Original Research Paper

Volume - 13 | Issue - 01 | January - 2023 | PRINT ISSN No. 2249 - 555X | DOI : 10.36106/ijar

General Medicine

CAN THYROID PROFILE PREDICT THE IMPENDING DANGER OF DECOMPENSATION IN LIVER CIRRHOSIS?

Keerthi Priyanka Injeti	M.D. Gen Med, Assistant Professor, Department of General Medicine, Government General hospital, Guntur, India
Atchala Mounika	M.D. Gen Med Junior Resident, Department of General Medicine, Government General hospital, Guntur, India
Atchuta Chytanya Paka	M.D. Gen Med Associate Professor, Department of General Medicine, Nimra Institute of medical sciences, Vijayawada, India
Gandhi Parise*	M.D. Gen Med Assistant Professor, Department of General Medicine, Government General hospital, Guntur, India*Corresponding Author

ABSTRACT **Background:** Chronic liver disease is one of the world's leading causes of mortality and morbidity. Thyroid and liver are interdependent in their functioning, Thyroid gland regulates basic metabolic rate in hepatocytes and liver being the site of thyroid hormone metabolism, modulates hormone levels. Assessment of thyroid levels in cirrhosis may prove useful to identify severity of disease and probability of complication rates. In this context we conducted a study to signify the association between thyroid hormones and severity of hepatic disorder in cirrhosis through usage of Child Pugh score. **Method:** 100 patients aged 18 years and above, with liver cirrhosis were evaluated in our institute. Thyroid profile and other relevant investigations were carried out to assess severity of liver cirrhosis, correlated with Child Pugh scoring. Results: 74% of the patients in the study were in euthyroid state. Total and free T3, T4 levels were significantly low and inversely correlated with severity of liver cirrhosis. Most of the patients had normal T4 and TSH levels. Among all, free T3 was found to be the most sensitive marker to assess severity of cirrhosis. **Conclusion:** Thyroid dysfunction is often observed in liver cirrhosis which calls for thyroid profile tests to be conducted with a potential role as prognostic marker.

KEYWORDS : Child Pugh score, 5'deiodinase, Euthyroid, Hepatic encephalopathy

Introduction:
Liver disease, considered as 11th leading cause of death globally, contributes to approximately two million deaths per year across the world. Of these one million are due to complications of cirrhosis [1]. It leads to both financial burden and low quality of life indices [2]. Decompensated state in liver disease is associated with higher mortality rates. Decompensation is marked by the onset of features like ascites, upper gastro intestinal bleed, peritonitis and encephalopathy[3]. Over the last two decades, the association between thyroid gland and liver both in health and disease has gained a lot of attention [4]. Abnormal thyroid function may result in altered liver function [5]. Similarly liver disease can lead to a disorder of thyroid functioning[6]. The altered thyroid levels could be used to judge severity in liver cirrhosis patients [7]. Severity of cirrhosis was correlated with Child Pugh score which was introduced to predict mortality and the risk of developing complications [8] in liver. Identification of markers to predict progression to decompensated state in cirrhosis may prove useful to bring down the mortality rate. In this context, it needs to be ascertained whether the changes noted in thyroid profile during liver disease can predict progression to decompensated state. We have conducted a prospective study on 100 patients of cirrhosis diagnosed as per world health organization criteria and evaluated for thyroid profile with results analysed for the correlation with disease severity. The study was done to understand thyroid dysfunction during liver cirrhosis and its relation with severity of cirrhosis in order to identify any prognostic role.

Patients and method:
A prospective observational study was done on 100 patients, aged 18 years and above, with liver cirrhosis, attended out outpatient unit of our institute, between December 2019 and November 2021. The diagnosis was based on clinical, biochemical and radiological evidence of the same and in line with the criteria laid down by World health organization (WHO). Institutional ethics committee approval was obtained prior to initiating the study. All the patients satisfying the inclusion criteria were included in the study only after taking their informed written consent for participation in the study. Severity of liver cirrhosis in patients was graded according to Child Turcott Pugh classification.

