



Interrelationship between thyroid hormones and liver function biomarkers in patients with liver disease: A case-control study

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Article info

Received 06.11.2025

Received in revised form 09.12.2025

Accepted 12.01.2026

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Faisal, A. N., Falgoos, N. S., Hommoood, A. K., Abed, S. J., & Mohsein, O. A. (2026). Interrelationship between thyroid hormones and liver function biomarkers in patients with liver disease: A case-control study. *Regulatory Mechanisms in Biosystems*, 17(1), e26017. doi:10.15421/0226017

This study aimed to investigate the relationship between thyroid gland function and susceptibility to liver disease in an Iraqi patient population. The researchers worked in Iraq and surveyed consenting patients of different ages who attended the Al-Hussein Teaching Hospital and the Ibn Al-Bitar Laboratory in Thi-Qar province. Further, there were fifty healthy controls, both male and female and of different ages who were sampled. In order to examine the association between thyroid hormones and liver functioning, blood serum was measured in terms of TSH, T₃, T₄, AST, ALT, and bilirubin in patients as well as controls. The results showed that patients who suffered liver disease had a lower body mass index (BMI) than the control group and that there were also no statistically significant differences in age. AST levels had a positive relationship with T₄ ($r = 0.260$) and a negative relationship with TSH ($r = -0.131$). Also, age had a positive correlation with the BMI ($r = 0.381$) and negatively correlated with bilirubin levels ($r = -0.274$). The liver is the important part of the metabolism of thyroid hormones and, vice versa, the level of thyroid hormones is necessary to ensure the proper functioning of liver and bilirubin metabolism. In addition to the established correlation of thyroid dysfunction with autoimmune diseases of the liver such as primary biliary cirrhosis and hypothyroidism that affect the liver, thyroid diseases can also be a cause of liver injury or affect liver function tests.

Keywords: thyroid dysfunction; liver disease; TSH levels; liver enzymes; hypothyroidism; hyperthyroidism.

Introduction

The liver is the main organ of metabolism in the body and is involved in lipid storage, metabolite cleaning, and digestive enzyme and lipoprotein synthesis (Albuquerque-Souza et al., 2022). Cirrhosis, hepatitis and liver cancer are chronic liver diseases (CLDs) which disrupt hepatic lipid metabolism elevating the morbidity and mortality rates (Younossi et al., 2023).

These conditions consist of alcohol related liver disease, non-alcoholic fatty liver disease (NAFLD), non-alcoholic fatty liver disease, viral hepatitis and autoimmune hepatitis. Liver dysfunction is usually characterized by jaundice, which occurs because of high bilirubin. Acute liver failure is an acute onset of a condition in which the liver fails rapidly, unlike chronic diseases which develop over a period (Larson et al., 2005).

Although the term hepatitis is commonly used to refer to liver infection caused by virus, it can also be as a result of autoimmune reaction, toxins, medication, infection, genetic diseases, obesity, smoking and alcohol abuse. The steatotic liver diseases include NAFLD and alcohol-related liver disease (ALD), which are characterized by the presence of excess fat in liver cells (Li et al., 2022).

NAFLD is a global prevalence disease, affecting approximately 25% of the population, being associated with obesity, insulin resistance, and related illnesses (Polyzos et al., 2022). More recent studies suggest a renaming of NAFLD to metabolic-associated steatotic liver disease (MASLD) as it is more metabolically-related. Nonalcoholic steatohepatitis (NASH) is a severe form of this condition that leads to inflammation, fibrosis and may result in cirrhosis and liver cancer (Assy et al., 2009). Fatty hepatitis and cirrhosis are also covered in ALD; alcoholic cirrhosis is non-reversible and occurs in 10% to 20% of alcoholics. Some of the enzymes generated by the liver

include; alanine aminotransferase (ALT) and aspartate aminotransferase (AST) which are biomarkers of liver functions. High-levels are usually evidence of hepatic damage (Center et al., 2007).

