ISSN: 0975-3583,0976-2833 VOL15, ISSUE 10, 2024

ORIGINAL RESEARCH

Assessment of thyroid profile in patients of cirrhosis of liver

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Received: 25 August, 2024 Accepted: 17 September, 2024

Abstract
Background: Liver cirrhosis is associated with various clinical symptoms and consequences. Liver illness affects the metabolism of thyroid hormones and can interfere with thyroid function. Thus, the present study focused to evaluate the thyroid function tests in patients with cirrhosis of liver and to assess the severity of liver dysfunction in relation with interpretation of thyroid functions.
Methods: A total of 120 patients with liver cirrhosis were selected and thyroid levels were measured in them. The disease was categorized using CTP and MELD scoring methods.
Results: According to Child Turcotte Pugh score; out of total 120 study subjects, 11.7% (n=14) study subjects belonged to CTP class A; 32.5% (n=39) study subjects belonged to CTP class B and 55.8% (n=67) belonged to CTP class C. Out of total 120 study subjects who were distributed amongst CTP class A, B and C, Free T3 levels < 2.28 pg/mL was reported maximum in Class C as compared to B and A which was statistically significant as $p<0.05$. No thyroid dysfunction was reported among 23.3% (n=28) of the subjects. No significant association was found between higher MELD Na score and prevalence of thyroid dysfunction.
Conclusion: The thyroid profile can be used as a prognostic indicator in cirrhotic patients, and increased TSH levels may indirectly help in identifying patients with poor prognosis.
Keywords: Thyroid, CTPS, MELD, Liver, Cirrhosis

Introduction

Liver cirrhosis has been described histopathologically and is associated with numerous clinical symptoms and consequences. The common causes of liver illness are alcoholic liver disease, nonalcoholic steatohepatitis, viral hepatitis, Wilson disease, hemochromatosis, autoimmune hepatitis, primary sclerosing cholangitis, primary biliary cholangitis, and autoimmune hepatitis. The diagnosis of liver disease is made using a panel of laboratory tests, diagnostic imaging, and liver biopsy.[1] Grading is also used to categorize the disease into mild, moderate and severe. The common methods of scoring the disease are CTPS (Child-Turcotte- Pugh score) and MELD (Model for End-Stage Liver Disease). The liver being a key organ in the metabolism of thyroid hormones because Type 1 deiodinase converts thyroxine (T4) to triiodothyronine (T3) in the periphery.[2-3]Liver illness affects the metabolism of thyroid hormones and can interfere with thyroid function. Both of these organs

ISSN: 0975-3583,0976-2833 VOL15, ISSUE 10, 2024

are affected by a range of systemic disorders. Thyroid and liver illnesses are associated in both clinical and laboratory settings. Despite the fact that research on the nature and severity of thyroid dysfunction in cirrhosis varies throughout populations, the present study was done to evaluate the thyroid function tests in patients with cirrhosis of liver and to assess the severity of liver dysfunction in relation with interpretation of thyroid functions.

Materials and Methods

The present cross sectional study was conducted at Sri Guru Ram Das Institute of Medical Sciences and Research, Sri Amritsar among 120 subjects aged 18 years or above with clinical, biochemical and radiological evidence of cirrhosis of liver after obtaining their informed consent. A total of 120 patients with liver cirrhosis were enrolled after getting their detailed history including past, treatment and personal history.

Inclusion criteria

- Patients with clinical, biochemical and radiological evidence of cirrhosis of liver

Exclusion criteria

- Diabetes
- Pregnancy
- Patient receiving drugs that may interfere with thyroid hormone metabolism and function -propylthiouracil, methimazole, carbimazole.
- Patient with any other chronic illness (except liver cirrhosis)

Thyroid levels were analysed using electro chemiluminiscence assay. These levels were compared with CTP Score and Meld-Na score.

Meld Na score and mortality

Meld-Na Score	90 day mortality
<17	<2%
17-20	3-4%
21-22	7-10%
23-26	14-15%
27-31	27-32%
>=32	65-66%

Statistical methods

The recorded data was compiled and analysed using SPSS version 23. (SPSS Inc., Chicago, Illinois, USA). Percentages and Pearson chi-square test was calculated. The level of confidence interval and p-value were set at 95% and 5%.

