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# To Study Incidence of Thyroid Dysfunction and its Correlation With Severity of Liver Failure in Patients of Cirrhosis of Liver

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**Abstract**

**Introduction:-** Cirrhosis is defined as a diffuse process characterized by fibrosis and the conversion of normal liver architecture into structurally abnormal nodules. The liver plays an important role in the metabolism of thyroid hormones and subtle thyroid dysfunction are significantly associated with severity of cirrhosis of liver. Main objective of our study was to ascertain levels of fT3 , fT4, TSH and their correlation with severity of liver failure in patients of liver cirrhosis as per Child Turcotte Pugh(CTP) score.

**Material and methods:-** The case control study was carried out in 50 patients of cirrhosis of liver and age sex matched 50 healthy controls. Cirrhosis of liver was diagnosed based on clinical symptoms and signs, impaired liver function and ultrasonographic features consistent with cirrhosis. Severity of liver failure was assessed on the basis of Child Turcotte Pugh score. Thyroid function test such as fT3,fT4,TSH levels were evaluated within 24 hours of admission.

**Results and Conclusion:-** Our study found that serum fT3 and serum fT4 levels were lower among cases (3.63 ± 0.97 pmol/L & 14.67 ± 2.12 pmol/L) as compared to controls (5.24 ± 0.82 pmol/L & 16.28 ± 1.74 pmol/L) ($p<0.001$). Serum TSH level was found to be higher among cirrhotic cases (4.16 ± 0.61µIU/ml) as compared to controls (2.10 ± 1.04 µIU/ml) ($p<0.001$). Our study established the fact that incidence of low serum fT3, low serum fT4 with normal TSH are significantly associated with severity of cirrhosis.

**Keywords**: Cirrhosis of liver, Thyroid dysfunction, Child Turcotte Pugh(CTP) score

## Introduction

Cirrhosis is defined by the World Health Organization (WHO) as a diffuse process characterized by fibrosis and the conversion of normal liver architecture into structurally abnormal nodules.[1,2] According to WHO, deaths from cirrhosis have been estimated to increase and would make it a 12th leading cause of death in 2020. Fibrosis describes encapsulation or replacement of injured tissue by a collagenous scar. Fibrosis progresses at variable rates depending on the cause of liver disease, environmental and host factors. [3,4] Cirrhosis is an advanced stage of liver fibrosis that is accompanied by distortion of the hepatic vasculature. It leads to shunting of the portal and arterial blood supply directly into the hepatic outflow (central veins), compromising exchange between hepatic sinusoids and the adjacent liver parenchyma i.e. hepatocytes. Clinical features of cirrhosis are the result of pathologic changes and mirror the severity of the liver disease. Patients who have cirrhosis have varying degrees of compensated liver function, and clinicians need to differentiate between those who have stable, compensated cirrhosis and those who

have decompensated cirrhosis. Patients who have developed complications of their liver disease and have become decompensated should be considered for liver transplantation. Many of the complications of cirrhosis will require specific therapy. Portal hypertension is a significant complicating feature of decompensated cirrhosis and is responsible for the development of ascites and bleeding from esophageal & gastric varices, two complications that signify decompensated cirrhosis. Loss of hepatocellular function results in jaundice, coagulation disorders, and hypoalbuminemia and contributes to the causes of porto-systemic encephalopathy.[5] Cirrhosis can remain compensated for years before development of decompensating events like jaundice, ascites, encephalopathy and/or variceal hemorrhage. The median survival of patients with compensated cirrhosis is much longer than in patients with evidence of decompensation and is about 9 years [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 T3 by Type 1 deiodinase. Type I deiodinase is the major enzyme in the liver and accounts for approximately 30%–40% of extra thyroidal 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.[7,8 ] T4 and T3 regulate the basal metabolic rate of all cells, including hepatocytes, and thereby modulate hepatic function. The liver metabolizes the TSH 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] The available studies showed most frequent change in plasma level of thyroid hormones is decreased total T3 and free T3 concentration which is reported to be associated with severity of hepatic dysfunction. But no study clearly mentioned fT4 and thyroid stimulating hormone (TSH) levels with severity of liver cirrhosis. Serum T4 levels either remain normal or slightly low. However, serum TSH levels remain normal or slightly raised. Thyroid profile study is a very much cost effective study that is available in each and every corner of the world. Various studies have shown that subtle thyroid dysfunction are significantly associated with severity of cirrhosis of liver. Hence early recognization of such thyroid dysfunction may be a cost effective and handy method to recognize severity of liver and morbidity and mortality related to it.

