A Cross-Sectional Study of Thyroid Dysfunction in Patients Suffering from Liver Cirrhosis in a Tertiary Care Hospital in Bengaluru, India

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ABSTRACT

BACKGROUND

Thyroid abnormalities are seen in most of the patients suffering from liver cirrhosis. Cirrhosis of the liver is the major cause of morbidity and mortality worldwide. Cirrhosis plays a vital role in the thyroid hormone metabolism and thyroid hormone circulation by producing thyroid binding globulin. Hence, it is seen that the thyroid dysfunction is associated with the severity of liver disease. We wanted to study the changes in the levels of thyroid hormones in patients suffering from alcoholic liver cirrhosis.

METHODS

In this cross-sectional study, 50 patients who were admitted to the IP department and ICU of General Medicine Department of Akash Hospital, Devanahalli, for symptoms of cirrhosis of liver were evaluated for their thyroid profile along with other relevant investigations.

RESULTS

Among the 50 patients studied, 43 were male and 7 were female. 17 patients had an increase in their thyroid stimulating hormone (TSH). These patients also had a significant association with various LFT parameters such as indirect bilirubin, AST, ALT, APS, and GGT. These 17 patients who had increase in TSH also had associated hepatic complications such as - jaundice (41 %), hepatic encephalopathy (35.29 %), bleeding varices (29.4 %), and portal hypertension (82.35 %).

CONCLUSIONS

Thyroid abnormalities are not uncommon in patients with cirrhosis. Hypothyroidism is the most common abnormality that was detected. Rate of complications is also high in patients with elevated levels of TSH. A fair amount of suspicion is required for detecting thyroid abnormalities in patients suffering from cirrhosis.

KEYWORDS

Cirrhosis, Thyroid Hormone, Hypothyroidism, Hyperthyroidism, Thyroiditis

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DOI: 10.18410/jebmh/2021/358

How to Cite This Article:
Kalmani VM, Madhuvan HS, Ravishankar SN, et al. A cross-sectional study of thyroid dysfunction in patients suffering from liver cirrhosis in a tertiary care hospital in Bengaluru, India. J Evid Based Med Healthc 2021;8(23):1904-1908. DOI: 10.18410/jebmh/2021/358

Submission 31-12-2020,
Peer Review 11-01-2021,
Acceptance 21-04-2021,
Published 07-06-2021.

BACKGROUND

Cirrhosis is defined as the histological development of regenerative nodules surrounded by fibrous bands in response to chronic liver injury that leads to portal hypertension and end stage liver disease. Cirrhosis is described as 'compensated' or 'decompensated' clinically. Decompensation refers to having one or more of these features: jaundice, ascites, hepatic encephalopathy or bleeding varices.[1] The first sign is ascites. The compensated cirrhotic patients have none of the above-mentioned conditions.[2]

Liver is the site of metabolism for several amino acids and proteins produced in the body. One such function of the liver is the thyroid hormone conjugation and excretion, as well as the synthesis of thyroid binding globulin.[3,4] The thyroid gland produces the hormones thyroxine (T4) and triiodothyronine (T3). These hormones are responsible for cell differentiation and to maintain thermogenic and metabolic homeostasis in adults.

According to the studies, the concentration of T4 produced is much higher than the concentration of T3. Both these hormones are bound to the plasma proteins like thyroxine-binding globulin, transthyretin and albumin.[5] The liver is responsible for the peripheral conversion of tetraiodothyronine (T4) to triiodothyronine (T3) by Type-1 deiodinase.[3,6] There is 30 - 40 % of type-1 deiodinase in the liver accounting for extra thyroidal production of T3.[3]

Thyroxine and tri-iodothyronine modulate hepatic function by regulating hepatocyte basal metabolic rate, besides all other body cells. Liver also regulates circulating T3 and T4 by hormone metabolizing, resulting in a supervised endocrine effect. Two main enzymes acting in the liver as part of the iodothyronine selenodeiodinase enzyme system are type 1 and type 3 deiodinases, responsible for extra thyroidal production of T3 and inactivation of thyroid hormones, respectively.[7]

