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Thyroid Function Test Abnormalities in Patients with Liver Cirrhosis

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Abstract

Introduction: Liver plays a central role in thyroid hormone metabolism. A normal function of both the thyroid gland and the liver is therefore necessary to maintain normal thyroid hormone levels and action. This study was done to find the thyroid function test (TFT) abnormalities in patients presenting with liver cirrhosis. **Methods:** This was a single centre hospital based, cross-sectional observational study carried out from 21 April 2019 to 20 October 2019 in the Department of Internal Medicine, Universal College of Medical Sciences-Teaching Hospital (UCMS-TH), Bhairahawa, Nepal. All the patients presented with liver cirrhosis during the study period after using inclusion and exclusion criteria were included in the study. Data was collected as per predesigned proforma and TFT level (free T3, free T4 and TSH) was done. **Results:** Total 110 patients with liver cirrhosis and 110 healthy controls were enrolled in this study with mean age of 51.1±12.13 years and Male : Female ratio of 4:1. According to Child Pugh score (CPS) 62 (56.36%) patients were in Class C, 35 (31.82 %) patients were in Class B. Low level of FT3 was seen in 27 (24.6%) patients, low level of FT4 was in 11 (10 %) patients and high TSH level was seen in 25 (22.7 %) patients. Overall abnormal TFT levels were seen in 43 (39.1 %) patients. Among these overt hyperthyroidisms was seen in 3 (2.7%) patients, subclinical hypothyroidism was seen in 14 (12.7%) patients, overt hypothyroidism was seen in 11 (10%) patients. Isolated low FT3 level was seen in 15 (13.6%) patients. Correlation between AST ALT and ALP were found to be statistically significant with both FT3 and FT4. Correlation between different CPS categories was found to be statistically significant with mean score of FT3 (p=0.0048), and mean score of FT4 (p=0.045). **Conclusions:** Overall abnormal thyroid hormone levels were seen in 39.1 % patients with liver cirrhosis. Correlation between AST ALT and ALP were found to be statistically significant with both FT3 and FT4. So all the cirrhotic should be evaluated for thyroid dysfunction for early diagnosis and timely treatment.

Key Words: Hypothyroidism; liver Cirrhosis; thyroid dysfunction.

INTRODUCTION

Liver cirrhosis is an end result of a variety of liver diseases characterized by fibrosis and architectural distortion of the liver with the formation of regenerative nodules. It is a leading cause of morbidity and mortality worldwide. The Global Burden of Disease (GBD) reported that over one million people died due to cirrhosis in 2010 worldwide, compared with 676,000 deaths in 1980.[1] Thyroid hormone is very important in the growth and development in adults, and plays a critical role in the regulation of the function and metabolism of almost every organ system.[2,3] The liver plays a central role in thyroid hormone metabolism, transport, and clearance by producing thyroid binding globulin, albumin and transthyretin.[4] Liver is also the most important for the peripheral conversion of thyroxine (T4) to triiodothyronine (T3) by Type 1 deiodinase.[5] A normal function of both the thyroid gland and the liver is therefore necessary to maintain normal thyroid hormone levels and action.

T4 is secreted from the thyroid gland in about twenty-fold excess over T3 and both hormones are mostly bound to plasma proteins.[6] Thyroid diseases

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may perturb liver function; liver disease modulates thyroid hormone metabolism; and a variety of systemic diseases affect both the organs. Patients with chronic liver disease may have thyroiditis, hyperthyroidism, or hypothyroidism. Patients with subacute thyroiditis or hyperthyroidism may have abnormalities in liver function tests.[7]

Data regarding thyroid function abnormalities in patients with liver cirrhosis are variable and scarce from this part of world. So, this study was done to find the TFT abnormalities in patients presenting with liver cirrhosis and to look for any correlation between TFT abnormalities and severity of liver disease.

METHODS

This was a single centre hospital based, cross-sectional observational study. Study was carried out from 21 April 2019 to 20 October 2019 in the Department of Internal Medicine, Universal College of Medical Sciences, Bhairahawa, Nepal. The study protocol was approved by the Institutional Review Committee and written informed consent was taken from all the participants. All the patients aged more than 16 years presented with liver cirrhosis in the internal medicine department of UCMS-TH during the study period were included in the study. Patients who refused to give consent or age up to 16 years were excluded.

