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Original Research Article

PREVALENCE OF HYPOTHYROIDISM IN CIRRHOTIC PATIENTS AND NORMAL INDIVIDUALS

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Abstract

Background: The liver has an important role in thyroid hormone metabolism its manufactures of protein that bind thyroid hormone such as thyroxin binding globulin (TBG), prealbumin and albumin, it's also the major site of thyroid hormone peripheral metabolism and is involved in its conjugation of biliary excretion, oxidative deamination and extra thyroidal deiodination of thyroxin (T4) to triiodothyronine (T3) and reverse T3. The aim and objectives of this study was to compare the prevalence of hypothyroidism between cirrhotic patients and normal healthy individuals and to quantify the magnitude of hypothyroidism as a severity index of cirrhosis and compare it with other severity index e.g. child Pugh score. **Materials and Methods:** Present comparative study was conducted on 80 patients admitted to Department of General Medicine, Tertiary Care Teaching Institute of India and found to be clinically, biochemically and radiologically proved liver cirrhosis patients for the duration of 1 year. The diagnosis of cirrhosis was based on case history, clinical examination, biochemical, endoscopic and ultrasound findings, or liver biopsy. **Result:** Among the 40 cirrhotic patients, 34 (86%) were males and 6 (14%) were females, while in control 28 (64%) were males and 12 (36%) were females. Patients with child pugh A and B form 16% of patient and patients with child pugh grade C form 84%. From the above table it is seen that 89.47% increased TSH, 85.71% decreased T3 and 83.22% decreased T4 level of cirrhotic patients with hypothyroidism were in CPT grade C with indicating that as severity of liver disease increases, the prevalence of hypothyroidism increases. **Conclusion:** Cirrhotic patients were more prevalence thyroid dysfunction specially hypothyroidism because of many reasons.

INTRODUCTION

In clinical terms, cirrhosis is described as are either "compensated" or "decompensated." Decompensation means cirrhosis complicated by one or more of the following features: jaundice, ascites, hepatic encephalopathy (HE), or bleeding varices. Ascites is the usual first sign. Hepatorenal syndrome, hyponatremia, and spontaneous bacterial peritonitis are also features of decompensation, but in these patients, ascites invariably occurs first. Compensated cirrhotic patients have none of this features.[1]

If one excludes the direct consequences of the liver disease there is still 5fold increased risk of death in all disease categories. Alcoholic liver cirrhosis develops between 10-20% of individuals who drink heavily for a decade or more.[2] There is great variability in the amount of alcohol needed to cause cirrhosis. Infection with hepatitis C virus causes inflammation and low grade damage to the liver that over several decades can lead to cirrhosis.[3] Chronic hepatitis B is probably the most common cause of cirrhosis worldwide.[4] Many patients with cirrhosis have no symptoms in the early stage of the disease, however, as the disease progress, a person may experiences weakness; fatigue, loss of appetite, nausea, vomiting weigh lost, abdominal pain and bloating when fluid accumulates in abdomen, itching and spider like blood vessels on the skin.[5]

The thyroid gland produces two related hormones, thyroxine (T4) and triiodothyronine (T3). Acting through thyroid hormone receptors α and β, these hormones plays a critical role in cell differentiation during development and help maintain thermogenic and metabolic homeostasis in the adult. T4 is secreted from the thyroid gland in about twenty fold excess over T3. Both hormones are bound to plasma proteins, including thyroxine binding globulin, transthyretin, and albumin.[6] The 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

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T3 by Type 1 deiodinase.[7,8] Type I deiodinase is the major enzyme in the liver and accounts for approximately 30%–40% of extrathyroidal production of T3, it can carry out both 5' and 5 deiodination of T4 to T3. Moreover, the liver is involved in thyroid hormone conjugation and excretion, as well as the synthesis of thyroid binding globulin.[7] T4 and T3 regulate the basal metabolic rate of all cells, including hepatocytes, and thereby modulate hepatic function. The liver metabolizes the THS and regulates their systemic endocrine effects. Thyroid diseases may perturb liver function; liver disease modulates thyroid hormone metabolism; and a variety of systemic diseases affect both the organs.[9] There are clinical and laboratory associations between thyroid and liver diseases. Patients with chronic liver disease may have thyroiditis, hyperthyroidism, or hypothyroidism. Patients with subacute thyroiditis or hyperthyroidism may have abnormalities in liver function tests, which return to normal as the thyroid condition improves.9

