2024
11(2), 661

Chemical Biology
LETTERS

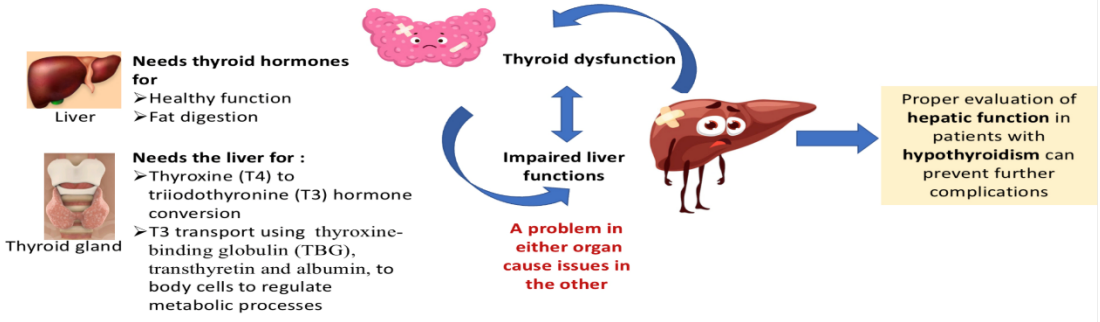
Correlation of Thyroid Stimulating hormone and Liver function test in Hypothyroid and Euthyroid subjects

Premjeet Kaur,[1*] Vijay Suri,[2] Navpreet Kaur[1]

[1]*Department of Biochemistry*, [2]*Department of Pathology*, *Adesh Institute of Medical Sciences and Research (AIMSR), Bathinda. India.*

Submitted on: 21-Jan-2024, Accepted and Published on: 24-Feb-2024

Article



ABSTRACT

The thyroid hormones play an important role in basal metabolic rate, and the liver is important in the metabolism of thyroid hormones, so, these two organs affect functioning of one another. The proper evaluation of hepatic functions (LFTs) in patients with thyroid disorders might be of clinical relevance for undertaking preventive and therapeutic strategies. The study was designed as hospital-based retrospective cross-sectional study conducted in Central Clinical Laboratory of Adesh Institute of Medical Sciences and Research, (AIMSR) Bathinda, a tertiary care teaching hospital in Punjab, India, from a period of Jan 2022 to Dec 2023. Cases included 100 newly diagnosed hypothyroid patients not undergoing any treatment for thyroid dysfunction and controls consisted of 100 euthyroid subjects. Levels of thyroid stimulating hormone (TSH) in cases were significantly high as compared to the controls (r=0.268, p=0.03). Levels of aspartate aminotransferase (AST) (r=0.352, p=0.003) and alanine aminotransferase (ALT) (r=0.27, p=0.006) were also significantly high in cases as compared to controls. Comparison of TSH levels in cases with various liver function tests (LFTs) depicted significant correlation with AST (r=0.334, p=0.001) and ALT (r= 0,399, p=0.001). This study is significantly important for consideration of liver injury due to hypothyroidism. Early detection and treatment can prevent further complications and would be helpful during management of hypothyroid patients.

Keywords: Hypothyroidism, Euthyroidism, Thyroid Stimulating hormone, Alanine aminotransferase, Aspartate aminotransferase