Similarly Patients with pregnancy, previously known thyroid disease, diabetes, nephrotic syndrome renal failure or any other acute or chronic illnesses were excluded. Patient receiving drugs that may interfere with thyroid hormone metabolism and function like amiodarone, phenytoin, β- blocker, steroids, estrogen and iodine containing drugs/contrast were also excluded.

Equal number of healthy age and sex matched controls were also taken. A detailed history including history suggestive of hypothyroidism, hyperthyroidism and liver cirrhosis was taken in all the patients as per predesigned proforma. Each patient was also subjected to a detailed clinical examination. Special attention was given to pallor, icterus, edema, hydration status, asterixis, stigmata of chronic liver disease like alopecia, spider naevi, parotid enlargement, palmar erythema, gynaecomastia and testicular atrophy. Detailed thyroid, abdominal and neurological examination was done in all cases. After cleaning the site with rectified spirit swab, a tourniquet and a 5 ml syringe were used to draw 5 ml of blood and the following investigations were done in all the cases: complete blood count, glucose, liver function test (LFT), renal function test (RFT), hepatitis B surface antigen, hepatitis C virus antibodies and thyroid function tests. LFT includes total bilirubin, direct bilirubin, alanine transaminase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP) total protein and albumin level. LFT and RFT, was measured by using Humastar 600 fully automated biochemistry analyser, (Human diagnostics, Germany). TFT included measurement of free T3 (FT3), free T4 (FT4) and thyroid stimulating hormone (TSH). For TFT the samples of blood were allowed to stand to clot. Serum was separated by centrifugation. Serum FT3, FT4 and TSH were measured by chemiluminescence immunoassay technique (CLIA) with Maglumi 2000 analyser (Snibe diagnostic, Shenzhen, China). Thyroid hormone abnormalities were made if patients thyroid hormones were outside the normal values; FT3 (2.0-4.2 pg/ml), FT4 (8.9-17.2 pg/ml) and TSH (0.3-4.5 mIU/ml). After keeping the patient nil per oral for 4 hours, patients underwent ultrasonography of abdomen and pelvis. The focus was mainly in the liver size, echotexture, portal vein diameter, presence of collaterals, gall bladder, common bile duct, spleen size, abdominal collection, renal size, echotexture and corticomedullary differentiation. Severity of liver cirrhosis was categorised by Child Pugh score (CPS).

All the statistical analysis was performed using SPSS Version 20 (IBM Corp.) and Microsoft Excel 2016. Categorical data were presented as frequencies and corresponding percentages. Quantitative data were presented in mean ± SD.

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Correlation between TFT with various biochemical parameters were calculated by using Pearson correlation. ANOVA test was used to compare the TFT level with CPS categories. The level of significance for all analytical test were set at 0.05 and 'p-value < 0.05 was considered significant

RESULTS

Total 110 participants with liver cirrhosis were enrolled in this study and analysed statistically. Baseline characteristics and the demographic profile of the study subjects in the Group 1 are depicted in table 1. Mean age of patients was 51.1±12.13 years (Range: 32 yrs to 94 years). Most of our patients were adults in their fifth and sixth decade of life and together they constituted 63% (n=69) of total study population. Males were 4 times more commonly affected with liver cirrhosis then females in the present study (M:F ratio 4:1) (Table 1).

Table 1: Demographic characteristics of patients with liver cirrhosis

Characteristics	N (%)
Age (yrs)	
31-40	22 (20)
41-50	38 (34.55)
51-60	31 (28.18)
61-70	12 (10.91)
>70	7 (6.36)
Sex	
Male	88 (80%)
Female	**22 (20%)**
Demographic data	
Rupandehi	50 (45.45%)
Kapilvastu	18 (16.36%)
Nawalparasi west	9 (8.18%)
Dang	9 (8.18%)
Gulmi	7 (6.36%)
Pyuthan	5 (4.55%)
Palpa	5 (4.55%)
Arghakhachi	4 (3.64%)
Rolpa	2 (1.82%)
Parbat	1 (0.91%)

