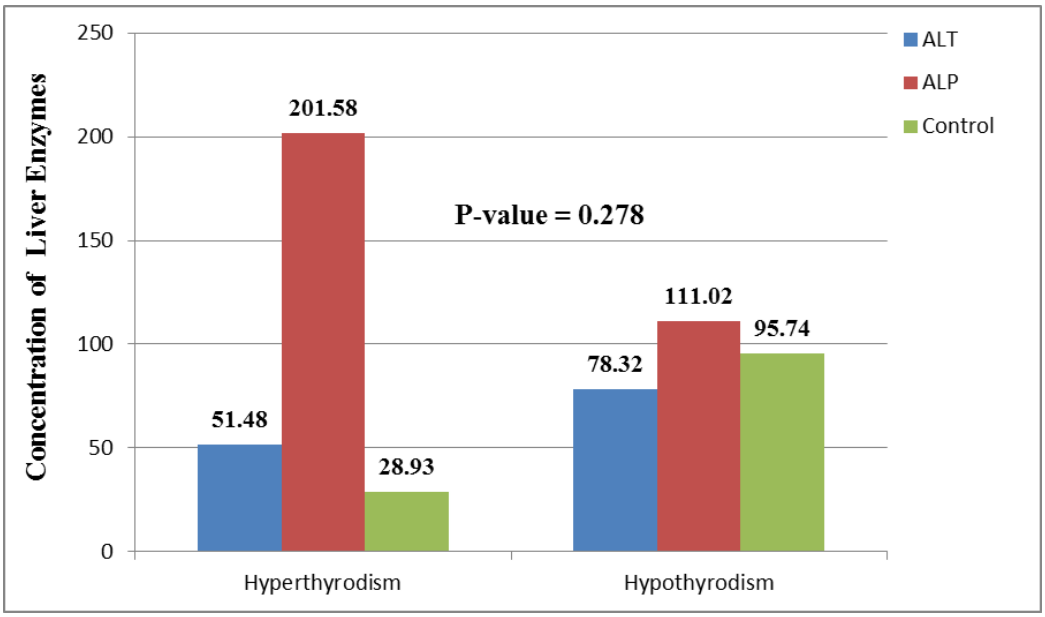


**Figure 2.** Correlation of ALT and ALP between hyperthyroidism and hypothyroidism patients. (units: IU/L).

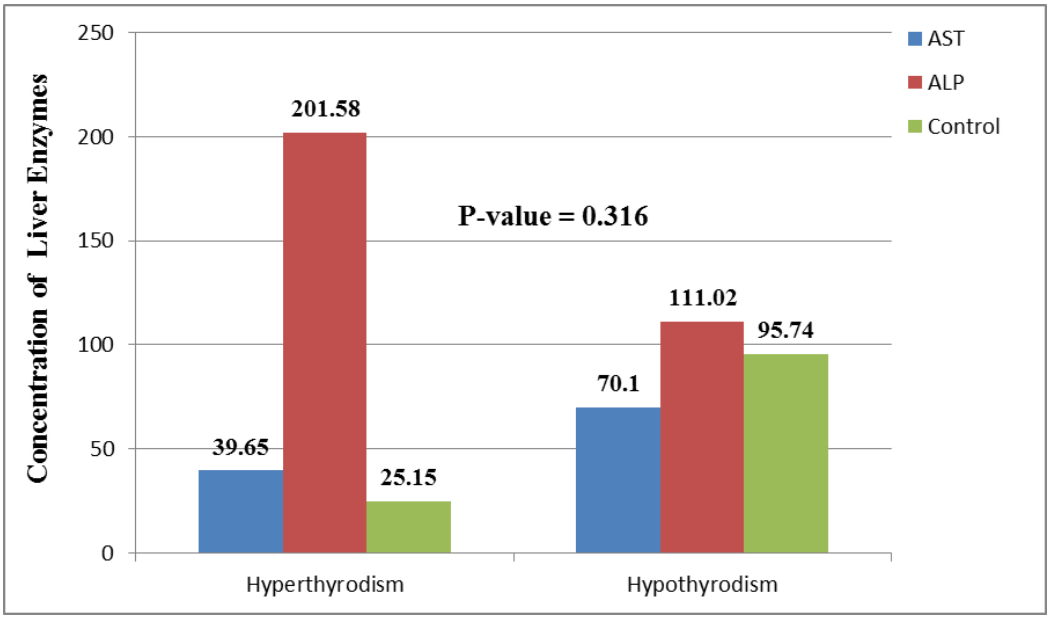


**Figure 3.** Correlation of AST and ALP between hyperthyroidism and hypothyroidism patients. (units: IU/L).

concentrations of ALT and AST enzymes were lower in hyperthyroid group compared to hypothyroid group (Figure 1). However, the concentration of the ALP enzyme was higher in hyperthyroid group than that in hypothyroid group, while ALT enzyme level of hyperthyroid group was lower than that in hypothyroid group (Figure 2). On the other hand, the concentration of ALP in the hyperthyroid was higher than that in the hypothyroid group, while the AST concentration was higher in the hypothyroid group than that in the hyperthyroid group (Figure 3).

## Discussion

Liver diseases cause T3 to be lowered *via* both increase of reveres T3 that is an inactive form of T3 and decrease of the activity of the enzyme that converts T4 into T3. Therefore, liver diseases may include reduced level of T3, the active form of thyroid hormone, elevated levels of reverse T3, and the symptoms of liver disease [35]. Thyroid function typically affects the liver function [36]. Therefore, T3, T4, and other pertinent thyroid parameters are measured as the first stage of laboratory examinations. Human organs, tissues, and cell activities are influenced by thyroid hormones [37]. The laboratory tests are advised for a variety of disorders, including liver dysfunction [35]. Laboratory measurements of thyroid hormones should be done in conjunction with the evaluation of the thyroid function in liver illness [38]. There have been numerous reports of liver enzymes' levels increase with hyperthyroidism. Numerous studies that linked an increase in liver enzymes' levels to hyperthyroidism has been done, which included the tests for ALT, AST, DBIL, and ALP (39, 40). The liver enzymes' increase seems to be caused by periventricular liver areas that are somewhat hypoxic [41]. According to Upadhyay *et al*, high levels of T3 activated the mitochondrial dependent pathway, which led to hepatocyte death and hepatic dysfunction [42]. The results of this study demonstrated that, as compared to the control, the thyroid diseases groups showed raised levels of ALP and ALT. The rises in AST and ALT values were observed with hepatic damage. The data suggested that people with hyperthyroidism frequently had abnormal liver function tests [43]. This study found a substantial positive connection between blood