INTRODUCTION

Since thyroid hormones play an important role in basal metabolic rate and because the liver is important in the metabolism of thyroid hormones, these two organs are certainly expected to affect one another.[1] The proper evaluation of hepatic functions in patients with thyroid disorders might be of clinical relevance for undertaking preventive and therapeutic strategies. Thyroid hormones are essential for the normal development of many human tissues and regulates the metabolism of virtually all cells and organs of the human body throughout life.[2] The thyroid gland secretes predominantly T4 and, to a lesser extent, T3, which accounts for up to only ~20% of circulating T3. The remaining T3 is produced by peripheral tissues, such as liver (Figure 1) and skeletal muscle, by the activating enzymes type 1 and type 2 iodothyronine deiodinase (DIO1 and DIO2, respectively), which cleave an iodine atom from T4. Liver plays an essential physiological role in thyroid hormone activation and inactivation, transport, and metabolism. Conversely, thyroid hormones affect activities of hepatocytes and hepatic metabolism. Hypothyroidism, the clinical condition of thyroid hormone deficiency, is a common disorder in the general population. Overt hypothyroidism is defined by thyroid stimulating hormone (TSH) levels above the upper limit of the reference range while levels of free thyroxine (fT4) below the lower limit of the reference range.[3] Severe hypothyroidism may have biochemical and clinical features, such as hyperammonemia and ascites, mimicking those of liver failure. Serum thyroid stimulating hormone (TSH), measurement is the best diagnostic test; an elevated TSH level almost always signals primary hypothyroidism.[4] While the effects of hyperthyroidism on the liver have been well described in the literature, those related to hypothyroidism are less well understood. [3] No study has been done in newly diagnosed hypothyroid patients which are not on

*Corresponding Author: Dr Premjeet Kaur, Biochemistry Department, AIMSR, Bathinda. India.
Tel: +91-9780484132 Email: premjeet9@gmail.com

URN:NBN:sciencein.cbl.2024.v11.661

https://pubs.thesciencein.org/cbl

treatment. Therefore we aimed to find out alterations in liver enzymes in newly diagnosed hypothyroid patients not undergoing any treatment for thyroid disorders visiting the tertiary care centre of Bathinda, Punjab.

MATERIAL AND METHODS

The study was designed as hospital-based retrospective cross sectional study conducted in Central Clinical Laboratory of Adesh Institute of Medical Sciences and Research, Bathinda, a tertiary care teaching hospital in Punjab, India, from a period of Jan 2022 to Dec 2023. Overt hypothyroidism was diagnosed as high TSH and free thyroxine (fT4) levels below the reference range.[4] Cases included 100 newly diagnosed hypothyroid patients not undergoing any treatment for thyroid dysfunction and controls consisted of 100 euthyroid subjects. Both indoor and outdoor patients were included in this study.

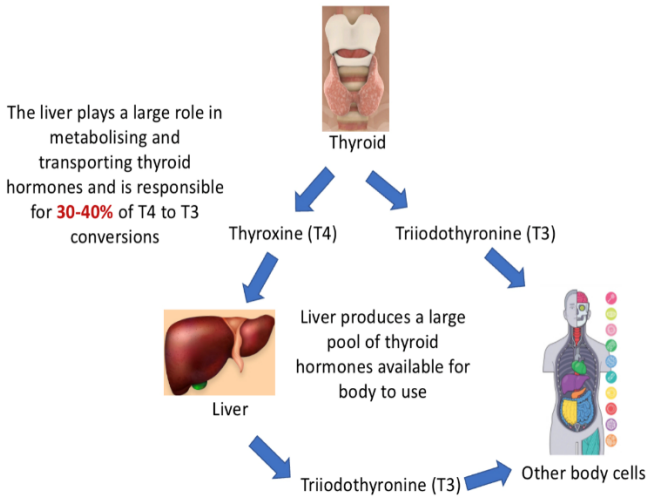


Figure 1. Schematics for relationship of liver functioning with thyroid.

Sample size:

The sample size was calculated based on the average prevalence rate of hypothyroidism (11%) [5] by using Cochran's formula. Z2 PQ/e2 ,Where Z is Z score. It was increased to 100 to have adequate number and to draw significant conclusion. Hence we included 100 subjects for cases and 100 subjects for controls.

Data collection:

The data was collected from the previous two year data (Jan 2022 to Dec 2023) maintained in the laboratory computer.

Sampling procedure:

Patients with newly diagnosed hypothyroid patients whose liver function tests (LFTs) were available in the records were enrolled for study analysis

Sample estimations:

The thyroid function tests were estimated by chemiluminescence assay (Maglumi 2000 Fully automated analyzer) and LFT panel test were analyzed by Biosystem BA200 fully automatic analyzer. Serum Aspartate aminotransferase (AST), Alanine aminotransferase (ALT) and Alkaline phosphatase (ALP) enzymes were estimated by kinetic spectrophotometric method.

Inclusion Criteria:

Patients with newly diagnosed overt hypothyroidism not undergoing any treatment.