Results

Out of 120 subjects, maximum number of subjects belonged to age group of 41-50 years (31.67%) (n=38) followed by study subjects >60 years of age (28.33%) (n= 34), 51-60 years (24.17%) (n=29) and 12.50% (n=15) belonged to 31-40 years of age respectively. Least number of subjects i.e. 3.33% (n=4) belonged to age group of 21-30 years. In case of gender

ISSN: 0975-3583,0976-2833 VOL15, ISSUE 10, 2024

distribution, male predominance (n=104; 86.70%) was seen in comparison to females (n=16; 13.30%). Thyroid levels were also measured and it was found that out of 120 study subjects, 30.00% (n=36) had free T3 levels below normal and 70.00% (n=84) had free T3 levels in normal range. Also, 12.50% (n=15) had free T4 levels below normal and 83.30% (n=100) had free T4 levels within normal range; 4.20% (n=5) had free T4 levels above normal.

TSH levels showed that out of 120 subjects, S. TSH (mIU/ml) levels within normal range were found in 52.50% (n=63) and levels above normal were found in 47.50% (n=57) of the study subjects respectively. Out of 120 study subjects, no thyroid dysfunction was reported among 23.30% (n=28) of the subjects. Subclinical hypothyroidism and hypothyroidism were reported in 39.20% (n=47) and 9.2% (n=11) of the subjects respectively. 20.8% (n=25) had low free T3, 3.3% (n=4) had low free T4 and 4.2% (n=5) had high free T4 levels.

In our study, 55.8% (n=67) of the subjects had MELD Na score <17, 9.2% (n=11) had score between 17-20, 6.7% (n=8) had score between 21-22, 10.8% (n=13) had score between 23-26 and 27-31 while score >=32 was revealed in 6.7% (n=32) of the subjects.

Table 1: Association of meld Na with free T3

Free T3 (pg/ml)	Meld Na Mortality score												Total	
	<17		17-20		21-22		23-26		27-31		>=32			
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%age
<2.28	19	28.36	1	9.09	1	12.50	6	46.15	5	38.46	4	50.00	36	30.00
2.28-6.16	48	71.64	10	90.91	7	87.50	7	53.85	8	61.54	4	50.00	84	70.00
Total	67	100.00	11	100.00	8	100.00	13	100.00	13	100.00	8	100.00	120	100.00

Table 1 showed that subjects having low free T3 were 30% (n=36) and normal free T3 levels were 70% (n=84) were distributed amongst MELD Na mortality score. It can be well appreciated that F.T3 <2.28 pg/ml were associated with higher MELD score. Although the data was not statistically significant. (p value- 0.211)

Table 2: Association of meld Na with free T4

Free T4 (ng/dl)	Meld Na Mortality score												Total	
	<17		17-20		21-22		23-26		27-31		>=32			
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%age
<0.78	8	11.94	0	0.00	0	0.00	3	23.08	2	15.38	2	25.00	15	12.50
0.78-2.19	56	83.58	10	90.91	8	100.00	9	69.23	11	84.62	6	75.00	100	83.33
>2.19	3	4.48	1	9.09	0	0.00	1	7.69	0	0.00	0	0.00	5	4.17

ISSN: 0975-3583,0976-2833 VOL15, ISSUE 10, 2024

Total	67	100.00	11	100.00	8	100.00	13	100.00	13	100.00	8	100.00	120	100.00

Table 2 showed that 12.5% (n=15) had low free T4, 83.3% (n=100) had normal free T4 and 4.2% (n= 5) had high free T4. The data was not statistically significant.

Table 3: Association of meld Na with S.TSH

S. TSH (mIU/ml)	**Meld Na Mortality score**												**Total**	
	<17		**17-20**		**21-22**		**23-26**		**27-31**		**>=32**			
	No.	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%age**
0.40-4.04	38	56.72	5	45.45	3	37.50	7	53.85	5	38.46	5	62.50	63	52.50
>4.04	29	43.28	6	54.55	5	62.50	6	46.15	8	61.54	3	37.50	57	47.50
Total	67	100.00	11	100.00	8	100.00	13	100.00	13	100.00	8	100.00	120	100.00

Table 3 showed that 52.5% (n=53) had S.TSH within normal limits and 47.5% (n= 57) had high S.TSH. No significant association was revealed between MELD Na score and S.TSH levels. (p value- 0.734).

