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TO FIND OUT THE CORRELATION BETWEEN SEVERITY OF CIRRHOSIS AND FT3 LEVELS IN PATIENTS OF CIRRHOSIS IN BUNDELKHAND REGION

General Medicine

Dr Rambabu Associate Professor and Head, Department of Medicine, Maharani Laxmi Bai Medical College, Jhansi, Uttar Pradesh.

Dr Mandavi Agarwal Assistant Professor, Department of Medicine, Maharani Laxmi Bai Medical College, Jhansi, Uttar Pradesh.

Dr Shikhar Garg* Junior Resident, Department of Medicine, Maharani Laxmi Bai Medical College, Jhansi, Uttar Pradesh. *Corresponding Author

Dr P K Jain Professor, Department of Medicine, Maharani Laxmi Bai Medical College, Jhansi, Uttar Pradesh.

ABSTRACT

Aims and objectives: To find out the correlation between severity of cirrhosis and thyroid function abnormalities in patient of cirrhosis.

Materials and methods: This was a cross sectional study conducted in M.L.B Medical College, Jhansi (U.P.). It comprised of a total of 100 patients of cirrhosis coming to OPD and Emergency of Department of General Medicine, Maharani Laxmi Bai Medical College, Jhansi during the period of May 2019 to October 2020. Patients were divided into various groups according to Child-Pugh score, MELD score and grades of HE.

Results: Child-Pugh Class C pts had statistically significant low levels of FT3 (p=0.0001) as compared to Class B & A pts. No significant correlation was observed for FT4 and TSH among Class A, B and C pts. FT3 levels were significantly lower in HE Grade 4 pts as compared to pts without HE (p= 0.0001). No significant correlation was observed for FT4 and TSH with grades of HE. FT3 & FT4 levels were significantly lower in pts with MELD score 30-39 as compared to pts with MELD score <9 (p= 0.0001 and 0.0334 respectively). No significant correlation was observed for TSH with MELD score. FT3 and FT4 levels were significantly low in patient with INR >2.3 as compared to INR <1.7 (p= <0.0001 and 0.0014 respectively). No significant correlation was observed for TSH with INR.

Conclusion: The most common etiology of cirrhosis in our study was Alcohol. FT3 levels are statistically significantly decreased with increasing severity of liver disease as measured by Grades of Hepatic Encephalopathy, INR levels, Child Pugh Scores and MELD Scores. FT4 levels are statistically significantly decreased with increasing severity of liver disease as measured by INR levels and MELD scores. Similar correlations could not be demonstrated for Child Pugh scores or grades of Hepatic Encephalopathy. Similar correlations could not be demonstrated for TSH. Our study demonstrates that FT3 level can be used as a predictor of declining hepatic function, decreasing as the severity of liver damage increases.

KEYWORDS

Ft3, FT4, liver cirrhosis, Child–Turcotte–Pugh.

INTRODUCTION

The liver is the foremost seat of metabolism in our body. It is responsible for the regulation as well as generation of a vast number of metabolites. It also plays a crucial role in activation and excretion of a large number of drugs. All this is achieved by a vast array of enzymatic reactions that occur here serving to tightly regulate the levels of virtually every substance in the blood, be it nutrients, hormones or drugs. As such dysfunction of the hepatobiliary system can have a myriad of manifestations.

Since the functions of the thyroid gland and liver are interlinked, liver dysfunction is expected to cause derangements in thyroid function as well. This relationship has been evaluated over the years via various studies. Though still a matter of much debate, the mechanism of thyroid dysfunction in liver disease is thought to be due to a multitude of metabolic disturbances including reduced peripheral conversion of T4 to T3 and alteration in the levels of various thyroid binding proteins in the plasma.

This study aims to evaluate the correlation between thyroid dysfunction and liver disease, particularly that of FT3 & also its relation to the severity of liver disease.