Exclusion criteria:

History of liver disease, pregnant women, chronic alcoholism, and diseases that alter serum LFT parameters like liver cirrhosis, bone diseases, cardiovascular diseases, diabetes mellitus, renal diseases, pneumonia, autoimmune diseases, malignancy patients taking drugs like amiodarone, mefloquine, antiepleptics like carbmazipine and patient undergoing radiotherapy were excluded.

Statistical analysis:

Data was analyzed using SPSS (Statistical Package for Social Sciences) software. Pearson's correlation was calculated. The data was presented as mean ± SD. A p value of < 0.05 was taken as statistically significant.

Overt Hypothyroidism:

- TSH levels above upper limit of reference range
- TSH levels in overt hypothyroidism are >10 uIU/ml.
- fT4 below lower limit of reference range
- Reference range for TSH is 0.3-4.5uIU/ml.

RESULTS

There was no significant difference in age and sex ratio in cases and controls. All participants were in the age group of 40 to 75 years.The present study showed a significantly high (r=0.268, p=0.03) levels of TSH in cases (90.9 ± 6.6 uIU/ml) as compared to the controls (1.6 ± 0.8 uIU/ml) (Table 1, Figure 2). Levels of AST were significantly high (r=0.352, p=0.003) in cases (77.3 ± 25.7 IU/L) as compared to controls (17.8 ± 5.5 IU/L). The levels of ALT in cases (73.9± 24.1 IU/L) were also significantly high (r=0.273, p=0.006) when compared to controls (17.9± 6.09 IU/L). But the ALP levels in cases (133.2 ± 69.1UL/L) and controls (85.8 ± 36.8 UL/) did not show any significant difference (r=0.226, p=0.056). Total bilirubin (T Bil) showed a non significant relation between cases and controls. A significant correlation was found between TSH and ALT (p=0.001) as well as AST (p= 0.001) in cases while other parameters showed non significant correlation with TSH in cases and controls (Table 2, Figure 3).

Table 1. Comparison of levels of TSH, T Bil, AST, ALT and ALP in cases and controls.

	Cases	Controls	R value	P value
TSH (uIU/ml)	90.0 ± 6.6	1.6 ± 0.8	0.268	0.03
Total bilirubin (mg/dl)	0.87 ± 0.4	0.66 ± 0.3	-0.078	0.44
AST (IU/L)	77.3± 25.7	17.8 ± 5.5	0.352	0.003
ALT(IU/L)	73.9± 24.1	17.9± 6.09	0.27	0.006
ALP (IU/L)	133.2± 69.1	85.8 ± 36.8	0.22	0.056

r is the correlation coefficient, p is the values obtained from Spearman correlation analysis, p<0.05 is considered statistically significant

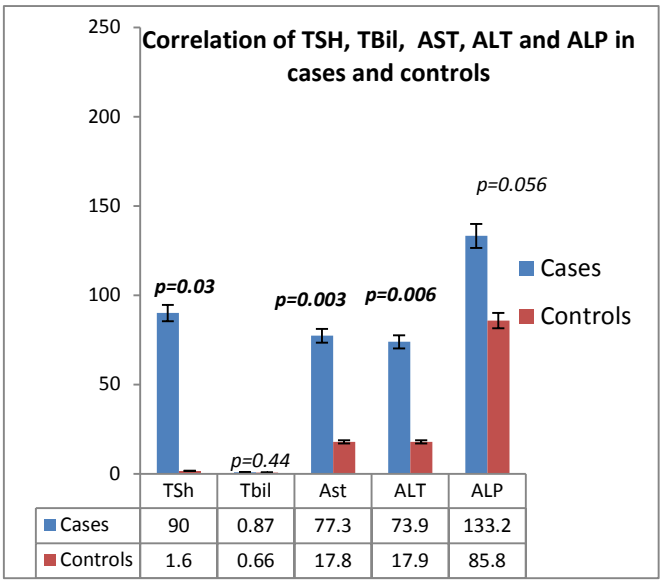


Figure 2: Bar chart showing comparison of TSH, T. Bil, AST, ALT, and ALP in cases and controls.

