



Original Research

Thyroid Profile as a Marker of Hepatic Encephalopathy Severity in Hepatitis B and C Related Cirrhosis

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Abstract

Objective: The spectrum of thyroid hormone profiles in hepatitis B and hepatitis C related hepatic cirrhosis were assessed in order to find if there is any correlation between thyroid hormone levels and severity of liver disease.

Materials and Methods: The study was carried out over a period of one year and involved 85 patients with HBV or HCV related cirrhosis. Of the 85, there were 58 male and 27 female patients with a mean age of 55 years. Patients diagnosed with hepatic cirrhosis due to hepatitis B or C were selected and evaluated for thyroid function. Child-Pugh and model for end-stage liver disease (MELD) scores were also calculated. On the basis of the result of thyroid function tests, patients were divided into three groups with low, normal, or high range of thyroid hormones, for each TSH, fT3 and fT4. The thyroid hormones were correlated with the severity of liver disease by assessing various factors (irrelevant talk for encephalopathy, ascites, total bilirubin, albumin, prothrombin time, Child-Pugh and MELD scores for severity of liver disease).

Results: Patients with a low fT3 levels (fT3 normal range 3.10-6.80 pmol/L) were significantly more likely to have irrelevant talk and hence encephalopathy ($p < 0.001$). Low fT3 levels also correlated with a higher Child-Pugh score C ($p < 0.001$) and were much more likely to have a higher MELD score ($P < 0.001$).

Conclusion: The serum fT3 levels are a very good indicator of liver function in those with HBV or HCV related cirrhosis. FT3 levels decrease as the severity of liver diseases increases.

Keywords: hepatitis B and C related cirrhosis, thyroid profile, Child-Pugh score, model for end-stage liver disease (MELD score), thyroid hormone profiles.

Introduction

The liver is the largest organ of the human body, weighs approximately 1500 g, and is located in the upper right corner of the abdomen. The spectrum of functions of liver includes the

synthesis of most essential serum proteins (albumin, carrier proteins, coagulation factors, many hormonal and growth factors), the production of bile and its carriers (bile acids, cholesterol, lecithin, phospholipids), the

regulation of nutrients (glucose, glycogen, lipids, cholesterol, amino acids), and metabolism and conjugation of lipophilic compounds (bilirubin, anions, cations, drugs) for excretion in the bile or urine.¹

The liver has an important role in thyroid hormone metabolism because it is the manufacturer of proteins that bind thyroid hormone, such as thyroxine-binding globulin (TBG), pre-albumin and albumin.² It is also the major site of thyroid hormone peripheral metabolism and is involved in its conjugation, biliary excretion, oxidative deamination and the extrathyroidal deiodination of thyroxine (T4) to triiodothyronine (T3) and to reverse T3. There are three groups of enzymes that regulate thyroid hormone metabolism, forming part of the iodothyronine seleno-deiodinase enzyme system, Type 1 = D1 (deiodinase 1), Type 2 = D2 (deiodinase 2) and Type 3 = D3 (deiodinase 3). They are responsible for the activation of T4 to T3, inactivation of T4 to rT3 and the conversion of rT3 and T3 to T2.³ The type 1 deiodinase is mainly found in the liver and kidney and accounts for approximately 30–40% of extra thyroidal production of T3 (12 nmol). Type 3 deiodinase system primarily exhibits inner-ring deiodination. It is found in the liver, skin and CNS, where it catalyses the conversion of T4 to rT3 and T3 to T2, both inactive metabolites; it also converts rT3 to T2. The patients with cirrhosis have low total and free T3 and an elevated rT3, probably reflecting a reduced deiodinase type 1 activity, resulting in reduced conversion of T4 to T3. This results in an increase in conversion of T4 to rT3 by the deiodinase type 3 systems, and an increase in the rT3 to T3 ratio.⁴ The level of thyroid hormones is also important for normal hepatic function and bilirubin metabolism. Thyroid hormones regulate the basal metabolic rate of hepatocytes, and thereby modulate hepatic function; low total and free T3 levels may be regarded as an adaptive hypothyroid state that serves to reduce the basal metabolic rate within hepatocytes and preserve liver function and total body protein stores.⁵ In experimental animal,

