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Original Research Article

Comparative study of prevalence of hypothyroidism in cirrhotic patients and normal individuals

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ABSTRACT

Background: Alcoholic cirrhosis has worse prognosis than primary billiary cirrhosis and cirrhosis due to hepatitis. The risk of death due to all cause is increased 12-fold with cirrhosis. Alcoholic liver cirrhosis develops between 10-20% of individuals who drink heavily for a decade or more. Chronic hepatitis B is probably the most common cause of cirrhosis worldwide. The aim and objective of this study was to compare the prevalence of hypothyroidism between cirrhotic patients and normal healthy individuals.
Methods: The present study constitutes of 50 patients with cirrhosis of liver who met our inclusion criteria. They were selected from the patients admitted in medical wards and gastroenterology ward of RNT medical college, Udaipur.
Results: Majority of patients were of serum albumin level class III about 67%. Increased TSH level as compare to level of serum albumin in cirrhotic patients. When serum albumin level decreases then percent of TSH level increases. Majority of patients were from serum bilirubin class III (71%). Majority were from serum bilirubin class III about 70%.
Conclusions: All cirrhotic patients should undergo for evaluation of endocrinological evaluation as these patients are associated with development of hypothyroidism. After diagnosis the treatment of endocrinological disorder especially hypothyroidism may increase survival.

Keywords: Liver disease, Alcoholism, Serum albumin, Hypothyroidism

INTRODUCTION

Established cirrhosis has a 10-year mortality of 34-66%, largely dependent on the cause of the cirrhosis.[1] Alcoholic cirrhosis has worse prognosis than primary billiary cirrhosis and cirrhosis due to hepatitis. The risk of death due to all cause is increased 12-fold with cirrhosis.[2] 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.[3] There is great variability in the amount of alcohol needed to cause cirrhosis (as little as 3-4 drinks a day in some men and 2-3 in some women). Infection with hepatitis C virus causes inflammation and low grade damage to the liver that over several decades can lead to cirrhosis.[4] Chronic hepatitis B is probably the most common cause of cirrhosis worldwide.[5] 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.[6]

Liver and thyroid gland: physiopathology[7]

T3 and T4 diminish due to inefficient hepatic deionization and defective hepatic cellular up take. T4 level decreases, most likely because of an inefficient production of thyroid binding globulin, or the action of a peripheral binding inhibitor. During acute liver disease and primitive billiary cirrhosis one can observe an increase of T4 and TBG together with an increase of the acute phase protein. Such complex hormonal mechanisms are not influenced by TSH, which appear normal or inhabited, as the TRH stimulus test in normal. The explication can be found in an enhanced conversion of T4 to T3 in the pituitary gland. The biological and clinical significance of these mechanisms might be that of creating a "protective" state for an organism in a catabolic state by reducing the circulating thyroid hormones T3. A relation has been found between circulating thyroidal hormone level particularly the T3, rT3 and rT3/T3 ratio, and the state of hepatic functional insufficiency.[7]

Thyroid status in alcoholic cirrhosis[8]

Liver is of considerable importance in metabolism of thyroid hormones, plasma level T4, T3 with their unbound fraction (FT4 and FT3), reverse T3 (rT3). An inactive isomer of T3-Thyrotrophic (TSH) and TSH response to thyrotrophic releasing hormone (TRH-250 µg). FT4 was elevated in patients (17.1 vs 13.1 pg/ml; $p<0.02$) although FT3 was slightly decreased (3.4 vs. 4.5 pg/ml; $p<0.10$) with an FT4: FT3 ratio (7.0 vs 3.0; $p<0.02$). rT3 was elevated (592 vs 206 ng/100ml; $p<0.01$) correlated with FT4/FT3:rT3/T3 ratio ($p<0.01$) and with the severity of the cirrhosis, Basal TSH level (3.3 µU/ml) and TSH responsiveness to TRH was normal though very scattered, and independent from T3 and T4 values. It may be concluded that; euthyroid in cirrhosis assessed by a normal responsiveness to TRH, result from a compensatory increase in FT4, the low T3 and FT3 levels may proceed from an impairment of peripheral T4 in to T3 conversion with a derivation pathway to word rT3.

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 (K-disappearance rate, ICG-indocyanine green test). No difference in serum TSH value were found between chronic liver disease and normal subject.[9] The present dates confirm the existence of several abnormalities of thyroid function tests in patient with chronic liver disease, although showing that euthyroidism is almost always maintained, probably as a result of low normal FT3 and high-normal FT4. Furthermore, T3 serum levels appear to parallel the severity of liver dysfunction.