Table 2. Correlation of the levels of TSH with AST, ALT, and ALP in cases and controls.

Variables		TSH in Cases	TSH in Controls
Total Bilirubin (mg/dl)	R	0.115	0.04
	P	0.26	0.67
AST(IU/L)	R	0.334	0.016
	P	0.001	0.88
ALT(IU/L)	R	0.399	0.171
	P	0.001	0.37
ALPP (IU/L)	R	0.184	0.04
	P	0.065	0.96

r is the correlation coefficient, p is the values obtained from Spearman correlation analysis, p<0.05 is considered statistically significant.

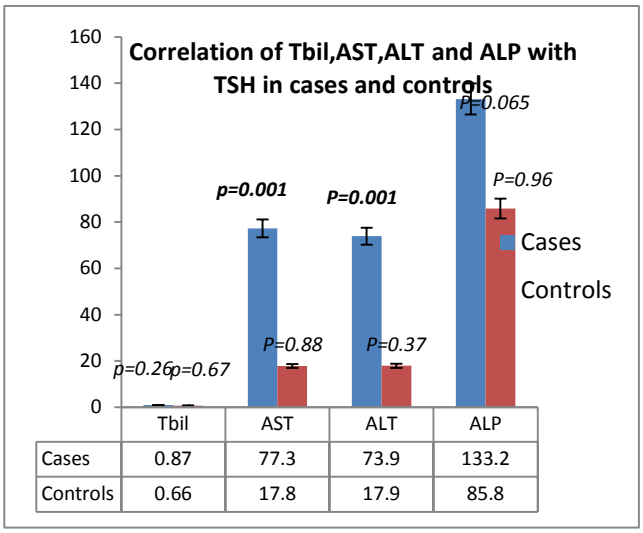


Figure 3. Graph showing correlation between TSH with T Bil, AST, ALT and ALP in cases and controls

DISCUSSION

The present study showed significant (r=0.268, p=0.03) levels of TSH in hypothyroid patients (90.9 ± 6.6 uIU/ml) as compared to euthyroid subjects (1.6 ± 0.8 uIU/ml). Similar results were found by Tamang B et al 2023[6] and S. Elshinshawy et al 2023.[7] Reference range for TSH is 0.3-4.5uIU/ml. TSH levels in overt hypothyroidism are >10 uIU/ml. Our study showed significant elevations of ALT and AST levels in hypothyroid cases as compared to euythyroid controls. Also correlation of TSH with AST and ALT was significantly high in hypothyroid patients. Cellular thyroid hormone transmission disturbances trigger various liver diseases. The metabolic dysregulations due to thyroid disorders may partly answer increased serum aminotransferase levels in hypothyroid patients. Normal biochemical processes and basal metabolic rate (BMR) within the hepatic cell may be disrupted by abnormal thyroid hormone, which may increase the production of hepatic enzymes, the permeability of the hepatic cell membrane, or both. Hence, normal circulating levels of thyroid hormones are required for healthy hepatic function, suggesting that altered thyroid function may cause hepatic dysfunction and vice versa. Similar results were found by Hyun Jin kim 2020[8] and others.[6,7]

There is a complex relationship between the thyroid gland and liver. The deiodinase enzyme system of liver plays a role in activation and inactivation of thyroid hormones. The liver metabolizes thyroid hormones through conjugation, excretion, peripheral deiodination, and in the synthesis of thyroid-binding globulin, and thus controls their endocrine effects. Liver affects bioavailability of thyroid hormones by synthesizing transport proteins such as thyroxine binding globulin, transthyretin and albumin. Serum liver enzyme abnormalities observed in hypothyroidism may be related to impaired lipid metabolism, hepatic steatosis or hypothyroidism induced myopathy. [7,9,10]

Thyroid abnormalities in hepatic diseases are the subject of numerous studies[11,12] whereas hepatic dysfunctions in thyroid disorders have been studied selectively especially when serum amino transferase levels are concerned. Regarding the latter, findings from some studies[13] were similar to ours, yet many other studies were distinguishably diverse. These disparities could at least be explained by the differences in estimation methods and uses of varied cut off values. Furthermore, variations in patients characteristics owing to diverse geographies and ethnicities could also contribute.