ALT is liver specific whereas AST is distributed across a number of tissues hence ALT is a more direct measure of liver injury. Bilirubin, a byproduct resulting in a breakdown of red blood cells, is also eliminated by the liver. Cholestasis, as well as disruptions in this process, may lead to accumulation of bilirubin and, as a consequence, this leads to the appearance of yellow skin and other symptoms (Lateef et al., 2024). The thyroid gland coordinates development, metabolism, and growth through such hormones as triiodothyronine (T₃) and thyroxine (T₄) (Rousset et al., 2015). These hormones have an effect on thermogenesis and cellular differentiation. The activity of the thyroid gland is always controlled by hypothalamic-pituitary-thyroid axis and such factors as the thyrotropin-releasing hormone (TRH) and thyroid-stimulating hormone (TSH), play significant roles (Maenhaut et al., 2015). Thyroid diseases are very prevalent. Spontaneous hypothyroidism occurs in 1–2% of the population and occurs more often in women. Subclinical hypothyroidism that presents in the form of high levels of TSH and normal T₄ is found in 3–15 percent of the people and is normally as a result of auto immune thyroiditis (Rondoni et al., 2010).

Subclinical hyperthyroidism is characterized by low levels of TSH and normal levels of T₃ and T₄ and may cause cardiovascular disease, dementia, and bone loss, especially in the elderly. The liver plays a vital role in the metabolism and transportation of thyroid hormones, whereas thyroid hormones influence hepatic metabolism (Piantanida et al., 2020). Hypothyroidism could be a contributor to hepatic steatosis and hypercholesterolemia, as well as having a relationship to symptoms of liver failure such as ascites. Thyroid dysfunction detection in patients with liver disease in its initial stage could en-

hance the results (Silveira et al., 2009). In other instances, cholestatic jaundice can be attributed to hypothyroidism. Conversely, hyperthyroidism may increase liver enzymes such as ALT and ALP, which is an indicator of hepatocellular injury (Lee et al., 2023).

This paper set out to examine the links between the thyroid gland functioning and liver disease predisposition among an Iraqi population of patients.

Materials and methods

The study was approved by the ethics committee at the Neurological Diseases Center, Nasiriyah General Hospital, under committee code 456, on October 1, 2024. All participants were fully informed about the study and provided written consent to participate. They were also assured that their personal information would remain confidential.

This cross-sectional study was conducted between January 1 and July 1, 2024, and included patients of both sexes and various age groups who attended Al-Hussein Teaching Hospital and Ibn Al-Bitar Laboratory, Thi-Qar Governorate, Iraq. The study population consisted of patients clinically diagnosed with thyroid and/or liver disorders, in addition to a control group of 50 apparently healthy individuals matched for age and sex.

Participants with chronic systemic diseases unrelated to the study objectives, those receiving medications known to interfere with thyroid or liver function, pregnant individuals, and subjects with acute infections were excluded to avoid confounding effects.

For biochemical analyses, 5 mL of venous blood was aseptically collected from the cubital vein using sterile disposable syringes. Blood samples were transferred into serum gel tubes and centrifuged at 5000 rpm for 5 minutes. The separated serum was aliquoted to avoid repeated freeze-thaw cycles. Three milliliters of serum were used for liver function assessment, including aspartate aminotransferase (AST), alanine aminotransferase (ALT), and total bilirubin, while the remaining 2 mL were utilized for thyroid hormone evaluation, namely thyroid-stimulating hormone (TSH), triiodothyronine (T_3), and thyroxine (T_4), using standardized and validated laboratory assays according to the manufacturers' instructions.

Anthropometric measurements were obtained for all participants. Body mass index (BMI) was calculated using the Quetelet formula: $BMI = \text{weight (kg)}/\text{height (m)}^2$. Participants were classified as underweight ($<18.5 \text{ kg/m}^2$), normal weight ($18.5\text{--}24.9 \text{ kg/m}^2$), overweight ($25.0\text{--}29.9 \text{ kg/m}^2$), or obese ($\geq 30 \text{ kg/m}^2$).

All laboratory procedures were performed under strict quality control conditions, and measurements were conducted in duplicate to ensure accuracy, reproducibility, and reliability of the results.

Statistical analysis is often used to analyze quantitative data, and provides methods for data description, simple inference for continuous and categorical data. The procedure involves the collection of data leading to test of the relationship between two statistical data sets. In this study all data are presented as frequency and percentage. We used SPSS (version 26) and the dependent t-test (two-tailed) and independent t-test (two-tailed) for variables that had a normally distributed distribution. For variables that did not have a normally distributed distribution, we used the Mann-Whitney U test, the Wilcoxon test, and the Chi-square test. $P < 0.05$ was seen as statistically significant.