Both T3 and T4 regulate the basal metabolic rate of all cells, including hepatocytes, thereby modulate hepatic function. Any disease of the liver is thereby involved in the modulation of thyroid hormone metabolism. Acute liver failure is associated with increased circulating endotoxins and pro-inflammatory mediators, which is quite similar to clinical states of sepsis and results in dysfunction of the thyroid gland like sick euthyroid syndrome.

Hence, it is seen that the thyroid dysfunction is associated with the severity of liver disease. Patients with cirrhosis might have thyroiditis, hypothyroidism or hyperthyroidism. Such patients have abnormalities in the liver function tests and tend to return to the normal values when the condition of thyroid improves. Thyroid dysfunction may perturb liver function, liver disease modulates thyroid hormone metabolism, and a variety of systemic diseases affect both organs.[8]

Till date, the studies show that cirrhosis leads to a decrease in the plasma concentration of total T3 and free T3, and the total T4 tends to remain normal or slightly low but no study has clearly shown the FT4 and thyroid-stimulating hormone levels in association to severity of liver disease.

It is observed that not many Indian studies on thyroid hormone functional studies in case of chronic liver diseases are available. The study of thyroid hormone function tests will throw a light on the functional aspects of liver diseases and gives some better understanding of the chronic liver disease and their inter-relationship with thyroid function and thus helps in the management of chronic liver diseases.

Keeping in mind the above said views, we wish to study the association between the thyroid abnormalities in patients suffering from liver cirrhosis and to understand their correlation with the severity of liver disease.

Objectives

1. To describe the changes in the levels of thyroid hormones - thyroid stimulating hormone in patients suffering from alcoholic liver cirrhosis.
2. To understand the correlation between the thyroid hormone level and the complications of cirrhosis.
3. To understand the correlation between the thyroid hormone level and the liver function tests.

METHODS

This cross-sectional study was done in 73 patients in the out-patient department, in-patient department and intensive care unit of General Medicine Department of Akash Hospital, Devanahalli, Bangalore rural from February 2019 to October 2019 coming with symptoms of cirrhosis of liver and were evaluated for their thyroid profile during the study period mentioned. Of the 73 patients studied, 50 of them fit in the inclusion criteria and were studied. The remaining 23 of them were a part of the exclusion criteria and were left out from the study. A detailed history and clinical examination was done for all such patients in order to confirm the diagnosis of liver cirrhosis and later sent for thyroid profiling. They were divided into two age groups (25 - 45, 45 - 65) and were evaluated for the change in the TSH. Investigations such as liver function test, complete blood count, renal function test were performed as per the requirement in the patients.

Inclusion Criteria

Patients of liver cirrhosis with age more than 18 years, both male and female showing signs of hepatocellular dysfunction, portal hypertension evident clinically and radiologically were included for the study.

Exclusion Criteria

Patients with sepsis, cardiac failure, diabetes, renal failure, nephrotic syndrome, pregnancy and family history of thyroid diseases and patients on drugs known to affect thyroid functions were excluded from the study. Also, the other patients who are non-alcoholic but suffer from cirrhosis were excluded.

Ethical Aspects

The study protocol for the purpose of research was approved by the Ethical and Research Committee. Before going about with the evaluation of thyroid profiles, an informed and written consent was taken from the patients explaining about the procedure and purpose of the study.

Diagnostic Tool

The diagnosis of cirrhosis was done by taking a detailed history, clinical examination and ultrasound findings. Such patients diagnosed to have cirrhosis were sent for thyroid profiling. The thyroid function tests were done by electrochemiluminescence immunoassay. The normal range of thyroid profile is as follows-

- T3: 0.79 - 1.58 ng/ml
- T4: 4.0 - 11.0 µg/dl
- TSH: 0.39 - 3.55 µl/ml

Based on these values, we evaluated the correlation between the thyroid abnormalities and the severity of the liver disease. The liver function test was also done in these patients to know the simultaneous implication thyroid abnormality had on the liver. This study helped in the inter link between both the liver and the thyroid gland.

