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ORIGINAL ARTICLE

LIVER FUNCTION TEST PARAMETERS IN HYPOTHYROID PATIENTS VISITING TERTIARY CARE CENTER OF WESTERN NEPAL: A CROSS-SECTIONAL STUDY

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ABSTRACT

Introduction: *Due to the complicated interactions between the thyroid gland and liver, thyroid hormone dysfunction may affect the liver function tests, and could be of clinical importance. We aimed to compare the hepatic function parameters between hypothyroid and euthyroid patients visiting tertiary care center of western Nepal.*

Methods: *This hospital-based cross-sectional study was conducted among 113 hypothyroid and 111 euthyroid patients. After consent, thyroid function and liver function parameters were analyzed using automated analyzers. Mann-Whitney U test, Spearman's correlation, and multiple linear regression analysis were performed for analysis. A p-value of <0.05 was considered statistically significant.*

Results: *Among hypothyroid group, the majority were subclinical hypothyroid (n=74, 65.49%) and the rest (n = 39, 34.51%) were overt hypothyroid. The serum bilirubin and liver enzymes levels were significantly higher in hypothyroid compared to euthyroid. The serum albumin levels were significantly lower in the hypothyroid group. Serum liver enzymes and bilirubin levels were correlated negatively and positively with the thyroid hormones (fT_3, fT_4) and TSH levels, respectively.*

Conclusions: *Patients with hypothyroidism and euthyroid patients had significantly different liver function test results. Although serum albumin was lower in the hypothyroid group, serum bilirubin and liver enzymes were higher.*

Keywords: *Hypothyroidism, Liver Function Test, Thyroid Function Test*

INTRODUCTION

Thyroid hormones are essential for the normal growth and development of the body. Both hypothyroidism and hyperthyroidism alter normal body physiology and metabolism.[1,2] There is a complex relationship between the thyroid gland and liver, both in health and disease. The liver plays a role in thyroid hormone activation and inactivation by the seleno-deiodinase enzyme system.[3]It also contributes to the bioavailability of thyroid hormones by synthesizing transport proteins such as thyroxine-binding globulin, transthyretin, and albumin. Reciprocally, thyroid hormones also contribute to hepatic metabolic activities through various mechanisms. They contribute to bilirubin production and composition and also have a direct pro-relaxing effect on Oddi's sphincter.[3-5]

Numerous investigations have demonstrated that hypothyroidism may be associated with the pathogenesis of hepatic diseases.Dysfunctions in the thyroid hormone status may influence the liver function test (LFT) parameters directly or indirectly.[6-8] The proper evaluation of hepatic functions in patients with thyroid disorders might be of clinical relevance for undertaking preventive and therapeutic strategies. Limited studies have been reported from Nepal regarding this. Therefore, our study aimed to find out alterations in LFT parameters in hypothyroidism patients visiting the tertiary care center of Western Nepal.

MATERIALS AND METHODS

This hospital-based cross-sectional comparative study was conducted by the Department of Biochemistry in collaboration with the Internal Medicine Department of Universal College of Medical Sciences (UCMS), Bhairahawa, Rupandehi district of Province number 5, Nepal. Ethical approval was obtained from the Institutional Review Committee (IRC) of UCMS (IUCMS/IRC/179/21) before the study. The study duration was six months from January 2022 to June 2022.

The study populations included the hypothyroid and euthyroid patients (>15 years) visiting internal medicine OPD for the evaluation of the thyroid and liver function tests (TFT and LFT) in the biochemistry laboratory of UCMS. Prior to enrollment, the objectives and benefits of the study were explained to the traced participants. Pregnant women, patients with hepatic abnormalities, chronic alcoholism, and diseases that alter serum LFT parameters like liver cirrhosis, bone disease, cardiovascular diseases, diabetes mellitus, renal disease, and pneumonia were excluded. Furthermore, those taking drugs that alter the LFT and TFT parameters like phenylbutazone, aspirin, oral contraceptives, steroids, and amiodarone, lithium, propylthiouracil, respectively were also excluded. Both verbal and written consent was obtained from the patients.