A previous study suggested the role of high TSH levels as a cardio metabolic risk marker and that dyslipidemia, hyperglycemia and liver abnormalities were associated with high TSH levels.[14] In present study, however, we could not evaluate such laboratory findings

Dysfunctions in the thyroid hormone status may influence the liver function test parameters directly or indirectly.[10] Thus, the role of thyroid hormones in hepatic function can have multiple explanations. Thyroid hormones play a significant role in cell metabolism throughout the body.[15]

No significant correlation was found for triiodothyronine (T3), thyroxine (T4), total bilirubin, total protein and albumin in cases and controls in the present study. Similar results were found in

study by Tamang B et al 2023.[6] While Ajala Mo et al 2019 reported increased bilirubin and liver enzymes in both hypothyroidism and hyperthyroidism. [13] Arora S et al found no significant difference in serum bilirubin and liver enzymes between hypothyroidism and euthyroid patients.[9]

While the ALP levels did not show any significant difference in cases and controls and non significant correlation with TSH in cases in our study, which was as opposed to the findings in other studies.[7] The high levels of ALP found in these studies may be due to increase in membrane cholesterol phospholipid ratio and diminished membrane fluidity, which affect a number of canalicular membrane transporters and enzymes including the Na+ and K+ ATPase.[7] Furthermore, dyslipidemia and abnormal lipoprotein metabolism could contribute to hepatic abnormalities, including hepatic steatosis.[6]

Gusson et al 2022, concluded that hypothyroidism, the major consequence of thyroidectomy, causes dysfunction in lipid metabolism and liver enzymes resulting in secondary hyperlipidemia and liver dysfunction. [16] Studies have shown that cellular thyroid hormone transmission disturbances trigger various liver diseases, including non-alcoholic fatty liver disease.[8,15,17]

Nikki Duond et al 2018[18] reported a case of 77 year old woman with hashimotto's thyroiditis who had stopped taking levothyroxine on her own for 6 months. Her TSH levels were consistent with severe hypothyroidism. The following month, her LFTs were significantly elevated. She resumed thyroid replacement therapy. Seven weeks after resumption of therapy, her TSH and liver tests had returned to normal. It may be attributed to mixed hepatocelluar injury to hypothyroidism that resolved on correction of the hypothyroid state. This case reminds that thyroid disease should be considered when evaluating acute liver injury.

The state of low circulating thyroid hormone levels might exert a direct injurious effect on the liver. Mechanisms include hepatic congestion from possible cardiac abnormalities or increased vascular endothelial permeability due to hypothyroidism.[19, 20]

LIMITATIONS OF THE STUDY

Limited generalizability: The study's findings may not be generalizable to populations with different demographics, healthcare settings, or regions. The sample characteristics and context in which the study was conducted should be considered when applying the findings to other populations

CONCLUSION

Liver functions are affected by thyroid status of the body. AST and ALT are raised significantly in hypothyroid conditions. Also, AST and ALT are significantly associated with TSH in the hypothyroid cases. Normal biochemical processes and basal metabolic rate (BMR) within the hepatic cell may be disrupted by abnormal thyroid hormone, which may increase the production of hepatic enzymes, the permeability of the hepatic cell membrane, or both. Furthermore, dyslipidemia and abnormal lipoprotein metabolism could contribute to hepatic abnormalities, including hepatic steatosis. This study is a significant reminder of the importance behind consideration of liver injury due to hypothyroidism. Early detection and treatment can prevent the further complications and will be helpful during management of hypothyroid patients.

CONFLICT OF INTEREST

Author declared no conflict of interest.