Patients included in the present study were from 10 nearby districts from the study site. Rupandehi, Kapilvastu, Dang and Nawalparasi west were the four most common districts respectively which constituted 78,18% of the total study population (table 1). Ethnically, majority of the patients 51.82% (n=57) were janjatis, followed by dalits 17.27% (n=19), chettris 10.21% (n=12), madhesis 10.21% (n=12), brahmins 7.27% (n=8) and muslims 1.82% (n=2) respectively. Majority of patients 29.09% (n=32) were farmers by occupation, followed by shopkeepers 20.91% (n=23), businessmen 12.73% (n=14), housewives 9.09% (n=10), driver 9.09% (n=10), servicemen 8.18% (n=9), retired army men 8.18% (n=9) and labourers 2.73% (n=3).

The most common cause of cirrhosis was ethanol ingestion which was found in 97 (88.18%) patients. Chronic hepatitis B infection was the second most common cause which was seen in 8 (7.27%) patients followed by chronic hepatitis C infection in 3 (2.73%) patients. The cause of cirrhosis was unknown in 2 (1.81%) patients. Clinical and laboratory characteristics are given in table 2.

Table 2: Clinical and lab characteristics of the patients

Parameters	Mean±SD
Pulse (Beats/min)	91.49±14.09
SBP (mmHg)	113.67±18.98
DBP (mmHg)	72.30±13.45
BMI (Kg/M2)	21.98±2.61
Haemoglobin (g/dl)	9.37±2.72
TLC (/cu.mm)	10380±801.76
Platelets (/Cu.mm)	98227.27±36206
Na (meq/dl)	137.15±3.97
K (meq/dl)	3.95±0.69
INR	1.59±0.59
Serum Urea (mg/dl)	32.96±7.63
Serum Creatinine(mg/dl)	0.88±0.43
Total Protein (mg/dl)	6.45±0.68
Albumin(mg/dl)	3.31±0.39
Total Bilirubin (mg/dl)	4.20±4.07
AST (IU/L)	158.77±89.42
ALT (IU/L)	85.73±78.23
Alkaline phosphatise (IU/L)	250.75 ±106
Duration of hospital Stay (days)	5.56 ±2.59

The patients were grouped according to CPS for the severity of liver cirrhosis, in which 62 patients (56.36%) were in Class C, 35 patients (31.82 %) were in Class B and remaining 13 patients (11.82%) were in Class A (Figure 1). Majority of our patients were in class C which shows that they were in advance stage of liver disease.

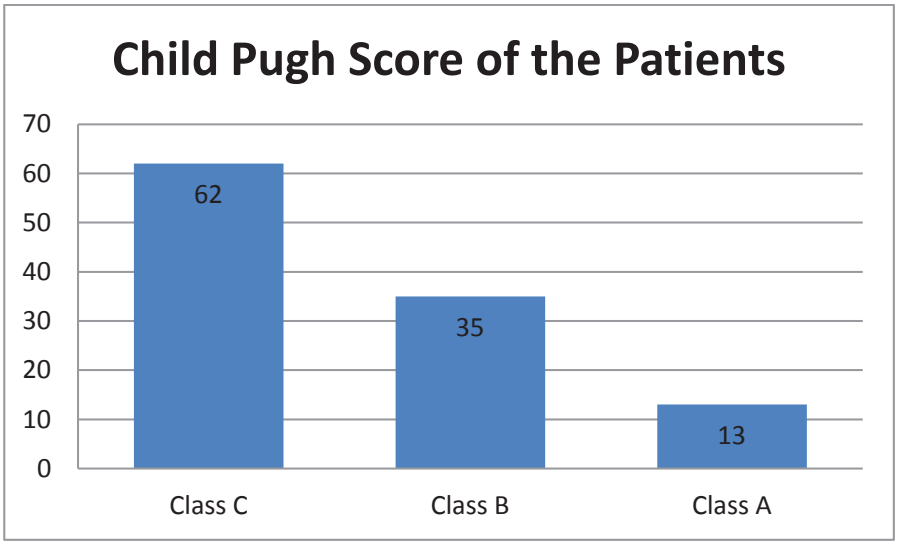

Figure 1: Distribution of patients according to Child Pugh Score

Table 3: Mean value of thyroid function test in liver cirrhotics

Thyroid Function Test	Mean±SD	Reference range
Free T3 (pg/ml)	2.53±0.78	(2.0-4.2)
Free T4 (pg/ml)	12.19±2.60	(8.9-17.2)
TSH (µIU/ml)	4.18±3.98	(0.3-4.5)