Statistical Analysis

All the statistical analysis was performed using SPSS (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp) and Microsoft Excel 2016. A statistical value < 0.05 was considered as significant.

RESULTS

A total of 50 patients with liver cirrhosis were chosen as they met the inclusion criteria among the studied 73 subjects. Among these 50 patients, 43 of them were male and 7 of them were female. All the patients that were chosen were found to have decompensated liver cirrhosis. In these 50 patients that were studied, the patients were divided into two groups based on their age. The groups were between 25 - 45 and 45 - 65 years of age. This was done to correlate the common age group and the severity of thyroid dysfunction. The number of patients in the 25 - 45 years category were 35 and the patients in 45 - 60 years category were 15. Their TSH values were evaluated in Table 1.

Age		TSH			Total
		Decreased	Normal	Increased	
25 - 45	Count	0	24	11	35
	Expected count	0	23.1	11.9	35.0
	%	0 %	68.5 %	31.5 %	100.0 %
45 - 60	Count	0	9	6	15
	Expected count	0	9.9	5.1	15.0
	%	0 %	60 %	40 %	100.0 %
Total	**Count**	**0**	**33**	**17**	**50**
	Expected Count	**0**	**33.0**	**17.0**	**50.0**
	%	**0 %**	**66 %**	**34 %**	**100.0 %**

Table 1. TSH Values of Patients in Relation to the Age

None of the patients had a decrease in TSH levels. The number of patients in the group 25 - 45 years were 35 patients and among them, 11 of them had an increase in TSH and the % of increase in TSH was 31.5 %. The number of patients in the group 45 - 65 years were 15 patients and among them, 6 of them had an increase in TSH and the % of increase in TSH was 40 %.

The same data has been illustrated in the form of a bar chart in Fig. 1 to depict the age group which is more prone to develop thyroid abnormalities. Among the 17 patients with increased TSH, a greater number of patients belonged to the middle-aged category i.e., 25 - 45 years. So, the patients suffering from liver cirrhosis in this age group are more prone to develop thyroid abnormalities.

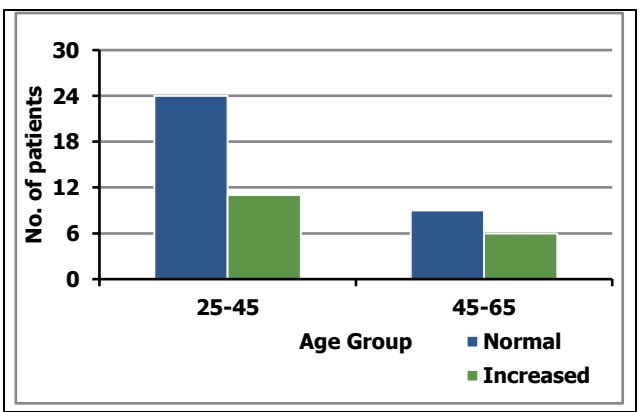

Figure 1. Age Groups

The significance between the age and TSH values were depicted in the chi square tests. According to the Pearson's chi-square test, the chi-square = 0.344 and P = 0.558. This test hereby tells that there is statistically no significant association between the age of the patient and TSH. The patients who had deranged TSH were subjected to the various liver function tests (LFT) in order to find the correlation between the thyroid abnormality and the severity of liver cirrhosis. Spearman's correlation is applied for this purpose in Table 2.