T3 and rT3 levels provide values index of the severity of the cirrhosis. In alcoholic cirrhosis, thyroid function and regulation are characterized by normal T4 and low T3 levels related to reduced extra thyroidal T4 and T3 conversion level and thus maintain the euthyroid state and by a hypothalamo-pitutary dysfunction. These alterations are related to the degree of liver dysfunction. In order to clarify an attention in thyroid function in patients with chronic liver disease serum total and free thyroxine (T4, FT4), total and free tri iodothyronine (T3, FT3), Total reverse T3 (rT3), thyrotropin (TSH), thyroxine-binding globulin (TBG) concentration, and T3 uptake (T3V) were measured by radio immunoassay. Serum TBG was increased and T3 was decreased in these patients. Serum TBG in chronic hepatitis and liver cirrhosis correlated positively with transaminase, and inversely with patients FT4 and T4/TBG ratio in chronic hepatitis and liver cirrhosis and FT3 and T3/TBG ratio in liver cirrhosis and HCC were significantly decreased.

Although T4/TBG ratio in HCC and T3/TBG ratio in chronic hepatitis were significantly decreased, FT4 in HCC and FT3 in CH were not decreased. The ratio of rT3/T3 in chronic hepatitis and liver cirrhosis correlated with various liver function tests. FT3 in Liver Cirrhosis and HCC correlated inversely with BSP (Bromosulphalein) and positively with KICG (Kdisappearance rate, ICG-indocyanine green test)

The aim and objectives of this study was to compare the prevalence of hypothyroidism between cirrhotic patients and normal healthy individuals and to quantify the magnitude of hypothyroidism as a severity index of cirrhosis and compare it with other severity index e.g. child Pugh score.

MATERIALS AND METHODS

Present comparative study was conducted on 80 patients admitted to Department of General Medicine, Tertiary Care Teaching Institute of India and found to be clinically, biochemically and radiologically proved liver cirrhosis patients for the duration of 1 year. All patients of age group 20-60 years male and female with confirmed case of liver cirrhosis were included in the study.

Patients >60 years of age, being treated with radioactive iodine, close relative having and autoimmune disease, radiation exposure, thyroidectomy, known cases of hyperthyroidism and patient with any other illness (except liver cirrhosis) e.g. cancer CKD were excluded from the study. The study was performed after taking ethical clearance from Institutional Ethical committee. The present study constitutes 40 patients with cirrhosis of liver who met inclusion criteria. Findings were compared between cirrhotic patients and equal number of normal healthy individual who were taken as controls.

Clinical Examination: Presence of ascites, splenomegaly, dilated superficial abdominal veins, palmar erythema, gynaecomastia, spider nevi and edema feet.

Laboratory Findings: Low serum albumin, reverse A:G ratio; increased prothrombin time; transudative ascites, SAAG ratio >1.1; Normal or elevated total serum bilirubin and aminotransferases and serologic tests HbsAg, anti-HCV were done.

Shrunken liver with uneven borders, coarse nodular echopattern, splenomegaly, dilated portal vein, and ascites were all found on ultrasonography. Splenomegaly, portosystemic collaterals, and reversal of the direction of flow in the portal vein were all indicators of portal hypertension on ultrasonography. A portal vein width more than 13 mm and the absence of respiratory changes in the splenic and mesenteric veins have been shown in certain studies to be sensitive but non-specific markers of portal hypertension. In most centres, these criteria are not commonly employed in clinical practise.

Diagnostic Tool: The diagnosis of cirrhosis was based on case history, clinical examination, biochemical, endoscopic and ultrasound findings, or liver biopsy. Liver biopsies were not performed if coma, reduced coagulability or extensive ascites was present. The functional severity of the liver injury was determined on the basis of the Child–Pugh grading system and model for end stage liver disease (MELD). The degree of encephalopathy was defined on the basis of previously reported criteria ranked between Grade 1 and Grade 4. Thyroid function tests (TFT) was done by electrochemiluminescence immunoassay. The normal range of thyroid profile as a following: FT3 is (2.1–4.4 pg/ml), FT4 is (0.8–2.7 ng/dl), and TSH is (0.35–5.5 µIU/ml).

Statistical Analysis: The recorded data was compiled and entered in a spreadsheet computer program (Microsoft Excel 2019) and then exported to data editor page of SPSS version 15 (SPSS Inc., Chicago, Illinois, USA). Quantitative variables were described as means and standard deviations or median and interquartile range based on their

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distribution. Qualitative variables were presented as count and percentages. For all tests, confidence level and level of significance were set at 95% and 5% respectively.