Patients with known history of thyroid disease, chronic kidney disease (CKD), nephrotic syndrome, cardiac disease, diabetes and other chronic/long standing disorders and those on drugs that interfere with thyroid metabolism were excluded from the study.

Blood samples were collected from the patients and sent for thyroid profile. Other investigations performed were complete blood count, liver function tests, serum proteins, serum electrolytes, renal function test, ascitic fluid analysis and ultrasound abdomen.

During follow up the patients were evaluated for developing any complications related to cirrhosis. Those patients who got admitted elsewhere were also followed up, through subsequent visits and phone calls. Euthyroid state was defined as thyroid-stimulating hormone TSH levels ranging between 0.45 to 4.49 mIU/L. Hypothyroidism and hyperthyroidism were defined as TSH levels more than 4.5 mIU/L and less than 0.45 mIU/L respectively.

Statistical analysis was done using SPSS software (IBM Corp. Released 2021. IBM SPSS Statistics for Windows, Version 28.0. Armonk, NY: IBM Corp). Descriptive method was used to analyse data. Sample size was calculated based on the Samarthana et al study[9]. Analysis of variance was used to find out statistical differences among means of various thyroid profile tests of three grade of Child Pugh scoring.

Results:
The present study is a prospective observational study including 100 patients of liver cirrhosis attended to and evaluated for thyroid profile with results analysed.

Majority of patients belonged to the age group 51 to 60 years (27%), followed by 41 to 50 years (26%) and 31 to 40 years (21%) (Table 1). 82 (82%) of the patients were males and the remaining 17 (17%) were females. 74 (74%) of patients were in euthyroid state, 24 (24%) in hypothyroid and 2 (2%) in hyperthyroid state. All the patients of Child Pugh grade A and B were in euthyroid state. 62.8% patients of grade C were in euthyroid state. As per Child Pugh scoring, 7 (7%) were of grade A, 23 (23%) of grade B and 70 (70%) of grade C. The mean Child Pugh Score observed in the present study was 10.20 ± 2.17. Mean duration of illness as per various grades of Child Pugh were 8 ±6.33 days for grade A, 25.14 ±21.62 for grade B and 15.38 1±1.87 for grade C. The duration of stay was significantly longer in cases with relatively high Child PUGH score.

Mean free T3 levels in grade A, B and C were 2.26 ±0.33, 2.48 ±0.55 and 1.53 ±0.44 respectively. Mean free T4 levels in grade A, B and C were 1.29 ± 0.25, 1.43 ± 0.49 and 1.02 ± 0.26 respectively. Mean total T3 levels observed were in Grade A, B and C were 126.28 ± 26.61, 125.17 ± 36.25 and 86.68 ± 37.27 respectively. Mean total T4 levels observed were in Grade A, B and C were 8.18 ± 1.14, 7.79 ± 1.81 and 5.78 ± 1.44 respectively. Mean TSH levels recorded in grade A, B and C were 3.87 ± 4.75, 3.08 ± 2.41 and 3.84 ± 2.48 respectively.

51% of patients in the study reported upper gastro intestinal bleed (Fig 1). The relative incidence of upper GI bleed was more in type C patients. Hepatic encephalopathy grade 1 or 2 was observed in 23% of patients (16% grade1 and 7% grade 2). 76% reported with ascites (62% grade 1 and 14% grade 2). Icterus and oedema were not noticed in type A of Child Pugh patients. 70 patients exhibited icterus and 57 presented with oedema upon clinical observation.

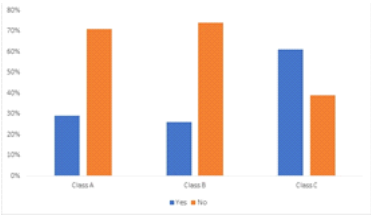

Figure 1: Distribution based on upper Gi bleed

Discussion:

In the present study, euthyroid state was prevalent in most of the liver cirrhotic patients. Thyroid hormone levels in cirrhotic patients were slightly low T3, and normal T4 and TSH. Hormone levels in decompensated liver patients were more effected than in patients in compensated state.