Sample size was calculated by using Cochran's formula Z^2PQ/d^2, where z =1.96, P = prevalence of hypothyroidism (20.29%),[9] Q = 100-P, d = allowable error (7.5%). From the above calculation, the estimated sample for each group was 111. Finally, 113 hypothyroid and 111 euthyroid patients were considered. A purposive sampling technique was used for the collection of data, and subject proforma was encoded for confidentiality. The proforma included socio-demographic data, and TFT & LFT parameters. Following standard aseptic conditions, five ml of blood was collected in plain vials. The serum was collected by centrifugation at 3000 rpm for 10 minutes. The sample was stored at -20° C until the analysis. The thyroid function parameters (fT_3, fT_4, and TSH) and the liver function tests [serum bilirubin, albumin, total protein, alanine transaminase (ALT), aspartate transaminase (AST), and alkaline phosphatase (ALP) were analyzed.

The thyroid function tests were estimated by chemiluminescence assay (Maglumi 2000 fully automated analyzer) and the LFT panel tests were analyzed by automated Humastar 600 analyzer. Serum bilirubin, albumin, total protein, and liver enzymes were estimated by modified Jendrassik-Groff method, bromocresol green (BCG) method, modified biuret method, and kinetic assay, respectively. The reference ranges for the laboratory parameters were considered as per the manufacturer's manual. They were as follows: serum total bilirubin: 0.1-1.2 mg/dl, direct bilirubin: 0-0.2 mg/dl, indirect bilirubin: 0.2-0.8 mg/dl, total protein:6.0-8.0 g/dl, albumin: 3.5-5.3 g/dl, AST: < 35U/L, ALT: < 45 U/L, ALP: 80-306 U/L, fT_3: 2.0 – 4.2 pg/ml, fT_4: 8.9 – 17.2 pg/ml and TSH: 0.3- 4.5µIU/L. Patients were categorized as hypothyroid and euthyroid based on the reference ranges of TFT. Furthermore, overt hypothyroidism was diagnosed as high TSH and low fT_4 levels. Similarly, sub-clinical hypothyroidism was diagnosed as high TSH and normal fT_4 levels.[10]

Data were introduced in Microsoft Excel and then analyzed by Statistical Package for Social Service (SPSS) for windows version 22. Categorical data were expressed in percentage and frequency. Numerical data were expressed as median and interquartile range. Since the numerical data deviated significantly from normality, as depicted by the Shapiro-Wilk test, non-parametric tests were used for the analysis. Specifically, the Mann-Whitney U test, Spearman's correlation, and multiple regression analyses were performed. P-value < 0.05 was considered statistically significant.

RESULTS

Of the 224 patients, 113 (50.45%) were hypothyroid and 111(49.55%) were euthyroid. The median age of the participants was 41 years (28-52 years). The majority of the participants were females (n = 159; 70.98%). The sex-wise distribution of the study population in each group is shown in figure 1. Among the 113 hypothyroid patients, the majority were subclinical hypothyroid (n =74; 65.49%), and the rest were overt hypothyroid (n = 39; 34.51). The female preponderance was observed in both hypothyroid sub-groups, with 79.7% prevalence in the sub-clinical and 71.8% in the overt sub-group.