RESULTS

The present study constitutes of 40 patients with cirrhosis of liver who met our inclusion criteria. Among the 40 cirrhotic patients, 34 (86%) were males and 6 (14%) were females, while in control 28 (64%) were males and 12 (36%) were females. [Table 1]

Among the patients with cirrhosis, the maximum number of patient (65%) were above 41 years and so also in the control group 19 (47.5%). Among total number of 40 cirrhosis patients, 32 (80%) had history of alcohol intake & in control group 3 (7.5%) had history of alcohol intake. All were male subjects. Not a single female in either of the group had history of alcohol consumption. Among the various etiologies, alcoholic liver disease was the most common causative factor (80%) for cirrhosis, followed by cirrhosis due to other causes. Etiology could not be found out in 12% of cirrhotic patient. Among patient with alcoholic liver disease 100% more males and among patients with cirrhosis due to HBV, 32% were male. Among patients in whom cause could not be elucidated, it was seen that majority more females. From Table 2 it is seen that patients with child pugh A and B form 16% of patient and patients with child pugh grade C form 84%. From the above table it is seen that 89.47% increased TSH, 85.71% decreased T3 and 83.22% decreased T4 level of cirrhotic patients with hypothyroidism were in CPT grade C with indicating that as severity of liver disease increases, the prevalence of hypothyroidism increases. CPT grade B was second most common among cirrhotic patients with hypothyroidism.

Decreased T3 level in cirrhotic patients as compare to serum albumin in cirrhotic patient, T3 level as compare to level of serum albumin cirrhotic patient in majority were from serum albumin class 3 about 58%. Decreased T4 level, as compare to level of serum albumin in cirrhotic patient the serum albumin level was decreased then percentage of decreased T4 level (low) was increased. Majority were from serum albumin level class III about 70%. Increased TSH level as compare to level of serum albumin in cirrhotic patients. When serum albumin level was decreases then percent of TSH level increase was increased.

Majority were from serum albumin level class III about 66%. Decreased T3 level as compare to level of serum bilirubin level in cirrhotic patients. Majority were from serum bilirubin class III about 70%. Decreased T4 level, as compare to level of serum bilirubin level in cirrhotic patients. Majority were from serum bilirubin class III about 70%. Increased TSH level among 18 patients with TSH level, as compare to level of serum bilirubin level in cirrhotic patients. Majority were from serum bilirubin level class III about 70%. Decreased T3 level, as compare to INR level in cirrhotic patients. Majority were from INR class 3 about 48%. Decreased T4 level, as compare to level of INR in cirrhotic patients.

Table 1: Age and Gender distribution.

Age (years)	Cirrhosis patients (N=50)			Control (N=50)		
	Male N (%)	Female N (%)	Total n (%)	Male n(%)	Female n(%)	Total n (%)
<30	2 (5.8)	0	2 (5)	5 (17.84)	5 (41.6)	10 (25)
31-40	10 (29.41)	2 (33.3)	12 (30)	9 (32.14)	2 (16.6)	11 (27.5)
>41	22 (64.7)	4 (66.6)	26 (65)	14 (50)	5 (41.6)	19 (47.5)
Total	34 (85)	6 (15)	40 (100)	28(70)	12 (30)	40 (100)

Table 2: Association between severity of liver disease and hypothyroidism

Child Pugh Turcotte grade	Increased TSH (hypothyroidism)	Decreased T3	Decreased T4
A	0	2 (14.28)	1 (5.5)
B	2 (10.52)	0	2 (11.11)
C	17 (89.47)	12 (85.71)	15 (83.22)
Total	19 (100)	14 (100)	18 (100)

DISCUSSION

The prevalence of hypothyroidism in chronic liver disease especially liver cirrhotic patients was found at this present study. The result of this study indicated that the case groups were significantly increased the total, direct, and indirect bilirubin levels compared to control groups. And also found serum enzymes have been elevated more than their normal reference levels compared control subjects.

The study included 40 patients with liver cirrhosis and 40 normal healthy individuals as control and compared the prevalence of Hypothyroidism in patient of cirrhosis. Out of 40 patient with cirrhosis 34 (85%) were male and 6 (15%) were female. In control group 28 (70%) were males and 30% were female. Most of the patient with cirrhosis were in >41 age group. Alcoholic liver disease was the cause of cirrhosis in 80% patients. All patients with alcoholic cirrhosis were males. HBV was next most common cause of cirrhosis. Etiology could not be elucidated in 12% patients. These finding are in accordance with the study by Borzoi et al where alcoholic cirrhosis formed the major etiology group. Study by Calvet et al had shown HCV infection as major etiological factor in cirrhosis followed by alcohol.[10,11]

The comparison of sex distribution in patients with cirrhosis between hypothyroidism and

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nonhypothyroidism group was not statistically Regarding the etiology of cirrhosis in those with hypothyroidism our study found alcoholic cirrhosis to be the most common etiology which in accordance with study by Jacques et al,[12] significant (p>0.05) which is in accordance in study by Jacques et al.12 In study by Tasi et al hypothyroidism was most common in HCC related cirrhosis.[13] The reasons for this were not known. Clinical signs of hypothyroidism develop after a prolonged period of thyroid hormone depletion. Our patients probably did not have T3 depletion long enough to become myxedematous although many of them had biochemical hypothyroidism. Symptomatic hypothyroidism disease was present in none of cirrhotic patients with hypothyroidism (0%) and compared to control. 4 out of 40 hypothyroidism without cirrhotic. The difference was not statistically significant (p>0.05).