TSH level and liver AST enzyme, which might be due to a myopathy linked to hypothyroidism. In a small number case report, hypothyroidism had been linked to cholestatic jaundice because of impaired bile excretion [44]. Although the overt hypothyroid group's average bilirubin levels were greater, neither clinical nor statistical significance could be determined for these values. This negligible discrepancy in bilirubin levels might be the result of the outpatient department's referral cases' selective data collection. However, in overtly hypothyroid patients, a highly significant change in blood ALP levels was observed, and these levels were positively associated with serum TSH levels. These findings could be explained by the fact that, in hypothyroidism, the ratio of membrane phospholipids to cholesterol increased and the fluidity of the membrane decreased, which altered the ALP enzyme and had an effect on a number of the membrane's enzymes and transporters including $Na^+$, $K^+$-ATPase [45]. Serum total protein in hypothyroid individuals increased statistically significantly compared to control group. However, neither a clinically nor statistically significant difference in serum albumin could be identified. Both subclinical and overt hypothyroid patients' albumin levels significantly positively correlated with free T4 levels, while overt hypothyroid patients positively correlated to free T3 levels, which suggested that the liver might manufacture proteins other than albumin in hypothyroidism. The liver is known to produce many plasma proteins that bind the lipophilic thyroid hormones. Additionally, even mild hypothyroidism can cause low-grade inflammation, which can increase inflammatory proteins and immunoglobulin levels [46].

## Conclusion

The results of this study demonstrated that the AST, ALP, and AIT levels in hypothyroid and hyperthyroid patients were higher than that in normal control people.

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