Results

The study findings revealed that the mean age of those individuals who belonged to the patient group (39.9 ± 13.1 years) and the healthy group (36.5 ± 12.8 years) did not differ significantly and the probability value ($P = 0.165$), which was not statistically significant. Conversely, the outcome of the body mass index (BMI) revealed a statistically significant difference between the two groups with the mean BMI of the patients at $27.6 \pm 6.19 \text{ kg/m}^2$ versus $30.2 \pm 6.81 \text{ kg/m}^2$ in the healthy population (having a probability value $P = 0.044$).

The research findings demonstrated statistically significant variables in the levels of the thyroid hormones between the patient popu-

lation and the healthy population. The TSH level ($4.05 \pm 4.38 \text{ mIU/L}$) of the patient population was also significantly greater ($P = 0.042$) compared to healthy group ($1.89 \pm 1.04 \text{ mIU/L}$). A large difference in the T_3 level was also noted between the patients ($2.34 \pm 0.43 \text{ nmol/L}$) and control ($1.76 \pm 0.391 \text{ nmol/L}$) at a $P = 0.025$. Equally, the outcomes revealed that the level of T_4 of the patients ($98.4 \pm 23.2 \text{ nmol/L}$) was significantly higher than that of the healthy population ($88.7 \pm 12.9 \text{ nmol/L}$) and the $P = 0.009$. The existence of hormonal imbalance related to the disease is reflected in these results, implying that the disease could have an effect on the functioning of the thyroid.

Table 1

Assessment of anthropometric parameters (age and BMI) in study participants (single measurement per participant)

Parameter	Patients (mean \pm SD)	Controls (mean \pm SD)	P-value
Age, years	39.9 ± 13.1	36.5 ± 12.8	0.1647
BMI, kg/m^2	27.6 ± 6.2	30.2 ± 6.8	0.0444

The study findings demonstrated significant differences in the liver functioning indicators in the patient group as compared to the healthy group, which were highly significant. The mean average AST enzyme in the patients (57.0 ± 21.3 units/liter) was significantly higher than it was in the healthy controls (37.1 ± 13.0 units/liter) with a $P < 0.0001$. The outcome also revealed the increase in the level of ALT in patients (79.3 ± 20.9 units/liter) relative to the healthy controls (36.5 ± 12.8 units/liter) by the same $P < 0.0001$. Moreover, the mean total bilirubin level was found to be significantly higher in the patients ($2.14 \pm 0.83 \text{ mg/dL}$) compared to the healthy controls ($0.95 \pm 0.74 \text{ mg/dL}$) with $P < 0.0001$, which is high enough to ascertain the relationship between these indicators and liver functional impairment in the patients.

Table 2

Serum levels of AST, ALT, and total bilirubin in patients and controls (each parameter measured in duplicate)

Variables	Patients (mean \pm SD)	Control (mean \pm SD)	P-value
AST, U/L	57.0 ± 21.3	37.1 ± 13.0	<0.0001
ALT, U/L	79.3 ± 20.9	36.5 ± 12.8	<0.0001
Total bilirubin, mg/dL	2.14 ± 0.83	0.95 ± 0.74	<0.0001

Table 3

Serum concentrations of TSH, T_3 , and T_4 in study participants (each hormone measured in duplicate)

Variables	Patients (mean \pm SD)	Control (mean \pm SD)	P-value
TSH, mIU/L	4.05 ± 4.38	1.89 ± 1.04	0.0417
T_3 , nmol/L	2.34 ± 1.43	1.76 ± 0.39	0.0245
T_4 , nmol/L	98.4 ± 23.2	88.7 ± 12.9	0.0090

Pearson correlation analysis results showed statistically significant relationships between some of the studied variables. A moderate positive correlation was observed between age and body mass index ($r = 0.381$, $P < 0.05$), while there was a weak and statistically significant negative correlation between age and both AST ($r = -0.299$) and bilirubin ($r = -0.274$). A weak negative correlation was also observed between AST and TSH ($r = -0.131$), while a moderate and statistically significant positive correlation was found between AST and both T_4 ($r = 0.260$) and bilirubin ($r = 0.264$). On the other hand, the remaining variables did not show statistically significant relationships, suggesting that some of the biomarkers in this study may be partially correlated with liver function or thyroid disorders, while other variables operate relatively independently.