REFERENCES

1. S.Y. Lee, E.N. Pearce. Hyperthyroidism. *JAMA* **2023**, 330 (15), 1472.
2. T.Y. Lin, A.O. Shekar, N. Li, et al. Incidence of abnormal liver biochemical tests in hyperthyroidism. *Clin. Endocrinol. (Oxf).* **2017**, 86 (5), 755–759.
3. L. Scappaticcio, M. Longo, M.I. Maiorino, et al. Abnormal Liver Blood Tests in Patients with Hyperthyroidism: Systematic Review and Meta-Analysis. *Thyroid* **2021**, 31 (6), 884–894.
4. L. Chaker, S. Razvi, I.M. Bensenor, et al. Hypothyroidism. *Nat. Rev. Dis. Prim.* **2022**, 8 (1), 30.
5. N. Tewari. Prevalence of hypothyroidism in adults: An epidemiological study in eight cities of India. *Indian J. Endocrinol. Metab.* **2014**, 18 (1), 116.
6. B. Tamang, K. Harijan, B.R. Pokhrel, et al. Liver Function Test Parameters in Hypothyroid Patients Visiting Tertiary Care Center of Western Nepal: A Cross-Sectional Study. *Med Phoenix* **2023**, 8 (1), 68–73.
7. S. Elshinshawy, H. Elhadad, S.A. Alem, O.Shaker. The interrelationship between hypothyroidism and non alcoholic fatty liver disease, a cross sectional study. J Clin Exp Hapatol.**2023**,13(4), 638-648.
8. H.J. Kim. Importance of thyroid-stimulating hormone levels in liver disease. *J. Pediatr. Endocrinol. Metab.* **2020**, 33 (9), 1133–1137.
9. S. Arora, R. Chawla, D. Tayal, et al. Biochemical markers of liver and kidney function are influenced by thyroid function-a case-controlled follow up study in Indian hypothyroid subjects. *Indian J. Clin. Biochem.* **2009**, 24 (4), 370–374.
10. Y.C. Chang, S.C. Hua, C.H. Chang, et al. High TSH level within normal range is associated with obesity, dyslipidemia, hypertension, inflammation, hypercoagulability, and the metabolic syndrome: A novel cardiometabolic marker. *J. Clin. Med.* **2019**, 8 (6).
11. E. Piantanida, S. Ippolito, D. Gallo, et al. The interplay between thyroid and liver: implications for clinical practice. *J. Endocrinol. Invest.* **2020**, 43 (7), 885–899.
12. N.K. Patira, N. Salgiya, D. Agrawal. Correlation of thyroid function test with severity of liver dysfunction in cirrhosis of liver. *J. Assoc. Physicians India* **2019**, 67 (March), 51–54.
13. M.O. Ajala, P.S. Ogunro, O.A. Fasanmade. Relationship between liver function tests and thyroid hormones in thyroid disorders. *Niger. Postgrad. Med. J.* **2013**, 20 (3), 188–192.
14. A. Kyriacou, J. McLaughlin, A.A. Syed. Thyroid disorders and gastrointestinal and liver dysfunction: A state of the art review. *Eur. J. Intern. Med.* **2015**, 26 (8), 563–571.
15. C. Luongo, M. Dentice, D. Salvatore. Deiodinases and their intricate role in thyroid hormone homeostasis. *Nat. Rev. Endocrinol.* **2019**, 15 (8), 479–488.
16. Gusson Al Janabi, Hayder Naemah Hassan, Ali Al Fahham. Biochemical changes in patients during hypothyroid phase after thyroidectomy. *J Med Life*. **2022,** 15(1),104-108.
17. A. Lonardo, S. Ballestri, A. Mantovani, et al. Pathogenesis of hypothyroidism-induced NAFLD: Evidence for a distinct disease entity? *Dig. Liver Dis.* **2019**, 51 (4), 462–470.
18. N. Duong, A. Lee, J. Lewis. Case of acute mixed liver injury due to hypothyroidism. *BMJ Case Rep.* **2018**, 2018, 1–3.
19. N. Sharma, I. Zahoor, S. Singh, et al. Expatiating the pivotal role of Dendrimers as emerging nanocarrier for management of Liver Disorders. *J. Integr. Sci. Technol.* **2023**, 11 (2), 489.
20. K. Ohkubo, K. Ihara, S. Ohga, M. Ishimura, T. Hara. Hypothyroidism and levothyroxine-responsive liver dysfunction in a patient with ring chromosome 18 syndrome. *Thyroid* **2012**, 22 (10), 1080–1083.