thyrotoxicosis is associated with an increase in bilirubin output in bile, which may result from increased degradation of hepatic heme.⁶ Thyroid-induced alterations in hepatic metabolism of bilirubin, specifically a decrease in glucuronyltransferase, may be responsible for the clinical occurrence of unconjugated hyperbilirubinemia, possibly by masking previously unorganized Gilbert's syndrome. Thyroid hormone decrease bile acid production and total bile acid pool size.⁷ Liver on the other hand metabolizes the thyroid hormones and regulates their systemic endocrine effects. Conceivably, the disorders of these two organs would interact or influence each other.

The derangements in thyroid profile in liver patients have been well documented in English literature. The plasma T3:rT3 ratio has a negative correlation with the severity of cirrhosis when assessed in non-alcoholic cirrhosis. In patients with acute hepatitis of mild or moderate severity, there is elevated serum levels of total T4, due to increased thyroxine-binding globulin, which is synthesized as an acute-phase reactant, but normal levels of free T4. In cirrhosis total and free T3 are found to be low, probably reflecting a reduced deiodinase type 1 activity, resulting in reduced conversion of T4 to T3.

This study was conducted on patients with hepatitis B or C related cirrhosis to observe the spectrum of the thyroid profile in these patients. The goal is to prognosticate liver damage based on the thyroid profile.

Aim

Aim of the study was to evaluate the spectrum of thyroid profile in patients with hepatitis B, C related cirrhosis and association between thyroid profile and severity of liver damage.

Methodology

This was a cross-sectional study carried out on patients admitted to Dayanand Medical College and Hospital with the diagnosis of hepatic cirrhosis due to hepatitis B and C during period of

one year. Ethical approval for this invasive study was obtained from the institutional committee on the ethics of human research. Informed consent for involvement in the study was obtained from every participant. Patients suffering from previously known thyroid dysfunction or under treatment for thyroid dysfunction were excluded.

A detailed history including age, gender, history of presenting symptoms and features was taken. Liver function tests, thyroid function tests and other relevant investigations were done for each patient. The diagnosis of cirrhosis was confirmed by laboratory findings of liver dysfunction, evidence of cirrhosis and portal hypertension on ultrasound. All the patients underwent a clinical examination, and liver function and thyroid function tests along with other relevant or essential investigations. The severity of liver disease was assessed by two criteria, model for end stage liver disease (MELD) (score < 20 and > 20) and Child-Pugh Score (A, B & C).

Univariate statistical analysis was performed on the data collected. Chi square test was applied.

Correlation coefficient was computed. A p-value < 0.05 was taken as significant.

Results

The study involved 85 patients of hepatitis B and C related cirrhosis. In our study 68% of the patients were male and 32% female and the mean age was 55 years. 87% of total subjects were HCV positive and the remaining was Hepatitis B reactive. When patients are divided into two groups with lower than normal and normal range of thyroid hormone test, only for fT3, significant difference is found in number of patients suffering from encephalopathy, albumin, Child-pugh scores and MELD scores. Among the 43 patients presented with hepatic encephalopathy, 33 patients (77%) had low fT3 levels. 40% of the patients without encephalopathy had evidence of low fT3 emphasizing the finding that patients with hepatic encephalopathy are much more likely to have low fT3 ($p < 0.001$) (Table1).

Table 1: Correlation between fT3 groups and hepatic encephalopathy

fT3 (pmol/l) group		Hepatic encephalopathy		Total	p value
		Absent	Present		
Low	No.	17	33	50	0.001
	%age	34.0%	66.0%	100.0%	
Normal	No.	25	9	34	
	%age	73.5%	26.5%	100.0%	
High	No.	0	1	1	
	%age	.0%	100.0%	100.0%	
Total	No.	42	43	85	
	%age	49.4%	50.6%	100.0%	

There is a significant positive correlation between albumin levels and fT3. The correlation between albumin and fT3 is expressed in table 2.