There is no clarity regarding any association between hypothyroidism and chronic liver disease [10]. In different types of liver diseases, a sick euthyroid syndrome [11] like state is observed in thyroid gland. Thyroid pattern of chronic liver disease can be classified as low T3 syndrome, low T3 and T4 syndrome, or high T4 syndrome mixed form [12].

Mean age in this study was in near consonance with that of Punekar P et al. [13] (43 years ± 14 years) and Elias RM et al. [14] (45 years). High Child Pugh scores were noticed in younger patients, males and in patients with severe ascites, icterus, oedema or higher grades of encephalopathy. 5'deiodinase enzyme inhibition leads to a fall in T3 level [15,16,17] and an increase in reverse T3 (rT3) levels. Inefficient hepatic deiodination and poor hepatic cellular uptake also add to T3 and T4 level drop. Normal TSH levels are due to conversion of T4 to T3 outside the liver by the pituitary gland [18].

Hypothyroidism in liver patients is related with lesser degree of decompensation [19].Recent study stated that onset of hypothyroidism in cirrhosis patients resulted in a biochemical improvement in liver function [20]. It is associated with a decrease in hepatic basal metabolic rate, body protein stores, improved coagulation profile. Hypothyroid state is induced due to the following reasons i) atrophy following cirrhosis ii) change in blood flow and pH value of the gland iii) state of stress is induced in the body that dysregulates the hypothalamus-pituitary thyroid axis and iv) hypersplenism induced anaemia and decrease ATPase activity, iodine uptake and thyroid hormone levels are affected [21,22,23]. 63% of patients had low free T3 levels (Table 2). T3 levels were found to be low in decompensated liver disease patients similar to the study by Mansor et al [24]. Only 9% of patients had low T4 levels and 6% had low free T4 levels (Table 3). T4 levels were mostly in the normal range, close to the lower normal limit, irrespective of the grade of Child Pugh score in contrast to the studies of Kayacetin E et al and Kaya A et al [25]. TSH levels were observed in the normal range in 74 patients (Table 4).

The association observed in this study was a negative correlation between total T3, free T3 and no association has been observed with TSH levels and severity of thyroid disease. The results of our study for FT3 levels are consistent with Mobin et al study, but contradict for T4 and TSH levels which were normal compared to levels in the study by Mobin et al.

Table 1 Age distribution and Child PUGH Grade

	Class A		Class B		Class C		Total	
	N	%	N	%	N	%	N	%
21 – 30	0	0.0%	5	21.7%	3	4.3%	8	8%
31- 40	0	0.0%	5	21.7%	16	22.9%	21	21%
41-50	2	28.6%	10	43.5%	14	20%	26	26%
51-60	2	28.6%	3	13%	22	31.4%	27	27%
61-70	3	42.9%	0	0%	9	12.9%	12	12%
71-80	0	0.0%	0	0%	6	8.6%	6	6%
Total	7	100%	23	100%	70	100%	100	100%
Chi square test = 25.57, p=0.004*, Statistically significant								

Table 2 Distribution of patients according to T3 levels

T3 levels	No. of patients	%
< 0.4	63	63%
0.4 – 2.04	36	36%
> 2.04	1	1%
Total	100	100%

Table 3 Distribution of patients according to T4 levels

TSH levels	No. of patients	%
0.25-5.0IU/Ml	74	74%
10-5.0IU/Ml	24	24%
<0.25 IU/MI	2	2%
Total	100	100%

Table 4 Distribution of patients according to TSH levels

T4 levels	No. of patients	%
< 4.5	9	9%
4.5 – 12.6	90	90%
> 12.06	1	1%
Total	100	100%

In non-alcoholic cirrhotic, the plasma T3: rT3 ratio has a negative correlation with the severity of cirrhosis [26]. The T3 / rT3 ratio independent of protein binding, provide a correlation of liver function in cirrhosis but is rarely used. Serum T3 and liver factors like bilirubin can serve as useful indices to monitor the progression of thyroid liver disease. Some studies stated that serum T4 levels vary with each stage of liver disease and correlate with the severity of the disease.