AIMS AND OBJECTIVES:

- To find out the correlation between severity of cirrhosis and thyroid function abnormalities in patient of cirrhosis.

MATERIALS AND METHODS:

This was a cross sectional study conducted in M.L.B Medical College, Jhansi (U.P.). It comprised of a total of 100 patients of cirrhosis coming to OPD and Emergency of Department of General Medicine, MLB Medical College, Jhansi during the period of May 2019 to October 2020. Patients were divided into various groups according to Child-Pugh score, MELD score, INR levels and grades of HE.

Cut off values for thyroid hormones were taken as follows:

- TSH: 0.34-4.25 mIU/ml
- FT3: 2.4-4.2 pg/ml
- FT4: 0.7-1.24 ng/dl

Cirrhosis was defined by the presence of clinical features (ascites, splenomegaly, jaundice, upper GI bleed), biochemical characteristics (raised bilirubin, SGOT, SGPT, decreased albumin, seropositivity for Hep B or C) and radiological evidences (shrunken liver, coarse echotexture).

INCLUSION CRITERIA:

- Patients with clinical, biochemical, and radiological evidence of cirrhosis of liver.

EXCLUSION CRITERIA

- Patients on medications altering thyroid function such as thyroxine, propylthiouracil, carbimazole etc.
- Patients on medications that could affect the study outcome, including Carbamazepine, Phenytoin, Phenobarbitone, Salicylates.
- Patient of liver disease not having cirrhosis.
- Patient of ascites due to any other cause.
- Pregnant patients.

Location and period of study

The study was carried out in the Department of Medicine, M.L.B. Medical College, Jhansi (U.P.) from March 2019 to October 2020.

Methodology & statistical analysis:

The diagnosis of cirrhosis was confirmed by either, laboratory findings of liver failure or ultrasound proven portal hypertension. Hepatitis B and C were confirmed by ELISA for Hepatitis B and Hepatitis C & viral load was quantified by levels of HBV DNA & HCV RNA respectively. Patients of alcoholic liver disease were asked to specify the amount & duration of alcohol consumption. PT/INR was done to calculate both Child Pugh & MELD scores. Patients suffering from previously known thyroid dysfunction or with clinical findings of thyroid disease, were not considered in the study.

Patients fulfilling the inclusion criteria were recruited in the study after taking informed written consent. Blood samples were taken for assessment of thyroid function, liver function. Clinical complications including ascites, encephalopathy, bleeding varices, and spontaneous bacterial peritonitis (SBP) were also evaluated. Child Pugh score was recorded and MELD risk score was calculated according to the following formula: MELD = 9.57 x ln (creatinine mg/dL) + 3.78 x ln(bilirubin mg/dL) + 11.20 x ln (INR) +.6.43.

Circulating free T3 (FT3: 2.4-4.2 pg/ml) and free T4 (FT4: 0.7-1.24 ng/dl) were measured with ChemiluminiscentMicroparticle Immunoassay (CMIA).

USG whole abdomen was done to confirm cirrhosis of liver & to see the presence of dilated Portal Vein. Detailed history and examination was done for complications of cirrhosis such as varices, ascites, hepatic encephalopathy and SBP.

STATISTICALANALYSIS:

During analysis, in order to figure out significant differences, patients were divided into different groups according to Child-Pugh classes, grades of HE, INR levels and MELD scores. Statistical analysis was performed using SPSS 21.0 (SPSS Inc., Chicago, IL). ANOVA test was used as appropriate. A P-value < 0.05 was considered statistically significant.