Table 4: Association of meld Na with thyroid dysfunction

Thyroid Dysfunction	**Meld Na Mortality score**												**Total**	
	<17		**17-20**		**21-22**		**23-26**		**27-31**		**>=32**			
	No.	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%age**
Normal	19	28.36	3	27.27	2	25.00	1	7.69	2	15.38	1	12.50	28	23.33
Sub Clinical Hypothyroidism	24	35.82	6	54.55	5	62.50	4	30.77	6	46.15	2	25.00	47	39.17
Low T3	13	19.40	1	9.09	1	12.50	4	30.77	3	23.08	3	37.50	25	20.83
Low T4	2	2.99	0	0.00	0	0.00	1	7.69	0	0.00	1	12.50	4	3.33

ISSN: 0975-3583,0976-2833 VOL15, ISSUE 10, 2024

High T4	3	4.48	1	9.09	0	0.00	1	7.69	0	0.00	0	0.00	5	4.17
Total	67	100.00	11	100.00	8	100.00	13	100.00	13	100.00	8	100.00	120	100.00
P value	0.862													

Table 4 showed that out of 120 subjects, 67 subjects had Meld Na score <17. No significant association was reported between higher MELD Na score and prevalence of thyroid dysfunction.

Table 5: Association of thyroid dysfunction with CTP class

Type of thyroid dysfunction	CTP class						Total	
	A		B		C			
	No.	%age	No.	%age	No.	%age	No.	%age
Normal	7	50.00	13	33.33	8	11.94	28	23.33
Sub Clinical Hypothyroidism	3	21.43	15	38.46	29	43.28	47	39.17
Hypothyroidism	1	7.14	1	2.56	9	13.43	11	9.17
Low T3	0	0.00	6	15.38	19	28.36	25	20.83
Low T4	1	7.14	1	2.56	2	2.99	4	3.33
High T4	2	14.29	3	7.69	0	0.00	5	4.17
Total	14	100.00	39	100.00	67	100.00	120	100.00
p-value	0.002							

Table 5 showed that out of total 120 study subjects, 14 subjects were in CTP class A, 39 in class B and 67 in class C. Subclinical Hypothyroidism, Hypothyroidism and Low free T3 levels were reported maximum in CTP class C followed by B and A which was statistically significant as $p<0.05$.

Discussion

Liver plays an important role in the metabolism of thyroid hormones, as it is the most important organ in the peripheral conversion of tetraiodothyronine (T4) to triiodothyronine (T3) by type I iodinase resulting in 5' deiodination of T4.[4] Moreover, it is involved in the conjugation and circulation of thyroid hormones by the synthesis of thyroid binding proteins.[4-5] On the contrary, thyroid hormones have multiple effects on liver function, including stimulation of enzymes regulating lipogenesis and lipolysis as well as oxidative processes.[6-7] Thus, the nature of relationship between the thyroid and liver is a mutual one with each one affecting the function of other. Evidence of an association between chronic diseases of the liver and thyroid dysfunction has often been reported.[8]Given this bidirectional relationship, it is of interest to understand and evaluate the relationship between liver disease and thyroid functions under all possible conditions.[9-10] The present cross-sectional study was conducted at Sri Guru Ram Das Institute of Medical Sciences and Research, Sri Amritsar

ISSN: 0975-3583,0976-2833 VOL15, ISSUE 10, 2024

from 1st Jan 2023 to 31st Mar 2024 among 120 patients aged 18 years or above with clinical, biochemical and radiological evidence of cirrhosis of liver. The aim was to evaluate the thyroid function tests in patients with cirrhosis of liver and to assess the severity of liver dysfunction in relation with interpretation of thyroid functions.

In the present study, maximum subjects were from age group of 41-50 years (31.67%) followed by >60 years (28.33%) and 51-60 years (24.17%). Minimum subjects were from age group of 21-30 years. A study by Anbazhagan *et al*[11] (2015) observed mean age 49.2 with 40% patients belong to 41-50 years of age. 44% patients belong to more than 50 years of age and 16% patients were 40 years or younger. Another study revealed that 8 males (11.4 percent) and 4 females (13.3 percent) belong to younger age group, about 55 males and 20 females in the middle age group, about 7 males and 6 females in the elderly age group as studied by Kumar R *et al*[12] (2021). In a study by Patira NK *et al*,[13] majority of patients 36(72%) belonged to age group 41-60 yrs., 9 (18%) patients were below 40 yrs. of age and 5 (10%) patients were above 60 yrs. of age. Comparing with the other studies it was found that the liver diseases are more common in middle age group showing occurrence of disease more in this age group.

In the present study, male dominance was observed which was in consistence with studies by Kesavadas SM *et al*[14] (2007) who found 64 patients were males and 11 were females in their study; Anbazhagan *et al*[11] (2015) who observed 88% were males and 12% were females in their study. Sudhir Kumar Verma *et al*[15] and Punekar *et al*[16] also in their study noticed more males than females. Another study by Patira *et al*[13]had male predominance with 39 (78%) patients male, and 11 (22%) were female.