LFT	TSH Correlation Coefficient
Total Bilirubin	0.309
Direct Bilirubin	0.422
Indirect Bilirubin	-0.006*
AST	0.005*
ALT	-0.433*
APS	-0.493*
GGT	-0.151*
A/G Ratio	0.122

Table 2. Spearman's Correlation for Thyroid Abnormality and Severity of Liver Cirrhosis

* depicts that the values are significant

From the above table, the correlation of the TSH with that of liver function tests suggests the following-

- The correlation between TSH and total bilirubin (TB) has a weak positive correlation. [r = 0.309, P > 0.05] which tells that it is not significant.
- The correlation between TSH and direct bilirubin (DB) has a weak positive correlation. [r = 0.422, P > 0.05] which tells that it is not significant.

- The correlation between TSH and indirect bilirubin (IB) has a weak negative correlation. [r = -0.006, P < 0.05] hence it is significant.
- The correlation between TSH and aspartate transaminase (AST / SGOT) has no correlation. [r = 0.005, P < 0.05] which tells that it is significant.
- The correlation between TSH and alanine transaminase (ALT / SGPT) has a weak negative correlation. [r = -0.433, P < 0.05] therefore it is significant.
- The correlation between TSH and alkaline phosphatase serum (APS) has a weak negative correlation. [r = -0.493, P < 0.05] so it is significant.
- The correlation between TSH and gamma glutamyl transferase (GGT) has a weak negative correlation. [r = -0.151, P < 0.05] which tells that it is significant.
- The correlation between TSH and the A/G Ratio has no correlation. [r = 0.122, P > 0.05] which tells that it is not significant.

From the above correlations, we know that the thyroid abnormality is not significantly related to the total bilirubin, direct bilirubin and the A/G Ratio but it is significantly related to the indirect bilirubin, aspartate transaminase, alanine transaminase, alkaline phosphatase serum and gamma glutamyl transferase. This tells us that the thyroid abnormalities are interlinked with the severity of liver cirrhosis. The patients who had increased TSH were also seen to have several hepatic complications in them. The complications seen in them were -

- Jaundice.
- Hepatic encephalopathy.
- Bleeding varices.
- Portal hypertension.

These complications are illustrated in the form of a bar chart in Fig. 2 to tell the count of patients who had these complications among the 17 patients who had thyroid abnormalities.

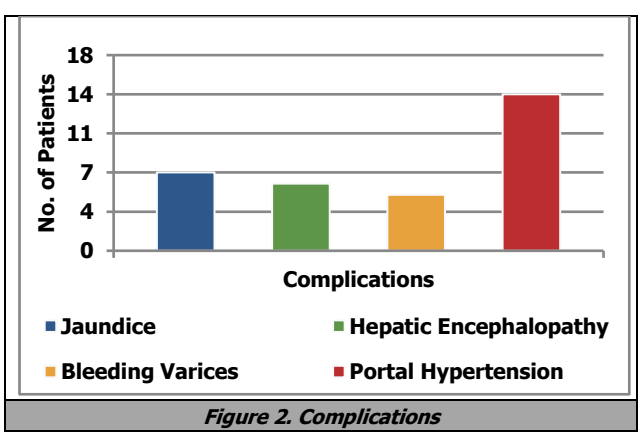

Figure 2. Complications

Among the 17 patients who had increased TSH levels,

- 7 of them had jaundice, i.e., 41 % of the patients with thyroid abnormality had jaundice.
- 6 among the 17 had hepatic encephalopathy, i.e., 35.29 % of the patients.
- 5 of them had bleeding varices, i.e., 29.4 % of the total patients.
- About 14 patients had portal hypertension, i.e. 82.35 % of the patients.

Since the data collected for T3, T4 and TSH did not follow the normal distribution the median and the inter-quartile range [IQR (Q1, Q3)] is reported and are as follows in Table 3.

Thyroid Hormones	Median [IQR]
T3	0.755 [0.547,0.972]
T4	6.400 [3.875,8.425]
TSH	2.740 [1.867,6.450]

Table 3. Thyroid Hormones in Relation to Median and IQR

DISCUSSION

The patients suffering from liver disease commonly face endocrine dysfunction.[9] In this study we have studied the thyroid functions in a wide spectrum of severity of liver diseases.