OBSERVATION AND RESULTS:

- Out of 100 pts 67 (67%) were males and 33 were females (33%).
- Most common etiology in our study was Alcohol (57%), followed by Others (29%) and Viral (14%).
- The distribution of Hepatic Encephalopathy in our study was as follows:
- None- 51%
- Grade 1- 0%
- Grade 2- 18%
- Grade 3- 20%
- Grade 4- 11%

Chart 1: Distribution of Etiologies

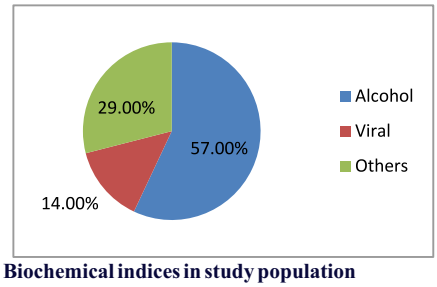

Table 1: Biochemical indices in study population

Class	Bilirubin	Albumin	SGOT	INR
A	0.96 ±0.6	3.3 ±0.28	44.8 ±11.26	1.01±0.16
B	1.76 ±1.06	3.03 ±0.34	61.07 ±58.85	1.47 ±0.32
C	4.63 ±3.65	2.95 ±0.43	112.3 ±104.9	2.29 ±0.99

Chart 2: Hepatic Encephalopathy in study population (n=100)

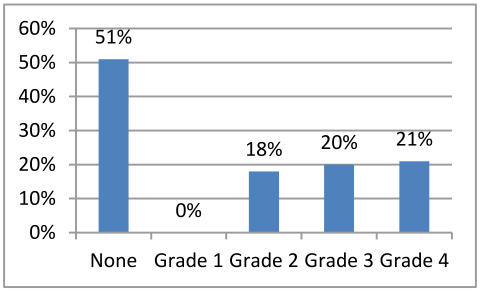

Table 2: Comparison of thyroid indices among Class A, Class B and Class C pts

Class	TSH	FT3	FT4
A (n=20)	2.64 ±0.59	3.05 ±0.5	1.06 ±0.16
B (n=37)	4.11 ±3.45	2.19 ±0.59	1.05 ±0.25
C (n=43)	2.46 ±2.09	1.67 ±0.71	1.17 ±1.01
p value (ANOVA test)	-	0.0001	0.7000

Table 3: Relation of thyroid profile with HE in study population

Thyroid Profile	None	Grade 2	Grade 3	Grade 4	p value (ANOVA)
FT3	2.51 ±0.73	1.85 ±0.64	1.71 ±0.83	1.69 ±0.34	0.0001
FT4	1.16 ±0.57	1.03 ±0.32	1.21 ±1.12	0.79 ±0.18	0.3603
TSH	3.48 ±2.45	3.45 ±3.28	1.58 ±1.35	3.61 ±2.91	-

Table 4: Comparison of thyroid indices in all pts according to MELD Score (n=100)

Thyroid Profile	≤9 (n=21)	10-19 (n=48)	20-29 (n=23)	30-39 (n=8)	p value (ANOVA)
Ft3	2.96 ±0.57	2.14 ±0.65	1.66 ±0.73	1.37 ±0.47	0.0001
FT4	1.1 ±0.22	1 ±0.27	1.46 ±1.3	0.79 ±0.2	0.0334
TSH	2.52 ±0.71	3.64 ±3.2	2.57 ±1.88	3.23 ±2.30	-

Table 5: Comparison of thyroid indices in all patients according to INR levels (n=100).

Thyroid Profile	INR <1.7 (n=64)	INR 1.7-2.3 (n=20)	INR >2.3 (n=16)	P value
FT3	2.45 ±0.72	1.55 ±0.63	1.65 ±0.67	<0.0001
Ft4	1.03 ±0.26	1.57 ±1.35	0.83 ±0.16	0.0014
TSH	2.78 ±2.6	4.31 ±2.37	2.93 ±2.58	0.0724

Child-Pugh Class C pts had statistically significant low levels of FT3 (p=0.0001) as compared to Class B & A pts.

No significant correlation was observed for FT4 and TSH among Class A, B and C pts.

FT3 levels were significantly lower in HE Grade 4 pts as compared to pts without HE (p= 0.0001).