Limitations of the study include small sample size, regional variations of thyroid disease, difference in severity of disease, age, sex and absence of a control group. A randomized control trail with control group and sufficient sample size is needed to over these shortcomings.

Most studies found to have consistently low FT3 in the face of a normal TSH and a clinical euthyroidism consistent with the findings of this study. FT3 level has also been correlated with the degree of liver dysfunction. These changes in thyroid hormone levels are so well established that some have advised its use as a sensitive index of liver function.

Conclusion:

Thyroid profile tests in cirrhotic patients of the study pointed toward a slightly low T3 and normal TSH levels. A negative/inverse correlation was found between serum level of FT3 and severity of disease. Free T3 levels were more sensitive than other levels and correlated well with disease severity. The study showed that as the severity of liver disease progresses from Child Pugh grade A to C the prevalence of reduced serum FT3 level increased (p value < 0.0001) and this confirms the presence of abnormalities in serum thyroid hormone levels in cirrhosis of liver. Alteration in FT3, T3 levels correlate well with disease severity and useful in assessing the course and prognosis in cirrhotic patients. Patients should undergo thyroid function evaluation as these patients are associated with development of hypothyroidism. These parameters can be used as markers of severity of cirrhosis.

REFERENCES:

1) Singal, A. K., Arora, S., Wong, R. J., Satapathy, S. K., Shah, V. H., Kuo, Y. F., & Kamath, P. S. (2020). Increasing burden of acute-on-chronic liver failure among alcohol-associated liver disease in the young population in the United States. Official journal of the American College of Gastroenterology| ACG, 115(1), 88-95.
2) Boonstra, K., Beuers, U., & Ponsioen, C. Y. (2012). Epidemiology of primary sclerosing cholangitis and primary biliary cirrhosis: a systematic review. Journal of hepatology, 56(5), 1181-1188.
3) Deepika, G., Veeraiah, N., Rao, P. N., & Reddy, D. N. (2015). Prevalence of hypothyroidism in Liver Cirrhosis among Indian patients. Int J Pharm Med Res, 3(3), 4-