Discussion

The results of the current study revealed no significant difference in age between the patient and control groups, with an age mean of 39.9 ± 13.1 years for the patient group and 36.5 ± 12.8 years for the control group ($P = 0.165$, Table 2). These findings are consistent with those of Punekar et al. (2018), who reported no significant age diffe-

rences between cirrhotic patients and controls. Similarly, Chen et al. (2022) found no significant age difference in their study on the relationship between thyroid hormones and fatty liver. Nevertheless, we did not achieve the same as Hassan et al. (2009) did, who reported a statistically significant difference in age, with patients of higher age compared to the healthy controls. Body mass index (BMI) is one of

the metrics used in determining the risk of having chronic diseases, such as liver disease. In the present research, BMI had statistically significant difference between patients (27.6 ± 6.19) and controls (30.2 ± 6.81 , $P = 0.044$, Table 2). These results are in agreement with the research of Carulli et al. (2013), who also observed the presence of pronounced differences between patient and control BMI.

Table 4

Pearson correlation coefficients among age, BMI, thyroid hormones, and liver function biomarkers (correlation analysis based on averaged duplicate biochemical measurements)

Correlation coefficients	Age	BMI	ALT	AST	Bilirubin	TSH	T ₃	T ₄
Age	1	0.381*	0.066	-0.299	-0.274*	-0.190	-0.111	-0.051
BMI	-	1	0.201	-0.273	-0.190	-0.016	-0.029	-0.189
ALT	-	-	1	-0.520*	0.095	0.209	-0.100	0.032
AST	-	-	-	1	0.008	-0.131*	-0.017	0.260*
Bilirubin	-	-	-	-	1	0.072	0.009	0.264*
TSH	-	-	-	-	-	1	-0.027	-0.097
T ₃	-	-	-	-	-	-	1	0.008
T ₄	-	-	-	-	-	-	-	1

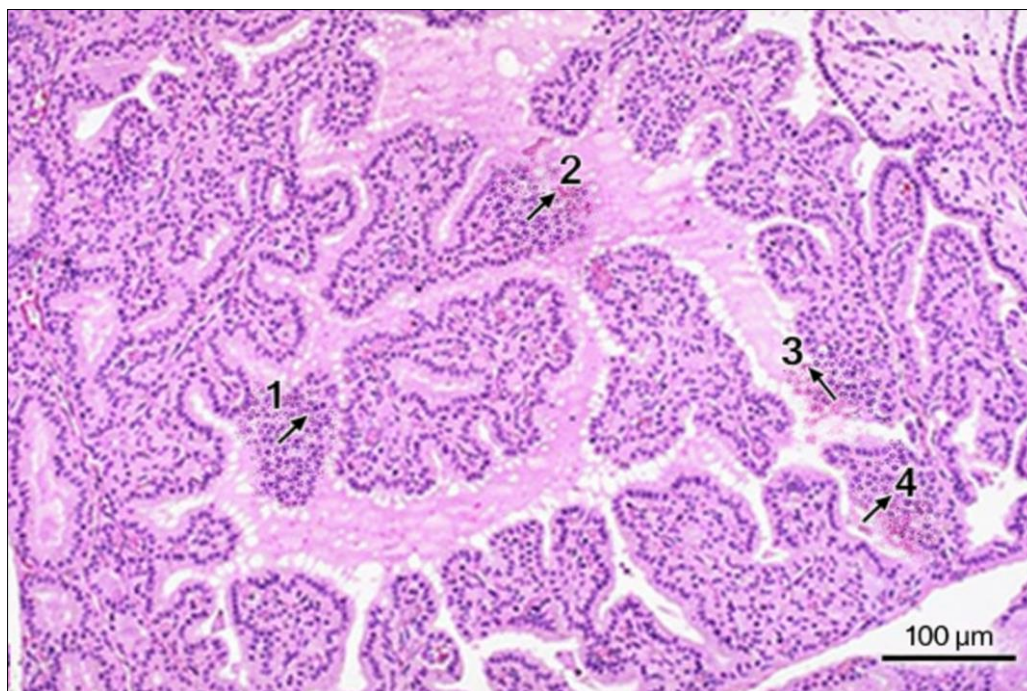


Fig. 1. Representative histological section of thyroid tissue showing disrupted follicular architecture and inflammatory cell infiltration: numbered labels (1–4) indicate key histopathological features

Moreover, Chung et al. (2012) have stated that hyperthyroidism is usually characterized by loss of weight, whereas hypothyroidism is usually characterized by gain of weight because of the low metabolic rate. It is also known that obesity causes the increased risk of liver diseases, which was proven by Chung et al. (2012). In the current study, liver enzymes AST and ALT were also significantly higher in the patient group (AST: 57.0 ± 21.3 , ALT: 79.3 ± 20.9) compared to the control group (AST: 37.1 ± 13.0 , ALT: 36.5 ± 12.8 , $P < 0.0001$ in both cases, Table 2). This is in agreement with the findings of Silveira et al. (2009), who established a significant difference in the levels of AST and ALT in patients with liver diseases and controls.