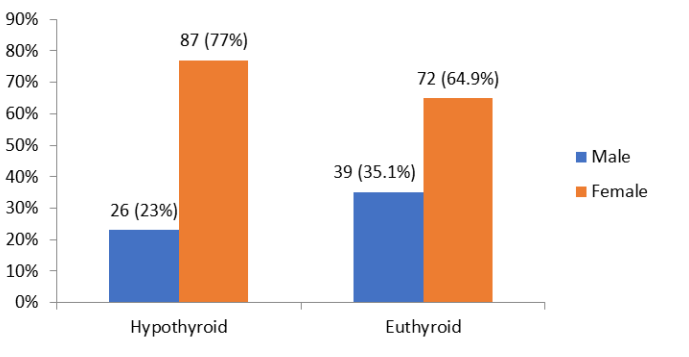

Figure 1: Sex-wise distribution of the study participants (N = 224)

The serum levels of total bilirubin, indirect bilirubin, AST, ALT, and ALP were significantly higher in hypothyroid compared to the euthyroid patients. The serum albumin

levels were significantly lower in the hypothyroid patients than euthyroid patients. Even after adjusting for the possible confounding effects of age and sex, all the LFT parameters except total protein were significantly differencebetween the hypothyroid and euthyroid groups (Table 1). Among the hypothyroid sub-groups, the serum liver enzymes were significantly higher in the overt hypothyroid patients (Table 2). Furthermore, all the LFT parameters except total protein correlated significantly with the TFT parameters. The correlation was positive for TSH and negative for the thyroid hormones (fT_3 and fT_4) and ranged from very weak to moderate (Table 3).

Table 1: Liver function test parameters within the thyroid group

LFT parameters	Total participants	Thyroid group		Unadjusted P-value	Adjusted P-value
		Hypothyroid	Euthyroid		
Total bilirubin(mg/dl)	0.7 (0.5-0.9)	0.8 (0.5-1.0)	0.5 (0.4-0.8)	<0.001	<0.001
Direct Bilirubin (mg/dl)	0.2 (0.2-0.3)	0.2 (0.2-0.35)	0.2 (0.2-0.3)	0.001	0.002
Indirect Bilirubin (mg/dl)	0.4(0.3-0.6)	0.5 (0.3-0.6)	0.3 (0.2-0.5)	<0.001	0.002
Total Protein (g/dl)	7.0 (6.6-7.4)	7.0 (6.6-7.3)	7.0 (6.6-7.4)	0.311	0.099
Albumin (g/dl)	4.3 (4.0-4.5)	4.1 (3.9-4.5)	4.3 (4.1-4.5)	0.005	0.042
AST (IU/L)	33 (24-45)	43 (30-52)	27 (22-36)	<0.001	<0.001
ALT (IU/L)	27 (18-39)	32 (21-44)	22 (17-32)	<0.001	0.003
ALP (IU/L)	236.7 (181.3-301.5)	267.6 (205.2-343.4)	214.1 (156.1-254.2)	<0.001	<0.001
Unadjusted p-values obtained from Mann-Whitney U Test. Adjusted p-values obtained from multiple regression analysis (outcome variables LFT parameters. Adjusted for age and sex). P < 0.05 considered statistically significant.					

Table 2: Liver function test parameters within the subclasses of hypothyroid group

LFT parameters	Hypothyroid subgroup		P-value
	Sub-clinical	Overt	
Total bilirubin(mg/dl)	0.75 (0.5-1.0)	0.8 (0.5-1.0)	0.981
Indirect Bilirubin (mg/dl)	0.25 (0.2-0.4)	0.2 (0.2-0.3)	0.555
Direct Bilirubin (mg/dl)	0.5 (0.3-0.6)	0.5 (0.3-0.6)	0.687
Total Protein (g/dl)	7.0 (6.5-7.4)	7.0 (6.6-7.2)	0.827
Albumin (g/dl)	4.1 (3.9-4.6)	4.0 (3.8-4.4)	0.285
AST (IU/L)	40 (27-50)	46 (37-56)	0.028
ALT (IU/L)	28 (18-41)	41 (27-46)	0.015
ALP (IU/L)	258.7 (200.7-334.5)	316.7 (240.8-359.0)	0.046
P-values obtained from Mann-Whitney U Test. P < 0.05 considered statistically significant.			