No significant correlation was observed for FT4 and TSH with grades of HE.

FT3 & FT4 levels were significantly lower in pts with MELD score 30-39 as compared to pts with MELD score <9 (p= 0.0001 and 0.0334 respectively).

No significant correlation was observed for TSH with MELD score.

FT3 and FT4 levels were significantly low in patient with INR >2.3 as compared to INR <1.7 (p= <0.0001 and 0.0014 respectively).

No significant correlation was observed for TSH with INR.

DISCUSSION

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 triiodothyronine (T3). Moreover, it is involved in conjugation and circulation of thyroid hormones by synthesis of thyroid binding proteins.

Hence, disorders of liver lead to a derangement in thyroid profile that may serve as an indicator of severity of and prognosis of the disease.

The mean age of patients in our study was 47.33+14.04 and maximum patients were in the age group of 31-40 years.

Etiology:

In our study, the most common etiology was Alcohol (57%). Patients whose etiologies did not fall under Alcoholic or Viral were grouped together as others and they amounted to 29% followed by Viral causes (14%). This is similar to the study by Punekar, et al[1] where Alcohol was the most common etiology (46%) followed by Hepatitis B (19%), Hepatitis C (3%), Wilson's disease (1%) and others. In the study by Nilesh Kumar, et al[2] too, Alcohol was the most common etiology (70%) along with Hepatitis B (26%) and Hepatitis C (4%).

Thus, alcoholism is the most common cause of cirrhosis of liver.

FT3:

The most significant finding in our study was the presence of low FT3 in patients of cirrhosis. 10% patients in Child Pugh Class A, 54% patients in Class B and 74% patients in Class C had a lower than normal level of FT3. The mean value of FT3 also follows a similar trend when compared among these classes with 3.05 ±0.5 for Class A, 2.19 ±0.59 for Class B & 1.67 ±0.71 for Class C and this difference is statistically

significant (p <0.05). When compared with grade of Hepatic Encephalopathy, there was a statistically significant difference between FT3 between patients with HE grade 4 (1.69 ±0.34) and patients without HE (2.51 ±0.73) (p <0.05). Also when compared on the basis of MELD scores patients with a score of 30-39 had a much lower FT3 as compared to those with and score <9 (1.37 ±0.47) vs 2.96 ±0.57) and this difference was statistically significant. With relation to INR levels also, FT3 showed a statistically significant difference between patients with INR <1.7 and INR >2.3 (p <0.0001). Similar results have been demonstrated in various studies.

Nilesh Kumar, et al[2] demonstrated that as the severity of cirrhosis increases, which is indicated by Child Pugh A to C serum level of FT3 reduces. All the patients of Child Pugh C had low FT3 levels and the findings were statistically significant (p <0.05). Mansour-Ghanei F, et al[3] found a negative correlation between Child Pugh scores total serum T3 level (r= -0.453, p<0.0001). Also a reverse correlation was observed between MELD score and FT3 level (r= -0.305, p=0.014). Punekar, et al[1] showed that cirrhosis patients has a statistically significant lower level of FT3 (<0.0001) compared with controls. Patients of cirrhosis with HE had significantly lower levels of FT3 (p=<0.0001) compared with patients of cirrhosis without HE. FT3 level was significantly low in HE Grade 4 patients compared to HE Grade 1 patients (p=0.0001). FT3 was negatively correlated with Child Pugh and MELD scores and also with Prothrombin Time but not INR.

Kayacetin E, et al[4] also showed that serum levels of FT3 were significantly lower in patients with HE compared to decompensated cirrhosis patients without HE (p <0.05). Also, an inverse correlation was found between INR and FT3 levels (r= -0.515, p= 0.001). SetsuoNomuira, et al[5] showed that the reduction of serum total and FT3 value were closely correlated with degree of liver damage. These findings suggest that impairment of T4 conversion in patients with advanced hepatic cirrhosis may lead to reduced T3 production and lower serum T3 levels.