Aim and objectives

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.

METHODS

The prospective comparative study was conducted on 100 patients admitted to RNT medical college and attached group of hospital (MBGH) and found to be clinically, biochemically and radiologically proved liver cirrhosis patients during the period April 2019 to March 2020. 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 50 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 like

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 (hepatofugal flow). 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.

Radioimmunoassay test for thyroid hormone

The current assay method is based on Berson and Yalow's concepts of radioimmunoassay.[15] A determined amount of patient serum or thyroxine standard is mixed with radioactively labelled thyroxine (T-4 125 I) and 8-anilino-1-napthalene sulphonic acid (ANS) in the preferred embodiment's test process, followed by the addition of an immobilised T-4 antiserum (T-4 antiserum covalently bound to aqueous suspendable hydrolyzed polyacrylamide beads). At room temperature, the mixture is left to incubate. Thyroxine is displaced from serum proteins by the ANS. On the basis of their relative concentrations, the displaced thyroxine competes with the tagged thyroxine for the immobilised thyroxine antibodies throughout incubation (Berson, 1960).[15]

This invention additionally includes a novel reagent for use in the immunoassay, which consists of hydrolyzed cross-linked polyacrylamide particles with at least one dye selected from Alcian yellow and Alcian blue absorbed thereon. The laboratory technician doing the assay will benefit greatly from these coloured particles. The coloured polyacrylamide particles make it easier to monitor the initial filling processes of the various vessels used, as the polyacrylamide particles are water white and difficult to notice. Following the pellet formation step of centrifugation, the dye allows the pellet to be easily located for the remaining manipulative steps. The dye also prevents the technician from accidentally decanting beads with the supernatant after centrifugation. The dyes used in this reagent have been found to be one-of-a-kind in that they can be surface absorbed on polyacrylamide particles and stay there in the ionic buffer environment that exists during the various steps of the assay procedure. The overall assay procedure has a number of distinguishing features.

The ability to form stable hydrophyllic suspensions distinguishes the hydrolyzed cross-linked polyacrylamide particles used as solid phase substrates for the antibodies. As a result, no agitation is required to maintain the desired homogeneous condition in the reaction mixture during which thyroid hormone is separated from serum proteins and competitive binding with the antibody occurs in the presence of radioactive tracer. The method calls for accelerating the incubation step by using heat, such as incubation at temperatures between 37 and 50 °C °C. Because agitation is not required, this heating can be accomplished quickly with the current method.

Prior art procedures such as those of Axen et al (dextran particles), sorin (cellulose particles), and corning (glass particles) differ in that such particles settle out relatively quickly, and the assays require continuous stirring of the immobilised reagents during addition and constant agitation of the solution throughout the incubation period. Constant agitation is a very inconvenient operation when heating is used. For completeness, it should be noted that in short assays, the Corning procedure, which uses glass particles to immobilise the antibody, may have less of a settling problem than the others. However, the settling issue still exists in general. The fact that commercially available materials come in factory pre-filled tubes for each assay sample demonstrates the difficulty in obtaining uniform suspensions for precise aliquot sampling. Other distinguishing features of the present invention are the polyacrylamide particles' low non-specific binding properties. Non-specific binding is so low that the radioactivity levels of the initially separated solid phase particles after incubation can be measured directly without any initial washings. Prior art solid phase supports, such as the one described in the Axen et al patent, require pre-washing steps before the radioactive tracer can be measured.

The removal of the washing steps, as well as the addition of other elements such as surfactants, as used by Axen et al to reduce non-specific absorption, improves the speed and convenience of the current assay procedure significantly. The above benefits are obtained by using hydrolyzed cross-linked polyacrylamide particles with a particle size of 0.1-10 µ in the unhydrolyzed form, usually about 1-5 µ, and preferably a particle size distribution centred around 5 microns.

Statistical analysis

Results were expressed as proportions for qualitative data and as mean±SD for quantitative data. For non parametric data chi-square test and for parametric comparison between two groups independent sample `t` test was applied. The p value was calculated based on the above tests and values <0.05 was considered significant.

RESULTS

The present study constitutes of 50 patients with cirrhosis of liver who met our inclusion criteria. They were selected from the patients admitted in medical wards and gastroenterology ward of RNT medical college, Udaipur. Among the 50 cirrhotic patients, 43 (86%) were males

and 7 (14%) were females, while in control 32 (64%) were males and 18 (36%) were females.