The mean value of FT3 was 2.53±0.78 pg/ml with minimum of 1.16 pg/ml and maximum 5.97 pg/ml. The low level of FT3 was seen in 27 (24.6%) patients out of which 23 patients were male and 4 female and high level of FT3 was seen in 3 (2.7 %) patients. The mean value of FT4 was 12.19±2.60 pg/ml with range of 5.59 to 21.41 pg/ml. In our study, 11 (10 %) patients had low FT4 level and 3 (2.7 %) patients had high FT4 level. Out of 11 patients with low FT4, 9 were male and 2 were female. The low level of both fT3 and fT4 was seen in 9 (8.18%) patients. The mean value of TSH was 4.18±3.98 µIU/ml with range of 0.024 to 25.61 µIU/ml. Serum TSH level was abnormal in 28 (25.5%) patients. Among these 28 patients, 25 (22.7 %) had high level of TSH and 3 (2.7 %) had low level of TSH (table 3 and 4).

Table 4: Abnormal thyroid hormone level

		Creatinine	Total bilirubin	AST	ALT	ALP	Total Protein	Serm Albumin	PT	INR
FT3	Pearson Correlation	.178	.015	.241*	.218*	.227*	-.064	.022	-.077	-.072
	P-value	.063	.878	.011	.022	.017	.510	.818	.425	.456
FT4	Pearson Correlation	.078	.037	.286**	.240*	.194*	-.186	-.036	-.152	-.094
	P-value	.420	.699	.002	.011	.042	.052	.706	.115	.331
TSH	Pearson Correlation	.024	-.008	-.063	-.017	.003	-.026	-.027	.006	-.072
	P-value	.803	.935	.510	.863	.971	.789	.781	.947	.453

We also compared mean score of FT3, FT4 and TSH with CPS score by using ANOVA test. It was seen that mean score of FT3 with different CPS categories was found to be statistically significant (p=0.0048). Similarly Mean score of FT4 with different CPS categories was found to be statistically significant (p=0.045). Mean score of TSH with different CPS category was found to be statistically insignificant (p=0.308) (table 6).

Table 6: Correlation between FT3 FT4 and TSH with different CPS categories

Thyroid function		N	Mean	Sandard Deviation	F-value	P-value
Free T3	CPS A	13	2.85	.801	5.59	0.0048
	CPS B	35	2.80	.994		
	CPS C	62	2.31	.642		
	Total	110	2.53	.821		
Free T4	CPS A	13	13.77	2.774	3.1882	0.045
	CPS B	35	12.31	2.908		
	CPS C	62	11.82	2.265		
	Total	110	12.21	2.595		
TSH	CPS A	13	2.69	2.10	1.1903	0.308
	CPS B	35	4.06	4.21		
	CPS C	62	4.59	4.28		
	Total	110	4.19	4.08		

DISCUSSION

The thyroid gland produces three hormones T3, T4 and calcitonin. These hormones play an important role in cell differentiation and also help to maintain thermogenic and metabolic homeostasis in the body. Thyroid hormone secretion is controlled by TSH secreted from the anterior pituitary gland, which itself is regulated by thyrotropin-releasing hormone (TRH) produced by the hypothalamus. T4 is secreted twenty

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times in excess over T3 from the thyroid gland. Both hormones are bound to plasma proteins, including thyroxine-binding globulin, transthyretin and albumin.8 The liver has an important role in thyroid hormone metabolism because it manufactures the proteins that bind thyroid hormone. It is also one of the major sites of peripheral metabolism of thyroid hormone and is involved in its conjugation, biliary excretion, oxidative deamination and the extrathyroidal deiodination of T4 to T3 and to reverse T3 (rT3).6 This peripheral conversion is accomplished by two enzymes, the type 1 (D1) and type 2 (D2) deiodinases. A third deiodinase, type 3 deiodinase (D3) participates in the clearance of both serum T4 and T3.9 D1 is expressed predominantly in liver and kidney and contribute approximately 24% of circulating T3 in healthy individuals. In some chronic systemic disease like hepatic cirrhosis rT3 increases simultaneously with the decrease of T3 level. Therefore, one can describe particular alteration of thyroid pattern of chronic liver disease; low T3 syndrome, low T3 and T4 syndrome or high T4 syndrome mixed form.[10]