The liver has an important role in thyroid hormone metabolism and the level of thyroid hormones is also important to normal hepatic function and bilirubin metabolism. In our study, we noted that hypothyroidism (increase in TSH) was seen in 34 % of the patients. i.e., 17 out of 50 patients in comparison with 16 % of the patients in Kharb S et al.[6] 20 % of the patients in P Punekar et al.[1] and 21.6 % of the patients in Joiemon et al.[10] which was almost similar to our study.

When compared to the study done by Samarthana V et al. they noticed normal TSH levels in 36 % of the patients studied and an increase in the TSH levels in 62 % among the cirrhotics of the study group. We noted only 34 % of the patients with increase in TSH and 66 % of the people with normal TSH. There is difference in the values obtained in these studies.[11]

When we looked at the common abnormality among the 50 patients studied we noted that there was a decrease in T3 in 52 % of the patients i.e., 26 out of 50 patients in comparison with a study done by Mobin et al.[12] where they noted a decrease in T3 levels in 76.3 % of the patients. This was also seen in the study done by Kharb S et al.[6] These findings are consistent to our study results. But a slight difference that can be observed could be because of the chosen sample size in these various studies.

Studies have shown a positive correlation for hypothyroidism where the chances of developing hypothyroidism increases with age. But in our study, we did not find a satisfactory relationship between the age of the patients and those who developed hypothyroidism.

In several studies, the most common abnormalities of serum thyroid hormone concentration in cirrhotic patients observed were, low serum T3 level, raised rT3 and raised TSH. These go in correlation with the findings done in our study. This happens due to several factors like alteration in plasma level of thyroid binding proteins, altered binding of T4 and T3 to their carrier protein, hepatic clearance of reverse T3 (rT3) impairment, and decreased extrathyroidal conversion of T4 to T3.[1]

The severity of the liver disease correlated with the low levels of the T3 hormone in the form of CTP or MELD. With a rise in the MELD score, the level of TSH also increases. This change in the levels of thyroid hormones is one of the prognostic markers in patients suffering from cirrhosis.[1]

The liver is responsible for the peripheral conversion of tetraiodothyronine (T4) to triiodothyronine (T3) by type - 1 deiodinase.[3,6] There is 30 - 40 % of type - 1 deiodinase in the liver accounting for extra thyroidal production of T3.[3] The thyroid hormones are > 99 % bound to thyroxine-binding globulin, thyroxine-binding pre albumin and albumin in plasma.

The complications found in our study correlates with and is well supported by the other studies like that in P Punekar et al.[1] and Kharb S et al.[6] Portal hypertension is one of the major complications seen in all the patients suffering from decompensated liver cirrhosis. Hepatic encephalopathy is one the leading complication contributing to mortality among the patients suffering from decompensated liver disease. These observations were similar in all the other related studies. The changes noted in the research study conducted by us when compared to the other researches could be because of the sample size chosen, the age of the subjects considered, the sex of the patients or the regional variations in the thyroid disease.

CONCLUSIONS

Thyroid abnormalities are not uncommon in patients with cirrhosis. Hypothyroidism is the most common abnormality that was detected. There is a positive correlation between TSH and the severity of the disease as evidence by statistically significant value for TSH and liver enzymes. Rate of complications are also high in patients with elevated levels of TSH. A fair amount of suspicion is required for detecting thyroid abnormalities in patients suffering from cirrhosis. Hence, it is evident that the patients with cirrhosis could also have hypothyroidism and should be recommended to undergo thyroid function tests during their course of the disease.

Data sharing statement provided by the authors is available with the full text of this article at jebmh.com.
Financial or other competing interests: None.
Disclosure forms provided by the authors are available with the full text of this article at jebmh.com.

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