Table 2: Correlation between fT3 groups and Albumin groups

fT3 (pmol/l) group		Albumin (g/dl) group		Total
		Low	Normal	
Low	No.	48	2	50
	%age	96.0%	4.0%	100.0%
Normal	No.	33	1	34
	%age	97.1%	2.9%	100.0%
High	No.	0	1	1
	%age	.0%	100.0%	100.0%
Total	No.	81	4	85
	%age	95.3%	4.7%	100.0%

Subjects were divided into subgroups using Child Pugh scores A,B and C in accordance to thyroid function test. Out of 85 patients, 53 patients (62%) were Child Pugh Class C, 30% Child class B and 7% were Child Class A. Our study showed, the

low ft3 group is much more likely to have a higher Child Pugh Score, as all but four of the patients with low ft3 were in Child Pugh Group C(p < 0.001) (Table 3).

Table 3: Correlation between ft3 groups and Child Pugh Score groups

ft3 group	(pmol/l)	Child Pugh Score Group			Total	p value
		A	B	C		
Low	No.	0	4	46	50	<0.001
	%age	.0%	8.0%	92.0%	100.0%	
Normal	No.	5	22	7	34	
	%age	14.7%	64.7%	20.6%	100.0%	
High	No.	1	0	0	1	
	%age	100.0%	.0%	.0%	100.0%	
Total	No.	6	26	53	85	
	%age	7.1%	30.6%	62.4%	100.0%	

The same analysis using MELD score using range of over 20 versus less than 20 showed that the group having higher MELD score is more likely to have low ft3 levels. Only 8.8% of the patients with normal T3 had MELD score > 20, while 64%

of subjects with low T3 had a MELD score > 20.Hence a reverse correlation was observed between MELD score and ft3 levels (p < 0.001) (Figure 1).