Most studies have reported that hypothyroidism in cirrhosis is often asymptomatic. In study of Kumamoto et al 100% hypothyroidism were asymptomatic. The present study showed that as severity of liver disease increases as indicated by CPT grade the prevalence of hypothyroidism is also increased 0 of 19 patients with hypothyroidism were in CPT grade. 'A' compared to 2 in CPT grade 'B' and compared to 17 in CPT grade 'C'. In our study all the patients are in compensated group. Statistical comparison of hypothyroidism and non-hypothyroidism group in cirrhosis without regard to CPT grade revealed that in 50% of cells the expected count. The findings are in comparison with study by Schlienger et al, Jacques et al, Sapin et al, which showed that hypothyroidism was common in patients with advanced liver disease.[12-14]

In present study serum decreased T3, serum decreased T4 and increased TSH significantly correlated with increased serum bilirubin, decreased serum albumin & increased prothrombin time in both group of patients. The findings were in comparison with study by Borzoi et al.10 Mobin et al,[15] reported that in all decompensated cirrhotic patients, 76% had low serum T3 levels, 14% had low serum T4 levels, and 2% had raised TSH levels. In several studies, the most common abnormalities of serum thyroid hormone concentration in cirrhotic patients observed were, low serum T3 level, raised rT3 level, and a normal TSH levels. There are many factors those may be responsible for these abnormalities, which includes alteration in plasma level of thyroid binding proteins, altered binding of T4 and T3 to their carrier protein, impaired hepatic clearance of reverse T3 (rT3), hyperglucagonemia, and reduced extrathyroidal conversion of T4 to T3. In cirrhotic patients, because of extensive hepatic inflammation and fibrosis, there is inhibition of Type 1 (D1) deiodinase enzymes that lead to decreased conversion of T4 to T3. Since the type 2 (D2) deiodinase enzymes remain active, now most of the T4 is converted into rT3 leading to increased rT3 levels.

The present study showed that severity of liver disease increases as indicated by serum bilirubin grade. The prevalence of decreased T3 level is also increased 3 of 15 patient with decreased level of T3 in cirrhotic patient with S. bilirubin grade I. The present study showed that as severity of liver disease increased as indicated by serum INR (prothrombin time) level grade. The prevalence of decreased T3 level is also increased with decreased level of T3 in cirrhotic patient with serum INR grade I. The liver has important role in thyroid hormone metabolism because it is the manufacturer of protein that bind thyroid hormone, such as thyroid-binding globulin (TBG), pre-albumin and albumin. It also the major site of thyroid hormone peripheral metabolism and is involved in its conjugation biliary excretion, oxidative deamination and the extra thyroidal deiodination of thyroxin (T4) to triiothyronine (T3) and to reverse T3 On the other hand the level of thyroid hormone is also important to normal hepatic function and bilirubin metabolism. Hypothyroidism may have features that mimic liver disease; example include myalgias, fatigue and muscle cramps in the presence of an elevated aspartate aminotransferase from a myopathy, coma associated with hyperammonaemia in Myxoedema coma and Myxoedema ascites.[16-18] There is also evidence that hypothyroidism may directly affect the liver structure or function. The liver is the major sites of cholesterol and triglyceride metabolism, and the thyroid hormones play an integral part in hepatic lipid homeostasis. The thyroid hormones increase the expression of LDL receptors on the hepatocytes and increase the activity of lipid lowering liver enzymes, resulting in a reduction in low-density lipoprotein levels. Thyroid hormones also increase the expression of Apo lipoprotein A1, a major component of high density lipoprotein.[19,20]

CONCLUSION

In this present study was found that a complex relationship exists between the thyroid gland and liver in both health and disease. The present study revealed that cirrhotic patients were more prevalence thyroid dysfunction specially hypothyroidism because of many reasons. All cirrhotic patients should undergo for evaluation of endocrinological evaluation as these patients are definitely associated with development of hypothyroidism. After diagnosis the treatment of endocrinological disorder especially hypothyroidism may increase survival.

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