Analysis of thyroid profile showed that 23.3% of the subjects had no thyroid dysfunction. Subclinical hypothyroidism and hypothyroidism were found in 39.2% and 9.2% of the subjects respectively. Similar findings were reported by Patira NK *et al*[13] in their study which showed that prevalence of hypothyroidism in cirrhosis patient was 62% i.e. 31 out of 50 cirrhotic patients had increased TSH level. The prevalence of hypothyroidism increases as the severity of liver cirrhosis increases. However, Joeimon *et al*[17] reported the prevalence of hypothyroidism was 21.6%. This difference may be due to sample size, age, sex, and regional variation in thyroid disease.

In our study, 55.8% of the subjects had MELD score <17 while >27 score was revealed in 17.5% of the subjects. F.T3 <2.28 was associated with higher MELD score. FT4 <0.78 score was found in higher MELD score. Lower S.TSH though <0.4.04 score was found in higher MELD score. This was also supported by Tas A *et al*.[18] According to Sudhir Kumar Verma *et al*,[15] based on MELD scoring, 2 groups were identified in our study, 62.7% (n=64) of patients belong to group 1 with MELD score 20. Significant inverse correlation was also found between free T4 levels and MELD score (p=0.019), which was in accordance with Dehghani SM *et al*.[19] Mansour Ghanaei *et al*.[20] reported negative correlation of T3 levels with MELD as well as CTP. The basis of this probably lies in increased conversion of free T4 to rT3 by type 3 deiodinase. We found no significant correlation between TSH and MELD score and this is similar to the observations made by previous studies (Patira NK *et al*.,[13] Dehghani SM *et al*[19] and Taş A *et al*.[18]

In the present study; as per Child Turcotte Pugh score; 14 patients (11.7%) belonged to class A; 39 patients (32.5%) belonged to class B and 67 patients (55.8%) belonged to class C. Our study was supported by Agha F *et al*[21] study which confirms the presence of abnormalities in serum thyroid hormone levels in cirrhosis of liver. Alteration in serum T3 and FT3 levels correlate well with the disease severity and may be useful in assessing the course and prognosis in cirrhotic patients. Another study byVerma SK *et al*[15] stated that four patients (3.92%) were classified as Child Pugh class A, 40 patients (39.22%) as Child-Pugh class B and rest of the 58 patients (56.86%) as Child-Pugh class C. It shows that patient with low free

ISSN: 0975-3583,0976-2833 VOL15, ISSUE 10, 2024

T3 levels were highest in Child-Pugh class C (82.76%) followed by Child-Pugh class B (60 %) and Child-Pugh class A (50%) and this difference was found to be statistically significant (p=0.027).Patira NK *et al*.,[13] Dehghani SM *et al*.[19] and Taş A *et al*[18] also suggested similar results i.e. free T3 levels were inversely correlated with the Child-Pugh class.In a study by Deepika *et al*.,[22] D'costa and Dhume,[23] Saleem and Wadea,[24] ElSawy and Tawfi,[25] Kayacetin *et al*.,[26] etc., the levels of FT3 were significantly low in liver cirrhosis patients.

Several mechanisms have been postulated for this occurrence of lower free T3 levels in patients with cirrhosis of liver and its inverse correlation with the severity of liver injury. Most common hypothesis states that loss of peripheral deiodination as the primary cause of decreased free T3 levels, the so called sick euthyroid syndrome. Poor nutrition in cases of liver cirrhosis has been linked to decrease in free T3. Release of cytokines such as Interleukin-6 (IL-6) might also be responsible for sick euthyroid syndrome. Further, alcohol intake has been associated directly with impaired hepatic deiodinase activity.[27-29]

Conclusion

It was concluded that the mean FT3 and FT4 levels were found to be significantly decreased and the mean TSH levels were significantly increased in subjects with liver cirrhosis. Low levels of FT3 also correlated with the severity of liver disease in the form of CTP score. Level of FT3 decreases as CTP Class (A–C) increases. Therefore, thyroid levels in cirrhotic patients may be used as a prognostic marker. Low free T3 and high S.TSH might be used as a predictor of mortality in liver cirrhosis patients, although death in cirrhotic patient is multifactorial. The results of our study suggests that the thyroid profile can be used as a prognostic indicator in cirrhotic patients, and increased TSH levels may indirectly help in identifying patients with poor prognosis. Moreover, further studies are needed to address the association of the severity of thyroid function tests with the grading of liver disease by Child-turcotte-Pugh score and Meld- Na score.

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ISSN: 0975-3583,0976-2833 VOL15, ISSUE 10, 2024

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