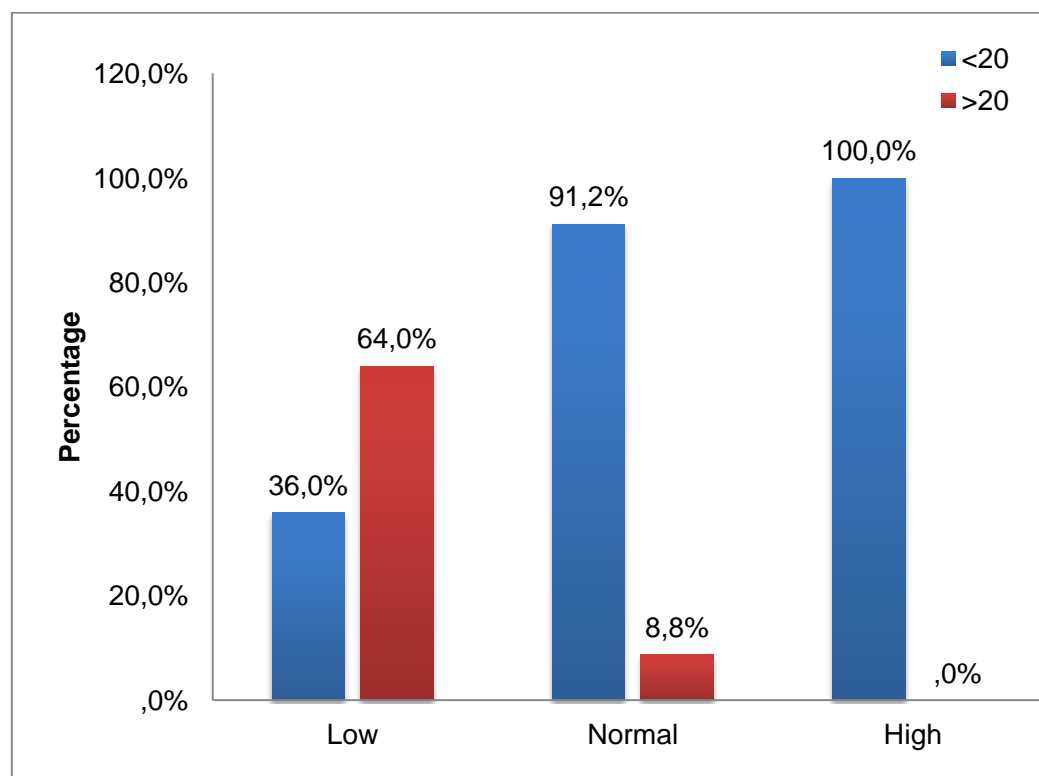


Fig. 1: Correlation between ft3 groups and MELD scores

Our study did not find a correlation between ft3 and bilirubin levels (p = 0.3), prothrombin time (p = 0.092) or ascites (p = 0.228). Nor was there any

relation between T4, TSH values and serum albumin, prothrombin time and serum bilirubin.

Discussion

Thyroxine and tri-iodothyronine play a central role in regulating the basal metabolic rate of all cells, including hepatocytes. Thyroid hormones influence hepatic function while liver in turn metabolizes the thyroid hormones and regulates their systemic effects.⁸ In cirrhosis, thyroid hormone metabolism changes result in the sick euthyroid syndrome, also known as low T3 syndrome.⁹ The decrease in total T3 reflects reduced deiodinase type 1 activity which leads to reduced conversion of T4 to T3 and an increase in conversion of T4 to reverse T3 by the deiodinase type 3 system in the liver of cirrhotic patient.¹⁰

Despite the alteration in serum T3, serum TSH and T4 are reported to be steady, indicating adaptive mechanisms by which the body reduces basal metabolic rate and preserve the liver function. Thyroid function has thus been evaluated as a marker of prognosis of liver disease and thyroid function abnormalities usually reverse following liver function improvement.¹¹

Viral hepatitis related cirrhosis is a global health problem. India has over 40 million HBV carriers and accounts for one lakh deaths due to illnesses related to HBV infection.¹² Hepatitis C infects an estimated 175 million people worldwide with prevalence rate of 0.5 to 1.5% in India and between 5 to 15% of these patients progress to liver cirrhosis over the next 20 years.¹³

Given the prevalence and importance of these ailments, it becomes necessary to identify lab parameters which can guide as to the severity of disease and help in further management. Thus, the aim of the study was to evaluate the alterations of thyroid function tests in hepatitis B and C related cirrhotic patients, establishing the intricate relation between the thyroid gland and liver.

A total of 85 with clinically established euthyroid patients were included in the study. Those with alcoholic related liver disease were excluded due to the direct toxic effect of alcohol on thyroid parenchyma.^{14,15}

The composition of the study groups was as follows: 68 % of patients were male and mean age

was 55 years. Out of the total 85 patients, 87% had HCV related chronic liver disease and the remaining 13% HBV related chronic liver disease. In this study, low fT3 levels were observed in 59% of patients while they were normal in 40% of patients with mean fT3 of 3.12 ± 1.32 . fT4 (mean: 14.5 ± 3.8) was low in only 23% of patients while it was normal in 74% of patients. TSH (mean: 2.69 ± 2.99) was normal in 77% of our patients. Thus the results showed a significant inverse correlation between serum fT3 levels and cirrhosis severity, ranging from decreased, normal to increased levels. Our observations are consistent with the similar studies which report low fT3 levels in cirrhotic patients.^{16,17}

The results of present study could be explained by these facts. Serum fT3 levels correlate negatively with the severity of the liver diseases. The serum fT3 elevation is related to hepatocyte damage and hence, increased TBG. The most consistent findings are elevation of T4 and TBG but normal free T4 (fT4) and thyroid stimulating hormone (TSH) in both acute and chronic liver diseases.