7.
4) Liu, C., Li, L., & Zeng, L. (2022). The Clinical Value of Thyroid Hormone Levels and Correlation with Severity of Liver Cirrhosis. Computational Intelligence and Neuroscience, 2022.
5) Malik, R., & Hodgson, H. (2002). The relationship between the thyroid gland and the liver. QJM: An International Journal of Medicine, 95(9), 559-569.
6) Yang, M., Li, B., & Ding, H. (2014). The effects of liver disease on endocrine hormone. Zhonghua gan zang bing za zhi= Zhonghua ganzangbing zazhi= Chinese journal of hepatology, 22(3), 168-170.
7) Yang, M., Li, B., & Ding, H. (2014). The effects of liver disease on endocrine hormone. Zhonghua gan zang bing za zhi= Zhonghua ganzangbing zazhi= Chinese journal of hepatology, 22(3), 168-170.
8) C. G. Child and J. G. Turcotte, Surgery and portal hypertension. The liver and portal hypertension. 1964:50-2
9) Samarthana, V., & Mamatha, B. P. (2020). Study of Thyroid Function Tests Incirrhosis of Liver And Correlation of Thyroid Function Tests Levels With Severity of Liver Dysfunction. J Endo Metabol Res, 1(2), 1-13.
10) Jaruvongvanich, V., Sanguankeo, A., & Upala, S. (2017). Nonalcoholic fatty liver disease is not associated with thyroid hormone levels and hypothyroidism: a systematic review and meta-analysis. European Thyroid Journal, 6(4), 208-215.
11) Malik, R., & Hodgson, H. (2002). The relationship between the thyroid gland and the liver. QJM: An International Journal of Medicine, 95(9), 559-569.
12) Dooley, J. S., Lok, A. S., Garcia-Tsao, G., & Pinzani, M. (Eds.). (2018). Sherlock's diseases of the liver and biliary system. John Wiley & Sons.
13) Punekar, P., Sharma, A. K., & Jain, A. (2018). A study of thyroid dysfunction in cirrhosis of liver and correlation with severity of liver disease. Indian journal of endocrinology and metabolism, 22(5), 645.
14) Elias, R. M., Dean, D. S., & Barsness, G. W. (2012). Hepatic dysfunction in hospitalized patients with acute thyrotoxicosis: a decade of experience. International Scholarly Research Notices, 2012.
15) Kayacetin, E., Kisakol, G., & Kaya, A. (2003). Low serum total thyroxine and free triiodothyronine in patients with hepatic encephalopathy due to non-alcoholic cirrhosis. Swiss medical weekly, 133(1314).
16) Malik, R., Mellor, N., Selden, C., & Hodgson, H. (2001). Characterising the effects of thyroid hormone on the liver: A novel approach to increasing liver mass. Gut, 48(3), A67-A67.
17) Moustafa, A. H. A., Ali, E. M., Mohamed, T. M., & Abdou, H. I. (2009). Oxidative stress and thyroid hormones in patients with liver diseases. European journal of internal medicine, 20(7), 703-708.
18) Jameson JL, Mandel SJ, Weetman AP. Harrison's Principles of Internal Medicine Textbook. Disorders of the Thyroid gland. In: Kasper DL, Hauser SL, Jameson JL, Fauci AS, Longo DL, Loscalzo J, editors. 19th ed. Ch. 405. New York: McGraw-Hill Education; 2015. pp. 2283–2308
19) Oren, R., Brill, S., Dotan, I., & Halpern, Z. (1998). Liver function in cirrhotic patients in the euthyroid versus the hypothyroid state. Journal of clinical gastroenterology, 27(4), 339-341.
20) Oren, R., Dabeva, M. D., Karnezis, A. N., Petkov, P. M., Rosencrantz, R., Sandhu, J. P., ... & Shafritz, D. A. (1999). Role of thyroid hormone in stimulating liver repopulation in the rat by transplanted hepatocytes. Hepatology, 30(4), 903-913.
21) Piantanida, E., Ippolito, S., Gallo, D., Masiello, E., Premoli, P., Cusini, C., ... & Tanda, M. L. (2020). The interplay between thyroid and liver: implications for clinical practice. Journal of Endocrinological Investigation, 43(7), 885-899.
22) Sorvillo, F., Mazziotti, G., Carbone, A., Morisco, F., Cioffi, M., Rotondi, M., ... & Carella, C. (2003). Increased serum reverse triiodothyronine levels at diagnosis of hepatocellular carcinoma in patients with compensated HCV-related liver cirrhosis. Clinical Endocrinology, 58(2), 207-212.
23) Kharb, S., Garg, M. K., Puri, P., Brar, K. S., Pandit, A., & Srivastava, S. (2015). Assessment of thyroid and gonadal function in liver diseases. Indian journal of endocrinology and metabolism, 19(1), 89.
24) Mansour-Ghanaei, F., Mehrdad, M., Mortazavi, S., Joukar, F., Khak, M., & Atrkar-Roushan, Z. (2012). Decreased serum total T3 level in hepatitis B and C related cirrhosis by severity of liver damage. Annals of Hepatology, 11(5), 667-671.
25) Verma, S. K., Kumar, V., Tiwari, P., Joge, N. K. P., & Misra, R. (2017). Thyroid Profile in Patients of Cirrhosis of Liver: A Crosssectional Study. Journal of Clinical & Diagnostic Research, 11(12).
26) Güven, K., Kelestimur, F., & Yücesoy, M. (1993). Thyroid function tests in non-alcoholic cirrhotic patients with hepatic encephalopathy. The European journal of medicine, 2(2), 83-85.