Table 1: Age and sex distribution.

Age (years)	Cirrhosis patients (N=50)			Control (N=50)		
	Male, N (%)	Female, N (%)	Total, N (%)	Male, N (%)	Female, N (%)	Total, N (%)
<30	3 (7)	0	3 (6)	6 (19)	6 (33)	12 (24)
31-40	12 (28)	2 (29)	14 (28)	10 (31)	3 (17)	13 (26)
>41	28 (65)	5 (71)	33 (66)	16 (50)	9 (50)	25 (50)
Total	43 (86)	7 (14)	(50)	32 (64)	18 (36)	(50)

Table 2: Prevalence of alcohol consumption in cirrhosis and control subjects.

Alcohol consumption	Cirrhosis			Control		
	Male	Female	Total, N (%)	Male	Female	Total, N (%)
Yes	41	0	41 (82)	4	0	4 (8)
No	2	7	9 (18)	28	18	46 (92)
Total	43	7	50	32	18	50

Table 3: Etiology of cirrhosis of liver in study group.

Variables	ALD	HBV	HCV	ALD+HBV	Other	Total
Males	40 (100)	1 (33.3)	0	1 (100)	1 (20)	43 (86)
Females	0	2 (66.6)	0	0	5 (80)	7 (14)
Total	40 (80)	3 (6)	0	1 (2)	6 (12)	50 (100)

Table 4: Association between severity of liver disease and hypothyroidism.

Child Pugh Turcotte grade	Increased TSH (hypothyroidism)	Decreased T3	Decreased T4
A	0 (0)	3 (18)	1 (5)
B	2 (9.5)	0 (0)	2 (10)
C	19 (90.5)	14 (82)	17 (85)
Total	21	17	20

Table 5: Association between serum albumin level and decreased T3 level in cirrhotic patient.

Variables		Serum albumin level (µg/ml) g/dl			Total
		>3.5 (I)	**2.8-3.5 (II)**	**<2.8 (III)**	
T3 Level	Decreased (<0.7 ng/ml)	4 (23)	3 (18)	10 (59)	17 (34)
T4 Level	Decreased (<5.5 µg/dl)	2 (10)	4 (20)	14 (70)	20
TSH Level	Increased (4.20 µU/ml)	0	7 (33)	14 (67)	21

Table 6: Association decreased T3 level and S. bilirubin level in cirrhotic patients

Variables		Serum bilirubin level			Total
		<2 (I)	**2-3 (II)**	**>3 (III)**	
T3 Level	Decreased (<0.7 ng/ml)	4 (23)	1 (6)	12 (71)	17
T4 Level	Decreased (<5.5 µg/dl)	4 (20)	2 (10)	14 (70)	20
TSH Level	Increased (4.20 µU/ml)	3 (14)	3 (14)	15 (72)	21

Among the patients with cirrhosis, the maximum number of patient (66%) were above 41 years and so also in the control group 25 (50%). Among total number of 50 cirrhosis patients, 41 (82%) had history of alcohol intake & in control group 4 (8%) 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, 33.3% were male. Among patients in whom cause could not be elucidated, it was seen that majority (80%) more females. From (Table 4) it is seen that patients with child pugh A and B form 22% of patient and patients with child pugh grade C form 78%. From the above table it is seen that 90.5% increased

TSH, 82% decreased T3 and 85% 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.

Table 7: Association between decreased T3 level and INR.

Variables		INR			Total
		<1.7 (I)	1.7-2.3 (II)	>2.3 (III)	
T3 level	Decreased (<0.7 ng/ml)	5 (29)	4 (24)	8 (47)	17
T4 level	Decreased (<5.5 µg/dl)	6 (30)	7 (35)	7 (35)	20
TSH level	Increased (4.20 µU/ml)	4 (19)	11 (52)	6 (29)	21

Decreased T_3 level in cirrhotic patients as compare to serum albumin in cirrhotic patient, T_3 level as compare to level of serum albumin cirrhotic patient in majority were from serum albumin class 3 about 59%. 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 67%. Decreased T3 level as compare to level of serum bilirubin level in cirrhotic patients. Majority were from serum bilirubin class III about 71%. 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 21 patients with TSH level, as compare to level of serum bilirubin level in cirrhotic patients. Majority were from serum bilirubin level class III about 72%. Decreased T3 level, as compare to INR level in cirrhotic patients. Majority were from INR class 3 about 47%. Decreased T4 level, as compare to level of INR in cirrhotic patients. Majority were from INR class II and III about equally 35% and 35%. Increased TSH level among 21 patients with TSH level, as compare to level of INR in cirrhotic patients. Majority were from INR class II about 52%.