This inference can further be emphasized by the fact that studies have shown that there is an elevation of T4 and TBG levels to their normal ranges as the patients recover.^{17,18,19,20}

Severity of liver cirrhosis has been graded according to various indices, the most commonly used ones include the Child Pugh score and the MELD score.²¹ These indices have been used to predict mortality in cirrhotic patients. These indices include clinical signs, specifically ascites and hepatic encephalopathy as well as certain lab parameters including serum bilirubin, prothrombin time, albumin and creatinine. Various studies have shown that fT3 levels decreased with the severity of cirrhosis.^{22,23,24} In our study as well, serum fT3 levels showed significant inverse relationship with the severity of the liver disease.

Out of 85 patients, low fT3 levels were observed in 59% of patients while they were normal in 40% of patients with mean fT3 of 3.12 ± 1.32 . fT4 (mean: 14.5 ± 3.8) was low in only 23% of patients while it was normal in 74% of patients.

TSH (mean: 2.69 ± 2.99) was normal in 77 % of our patients. A total of 53 patients (62%) of our study group were Child Pugh Class C with 26 (32%) Child class B and 6 (7%) were Child Class A. Out of the 53 patients in child class C, low fT3 levels were present in 46 (87%) patients. Out of 26 patients in child class B, only 4 patients (15%) had low fT3 levels, while none of the class A patients had low fT3 levels. In case of MELD score, out of 50 patients in < 20 group, low fT3 levels were present in 18 patients (36%), while significantly out of the 35 patients in MELD score > 20 group, 32 patients (91%) had low fT3 levels. Hence consistent with other reports in literature, we found a significant inverse correlation between fT3 levels and the severity of cirrhosis as measured by Child Pugh Score ($p < 0.001$) as well as MELD score ($p < 0.001$). However no correlation was found between T4 levels, TSH and the severity of liver dysfunction ($p = 0.427$ for T4, 0.831 for TSH). These findings can lead us to summarise that fT3 levels can be a handy tool in assessing the severity of cirrhosis and the prognosis of the patient.

In agreement with the results of studies of Kayacetin et al²⁵ and Guven et al²⁶ we found that lower the fT3 levels in a subject, likelihood of hepatic encephalopathy is more ($p < 0.001$). Out of 43 patients with hepatic encephalopathy, 33 patients (77%) had low fT3 levels, however out of 42 patients without encephalopathy only 40% had evidence of low fT3. However no correlation was present between T4, TSH levels and encephalopathy. Hence again fT3 levels correlate with one of the cardinal signs of cirrhosis and can be used as an index to predict the likelihood of hepatic encephalopathy in a given patient..

Our study did not find a correlation between fT3 and bilirubin levels ($p = 0.3$), prothrombin time ($p = 0.092$) and ascites ($p = 0.228$) as observed in other studies, nor was there any correlation between T4, TSH values on one hand and serum albumin, prothrombin time and serum bilirubin on other.^{27,28}

The shortcomings of the present study included its short duration of time as study was conducted in one year. Another limitation was that hypothyroidism was excluded on the basis of history, anti TPO test was not done on patients before including them into study to rule out prior hypothyroidism. Third limitation was that study was conducted only on admitted patients, OPD patients were not included.

Thus the present study showed that thyroid profile especially fT3 levels could be used as indicators to assess the severity of liver disease. fT3 levels could also be correlate with outcome or prognosis of the patient and return to normal with improvement in liver function. They can also predict whether a patient is more likely to present in hepatic encephalopathy or not. fT3 levels have a positive correlation with albumin levels, hence as albumin levels decrease, so do levels of fT3 in those with viral related cirrhosis. The measurement of albumin is routine in the investigations of liver function as it is a good indicator of hepatic synthetic activity. fT3 also has a strong inverse correlation with Child Pugh Score and MELD scores. Hence fT3 can be used as an index of severity in cirrhosis and predictors of outcome in HBV and HCV related cirrhosis.

Conclusion

Our study results confirm other study results in which serum fT3 concentration is reported to be good indicator of hepatic function. Hence, it is our conclusion that serum fT3 concentration can be used as an index of severity in cirrhosis and predictor of outcome in HBV and HCV related cirrhosis. fT3 levels can also predict likelihood of occurrence of hepatic encephalopathy in the patient.

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