Mean age of our patients was 51.1 years with males 4 times more commonly affected with liver cirrhosis then females. This is similar to study done by Patira NK et al. where majority of patients 72% belonged to age group 41-60 years with male predominance (78%).[10] Similar results were seen in other study done by Punekar et al. in Jabalpur where males (71%) were involve more than female.[11] The most common cause of cirrhosis in our study was ethanol ingestion which was found in 88.18% patients followed by hepatitis B and C infection. Findings are similar to another study from Rajasthan, India where also the most common etiology of liver cirrhosis was alcoholism which was seen in 70% patients followed by hepatitis B related cirrhosis.[10] This can be explained by the fact that ethanol consumption is predominantly seen in young males then females which leads to alcohol related problem occurring more in males then females. In our study, patients presented to us in the late stages of cirrhosis. According to CPS, most of our patients (56.36%) were in Child-Pugh class C followed by 31.82 % in Child-Pugh class B and remaining 11.82% were in Child-Pugh class A. This shows that most of our patients presented to us in advanced stage of decompensated cirrhosis of liver. Similar result was seen in the study carried out in Lucknow where 56.86% patients were classified as Child-Pugh class C, 39.22% were classified as Child-Pugh class B and rest of 3.92% were classified as Child-Pugh class A.[12] This can be explained by the fact that patient comes late to health facilities in developing country may be because of poor socio-economic condition and poor health insurance coverage. Overall abnormal TFT levels were seen in 39.1 % patients with hypothyroidism in 25% patients. Similar results were seen in another study where hypothyroidism was seen in 21.6% patients.[13] The low T3 syndrome has frequently been reported in patients with chronic liver disease. The low level of FT3 was seen in 24.6% patients in our study. Whereas in another study low free T3 levels were found in 67.8% (n=19/28) of patients with hepatitis B related cirrhosis, 54.5% (n=6/11) of patients with hepatitis C related cirrhosis, 67.6% (n=23/34) of patients with alcoholic cirrhosis and 83.8% (n=26/29) patients with cryptogenic cirrhosis.13 This is in contrast to the prevalence of hypothyroidism in the general population has been estimated 4.6% by the National Health and Nutrition Examination Survey (NHANES III).[14] In our study mean score of FT3 with different CPS categories was found to be statistically significant (p=0.0048). Similarly Mean score of FT4 with different CPS categories was found to be statistically significant (p=0.045). Similarly in the study done by Patira et al. has found association between serum T3 and CPS categories (p value 0.00).[10]

Certain potential limitations of this study should be noted. The present study was a single-centred hospital based study with small sample size so results obtained in this study can not be generalised. There is a potential for referral bias as the study was performed at a tertiary care center. In future, we need multi centric study with larger sample size. Another limitation of the present study is that liver cirrhosis was diagnosed based

on clinical, biochemical and radiological ground and liver biopsy was not done to confirm liver cirrhosis due to logistic constrains and as it is an invasive procedure. Detailed work up for thyroid profile like reverse T3 and thyroid antibodies lie thyroperoxidase antibody, thyroglobulin were also not carried out. Despite these limitations, there are several strengths in our study. This study has shown a significantly high prevalence of thyroid dysfunction in patients with liver cirrhosis. Which further indicate the association between thyroid dysfunction and liver cirrhosis.

CONCLUSIONS

Overall abnormal thyroid hormone level was seen in 39.1 % patients with liver cirrhosis. Most of these patients have various degree of hypothyroidism. Isolated low Free T3 was seen in significant number of patients. Correlation between AST ALT and ALP were found to be statistically significant with both FT3 and FT4. Correlation between different CPS categories was found to be statistically significant with the mean score of FT3, and the mean score of FT4. So all the liver cirrhotic patients should be evaluated for thyroid dysfunction for early diagnosis and it's management.

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