DISCUSSION

The study included 50 patients with liver cirrhosis and 50 normal healthy individuals as control and compared the prevalence of Hypothyroidism in patient of cirrhosis. Out of 50 patient with cirrhosis 43 (86%) were male and 7 (14%) were female. In control group 32 (64%) were males and 18% were female. Most (66%) of the patient with cirrhosis were in >41 age group. Alcoholic liver disease was the cause of cirrhosis in 40 (80%) patients. All patients with alcoholic cirrhosis were males. HBV was next most common (6%) cause of cirrhosis. Etiology could not be elucidated in 6 (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.[11,12] 4 (8%) patients with cirrhosis were in child pugh Turcotte (CPT) grade A, 7 (14%) were in grade B and 39(78%) were in grade C. In this cross- sectional study it was seen that prevalence of hypothyroidism in cirrhosis patient was 42% i.e. 21 out 50 cirrhotic patients had increased TSH level. This is in accordance with most studies in literature which show prevalence of hypothyroidism in range 10-49%. 18 (85%) out of 21 patients with hypothyroidism were male indicating hypothyroidism was more common in male cirrhotic. 3 (15%) out of 21 patients hypothyroidism were female indicating hypothyroidism was less common in female cirrhotic.

The comparison of sex distribution in patients with cirrhosis between hypothyroidism and non-hypothyroidism group was not statistically significant ($p>0.05$) which is in accordance in study by Jacques et al.[13] But in contrast to study by Sapin et al which showed that male sex was risk factor for hypothyroidism in cirrhosis.[14] Regarding the etiology of cirrhosis in those with hypothyroidism our study found alcoholic cirrhosis to be the most common etiology (80%) which in accordance with study by Jacques et al.[13] Review of data in literature on this aspect gives varying in formation. In study by Schlienger et al, Sapin et al, hypothyroidism was more frequent in HBV cirrhosis.[13,14] In study by Tasi et al hypothyroidism was most common in HCC related cirrhosis.[15]

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. 5 out of 50 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 (0%) of 21 patients with hypothyroidism were in CPT grade. 'A' compared to 2 (9.5%) in CPT grade 'B' and compared to 19 (90.5%) 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 <5, hence, Chi-square test was not possible. However, the value of Chi-square in this existing situation was 9.946 with probability of test which was significant. 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.[13-15] This was in contrast to study by Kumamoto, which showed that hypothyroidism prevalence is independent of severity of liver disease.[13]

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.[11] The present study showed that as severity of liver disease increases as indicated by serum albumin grade, the prevalence of decrease T3 level is also increase 4 (23%). Compared to 10 (59%) in albumin grade III and prevalence of decreased T4 level is also increased to 2 (10%) of 20 patients with decreased level of T4 in cirrhotic patient with albumin grade I. Compared to 14 (70%) in serum albumin grade III, prevalence of increased TSH level is also increased 7 (33%) of 21 patients with increased level of TSH in cirrhotic patients with albumin grade II compared to 14 (67%) in serum albumin grade III.

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 4 (23%) of 17 patient with decreased level of T3 in cirrhotic patient with S. bilirubin grade I. Compared to 12 (71%) in serum bilirubin grade III and prevalence of decreased T4 level is also increases 4 (20%) of 20 patient with decreased level of T4 in cirrhotic patient with serum bilirubin grade I. Compared to 14 (70%) in serum bilirubin grade III. Prevalence of increased TSH level is also increased 3 (14%) of 21 patient with increased level of TSH in cirrhotic patients with serum bilirubin grade I compared to 15 (72%) in serum bilirubin grade III.

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 5(29%) of 17 patient with decreased level of T3 in cirrhotic patient with serum INR grade I. Compared to 8 (47%) in serum INR grade III and prevalence of decreased T4 level is also increased 6 (30%) of 20 patient with decreased level of T4 level in cirrhotic patient with serum INR grade I. Compared to 7 (35%) in serum INR grade III. prevalence of decreased TSH level is also increased 11 (52%) of 21 patient with increased level of TSH in cirrhotic patients with serum INR grade II. Compared to 6 (28%) in serum INR grade III.

CONCLUSION

According to this study 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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