Table 3: Correlation of liver function tests parameters with thyroid function test parameters

VARIABLES		fT3	fT4	TSH
Total Bilirubin (mg/dl)	ρ	-0.202	-0.250	0.310
	P-value	0.002	<0.001	<0.001
Direct Bilirubin (mg/dl)	ρ	-0.147	-0.197	0.222
	P-value	0.027	0.003	0.001

Indirect Bilirubin (mg/dl)	ρ	-0.212	-0.256	0.319
	P-value	0.001	<0.001	<0.001
Total protein (g/dl)	ρ	0.052	0.047	-0.085
	P-value	0.435	0.482	0.204
Albumin (g/dl)	ρ	0.215	0.175	-0.191
	P-value	0.001	0.009	0.004
ALT (IU/L)	ρ	-0.255	-0.298	0.332
	P-value	<0.001	<0.001	<0.001
AST (IU/L)	ρ	-0.364	-0.393	0.443
	P-value	<0.001	<0.001	<0.001
ALP (IU/L)	ρ	-0.286	-0.407	0.403
	P-value	<0.001	<0.001	<0.001

ρ = correlation coefficient. P- values obtained from Spearman's correlation analysis. P < 0.05 considered statistically significant.

DISCUSSION

In our study, all the LFT parameters (serum liver enzymes, albumin, and bilirubin levels) were significantly different between the hypothyroid and euthyroid patients, except for serum total protein, which was comparable between both groups. Serum liver enzymes and bilirubin levels were higher in the hypothyroid groups, whereas serum albumin levels were lower in the hypothyroid groups. The results were similar even after adjustment for the possible confounding effects of age and sex. Furthermore, the correlation analysis showed a significant association between LFT and TFT parameters. Serum liver enzymes correlated negatively and positively with the thyroid hormones and TSH levels, respectively.

Ajala MO et al. reported increased bilirubin and liver enzymes in both hypothyroid andhyperthyroid patients.[11] In a retrospective study by Targher G et al. hypothyroidism was associated with increased serum ALT levels.[12] In contrast, Arora S et al. reported no significant difference in serum bilirubin and liver enzymes between hypothyroid and euthyroid patients. However, the serum liver enzymes decreased in the patients after six weeks of thyroxine replacement therapy.[13]Saha B et al. concluded that elevated serum liver enzymes might not be as common as previously postulated. In their study, 37% and 35% of the primary hypothyroid patients had elevated AST and ALT levels, respectively.[14]

Thyroid abnormalities in hepatic diseases are the subject of numerous studies,[15-17] whereas hepatic dysfunctions in thyroid disorders have been studied selectively, especially when serum aminotransferase levels are concerned. Regarding the latter, findings from some studies were similar to ours,[11,12] yet many other studies were distinguishably diverse.[13,14] These disparities could at least partly be explained by the differences in estimation methods and uses of varied cut-off values. Furthermore, variations in patient characteristics owing to diverse geographies and ethnicities could also contribute.

Hepatic and thyroid activities interact with one another.[3,18] The role of the liver in thyroid hormone activation, transportation, and metabolism has already been established.[3,19]Similarly, the role of thyroid hormones in hepatic function can have multiple explanations. Thyroid hormones play a significant role in cell metabolism throughout the body. Studies have shown that cellular thyroid hormone transmission disturbances trigger various liver diseases, including non-alcoholic fatty liver disease (NAFLD).[8,20,21]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.[22] Furthermore, dyslipidemia and abnormal lipoprotein metabolism could contribute to hepatic abnormalities, including hepatic steatosis.[23] However, it is still difficult to assess whether these alterations in the LFT parameters in the dysthyroid population translate to clinically significant levels. Further molecular studies and clinical trials are necessary before establishing a clinical mandate of whether hepatic function assessment in patients with thyroid disorders and vice versa.

CONCLUSION

The LFT parameters were significantly different between hypothyroid and euthyroid patients. Serum bilirubin and liver enzymes were higher whereas serum albumin levels were lower in the hypothyroid group.

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