FT4:

In our study FT4 was reduced in 5% patients in Class A, 5.41% patients in Class B and 30.23% patients in Class C. Upon comparison with Child Pugh class, FT4 did not show a significant difference among the classes (p=0.7). Similarly, FT4 did not show a correlation with HE in our study (p=0.3603). FT4 showed a statistically significant difference between patients with MELD score <9 and MELD 30-39 (p=0.0334). Also when patients were divided into various groups based on INR levels, FT4 showed a statistically significant difference among groups (p=0.0014).

This is in contrast to Nilesh Kumar, et al[2] who demonstrated that FT4 levels had significant inverse correlation with severity of cirrhosis as measured by Child Pugh score. Our results are in agreement with Kayacetin E, et al[4] who showed that level of total T4 but not FT4 were lower in patients of Hepatic Encephalopathy as compared to decompensated patients without HE. They also found an inverse correlation between T4 levels and Prothrombin Time (INR) (p=0.001). Mansour-Ghanei F, et al[3] also did not find any significant correlation between FT4 and severity of cirrhosis on the basis of clinical manifestations, Child Pugh class or MELD score. Punekar, et al[1] similarly showed that there was no statistically significant difference between FT4 levels in patients of cirrhosis with HE compared with patients of cirrhosis without HE. They however found a negative correlation between FT4 and Child Pugh score but no significant correlation was found for MELD score (p=0.27). They also found a negative correlation between FT4 levels and Prothrombin Time. This difference may be due to difference in sample size, severity of disease and regional variation in thyroid profile.

TSH:

The mean value of TSH in our study was 2.64+2.09 in Class A patients, 4.11 ±3.45 in Class B and 2.64 ±2.09 in Class C patients. TSH was within normal range in class A patient, while 29.73% patients had increased TSH in class B and 18.6% patients had increased TSH in Class C. TSH did not show a significant variation with grades of HE with mean TSH in all groups within normal range. In relation to MELD score, serum albumin and INR levels also TSH did not show a particular correlation.

This is in agreement with the study by Kayacetin E, et al[4] who showed that there was no significant difference in serum TSH levels in controls, patients with Hepatic Encephalopathy and decompensated cirrhotic patients (Child C group). Also there was no significant difference in TSH levels in cirrhotic patients with HE compared to all cirrhotic patients. No significant differences were observed when TSH levels were compared among Child A, B and C groups. Similarly in the study by Mansour-Ghanei F, et al[3] no significant difference was found for TSH when patients were divided on the basis of Child Pugh class or MELD scores.

Our findings are in contrast to Nilesh Kumar, et al[2] who found that as the severity of cirrhosis increased from Child Pugh A to C serum level of TSH started to rise above normal (p<0.05). Similarly in the study by Punekar, et al[1] high TSH levels were found in 20% patients of decompensated cirrhosis. There was a statistically significant difference between levels of TSH between cirrhosis patients and healthy controls (p<0.05). However patients of cirrhosis with HE did not show a significant difference in TSH levels compared to patients without HE.

CONCLUSION

- The most common etiology of cirrhosis in our study was Alcohol.
- FT3 levels are statistically significantly decreased with increasing severity of liver disease as measured by Grades of Hepatic Encephalopathy, INR levels, Child Pugh Scores and MELD Scores.
- FT4 levels are statistically significantly decreased with increasing severity of liver disease as measured by INR levels and MELD scores. Similar correlations could not be demonstrated for Child Pugh scores or grades of Hepatic Encephalopathy.
- Similar correlations could not be demonstrated for TSH.
- Our study demonstrates that FT3 level can be used as a predictor of declining hepatic function, decreasing asthe severity of liver damage increases.
- Our study is limited by the fact that other etiologies of cirrhosis apart from Alcohol and Viral could not be evaluated in detail. Further large multi-center studies are needed to evaluate their relationship with thyroid profile.

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