High levels of AST and ALT are a reflection of liver damage, which is prevalent in patients with all forms of liver diseases. The study also established that the levels of total bilirubin were significantly higher in the patients (2.14 ± 0.83) than in the controls (0.95 ± 0.74 , $P < 0.0001$, Table 2). High bilirubin concentrations are a characteristic feature of liver dysfunction, which in most cases is indicative of the destruction of the hepatocytes by either drugs or infection (hepatitis) caused by virus (Rutherford et al., 2008). Bilirubin has an important role in the pathophysiology of liver disease as it is used as a diagnostic tool for the disease (Abbas et al., 2025). The patient group (4.05 ± 4.38) showed a high level of thyroid-stimulating hormone

(TSH) in comparison to controls (1.89 ± 1.04 , $P = 0.042$, Table 2). These findings agree with Punekar et al., who reported a high level of TSH in patients with liver disorders (Punekar et al., 2015).

This observation can also be attributed to the studies that indicate that TSH levels are elevated in patients with primary biliary cirrhosis when compared to normal individuals (Silveira et al., 2009). There were also major disparities in thyroid T₃ and T₄ hormones. The T₃ (2.34 ± 1.43) and T₄ (98.4 ± 23.2) levels were higher in the patient group than in the control group (T₃: 1.76 ± 0.39 , T₄: 88.7 ± 12.9 , $P < 0.05$). These findings are consistent with the findings by Carulli et al. (2013), who reported that T₃ and T₄ are elevated in liver disease patients. However, the opposite is not true as Silveira et al. (2009) observed that the prevalence of hypothyroidism was higher in the non-alcoholic steatohepatitis patients, unlike our results (Opoku-Akyeampong et al., 2020).

Table 3 has indicated a correlation analysis that age had a positive relationship with BMI (0.381) and ALT (0.066) and a negative relationship with TSH (-0.190), T₃ (-0.111), T₄ (-0.051), AST (-0.299), and bilirubin (-0.274) at $P < 0.05$. BMI had a positive correlation with ALT (0.201) and age (0.381), and negative correlation with TSH (-0.190), T₃ (-0.029), T₄ (-0.189), AST (-0.273), and bilirubin (-0.190). TSH was positively correlated with ALT (0.209) and bilirubin

bin (0.072) and negatively correlated with age (-0.190), BMI (-0.016), T₃ (-0.027), T₄ (-0.097), and AST (-0.131). T₃ had a positive relation with T₄ (0.008) and bilirubin (0.009), whereas it had a negative relation with age (-0.111), BMI (-0.029), TSH (-0.027), ALT (-0.100) and AST (-0.017). Liver enzyme abnormalities are normally associated with thyroid dysfunction. Hyperthyroidism, e.g., may cause an increase in alkaline phosphatase and AST, and hypothyroidism in AST may cause an increase in ALT. Past research has demonstrated that thyroid dysfunction can also affect the liver function tests, hyperthyroidism increases the chances of liver dysfunction (Le Couteur et al., 2010).

On the same note, it has been observed that increased levels of AST are linked to increased TSH levels among patients with liver cirrhosis (Oh et al., 2016). The correlation between liver enzymes and thyroid functioning has been well-reported. According to a study by Martínez-Escudé et al. (2021), high TSH level poses a risk of non-alcoholic fatty liver disease and cirrhosis development. Likewise, Carulli et al. (2013) discovered that TSH and AST levels showed positive correlation with each other, which correlates with those seen in the present study. Yet, there are other studies, including those by Murali Krishna et al. (2024), which emphasized that additional research needed to be conducted on the interacting nature of the thyroid functioning and the liver disease.

Conclusion

The present research highlights the relation between thyroid hormones, liver enzymes and BMI, and strong links are observed between these variables in liver disorder patients. More studies need to be conducted to understand better the mechanism of action and how thyroid hormones may contribute to the development of liver disease.

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