## Objectives

Main objective of our study was to ascertain levels of fT3 , fT4, TSH and their correlation with severity of liver failure in patients of liver cirrhosis as per Child Turcotte Pugh(CTP) score.

## Material And Methods

The case control study was carried out in 50 patients of cirrhosis of liver admitted in various wards and ICUs of Govt. medical college, Kota & associated group of hospitals and age sex matched 50 healthy controls. Cirrhosis of liver was diagnosed based on clinical symptoms and signs, impaired liver function and ultrasonographic features consistent with cirrhosis i.e. diffuse alteration and nodular transformation of liver parenchyma. Severity of liver failure was assessed on the basis of Child Turcotte Pugh score. As per CTP score the patients were grouped in class-A(5-6), class-B(7-9), class-C(10-15) and they were compared with different parameters of thyroid dysfunction.Thyroid function test such as fT3,fT4,TSH levels were evaluated within 24 hours of admission by cobas e 411 thyroid immune analyser by ELISA chemiluminescence immune assay(CLIA) method. Normal reference range for free T3=3.10-6.80 pmol/L, free T4=12.0-22.0 pmol/L and TSH=0.25-5.0mIU/mL was considered.

**Inclusion criteria:-** (1) Cirrhotic patient with or without ascites diagnosed on -Unequivocal clinical ground (chronic liver disease stigmata, jaundice, ascites, esophageal varices, impair liver function) and ultrasonographic features consistent with cirrhosis i.e. diffuse alteration and nodular transformation of liver parenchyma & sign of portal hypertension, (2) Patient who himself or his/her relatives gave consent, (3) Healthy controls will be free of chronic liver disease, thyroid illness and any chronic disease that affect thyroid function eg. CKD, malignancy, chronic inflammatory conditions etc. **Exclusion critera**:-(1) Patients with prior history of thyroid disease, diabetes, any other chronic illness(except liver cirrhosis) eg. CKD, malignancy, chronic inflammatory conditions etc, (2) Pregnant subjects, (3) Patient receiving drugs that may



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interfere with thyroid hormone metabolism and functions eg. amiodarone, lithium, iodine with contrast etc. **End point of study**: Upto the time of patient discharge, upto the time of patient expired in hospital.

The data were compiled and analyzed using standard statistical methods and relevant conclusions were drawn using a computer based software SPSS version 16.0. Continuous data were expressed as mean ± standard deviation(SD), categorical data were expressed as percentages, and were compared using chi-square test and Fisher's Exact test, wherever applicable. Correlation between variables was ascertained using Pearson's correlation coefficient, a value of $p>0.05$ was considered as not significant and $p<0.05$ as statistically significant. The study protocol and consent forms were reviewed and approved by the ethical committee of Govt. Medical College and attached group of hospitals, Kota. All participants had given written informed consent for the study and for subsequent medical research.

## Observations And Results

**Table 1.: Distribution of study subjects according to age**

| Age Groups(years) | Cases | | Controls | | Total | |
|---|---|---|---|---|---|---|
| | N | % | N | % | N | % |
| 20 – 39 | 15 | 30 | 14 | 28 | 29 | 29 |
| 40 –59 | 24 | 48 | 25 | 50 | 59 | 59 |
| ≥60 | 11 | 22 | 11 | 22 | 22 | 22 |
| Total | 50 | 100 | 50 | 100 | 100 | 100 |
| Mean ± SD | 47.18 ± 13.04 | | 47.20 ± 13.03 | | | |
| Chi-square = 0.055 with 2 degrees of freedom; P = 0.973 (NS) | | | | | | |

This table showed that most of the study subjects in both the cirrhotic cases group (48%) as well as control group (50%) were aged 40 to 60 years. 11 (22%) subjects in both cases and controls belonged to ≥60 years age group. Mean age of cirrhotic cases was 47.18 ± 13.04 years, while that of control group was 47.20 ± 13.03 years. No significant difference was observed in age composition of the groups ($p>0.05$).

**Table 2: Comparison of Thyroid Function Tests among study subjects**

| Thyroid Function Tests | Cases | Controls | P value |
|---|---|---|---|
| | Mean ± SD | Mean ± SD | |
| f T3 | 3.63 ± 0.97 | 5.24 ± 0.82 | <0.001(S) |
| f T4 | 14.67 ± 2.12 | 16.28 ± 1.74 | <0.001(S) |
| TSH | 4.16 ± 0.61 | 2.10 ± 1.04 | <0.001(S) |

This table revealed that mean Serum fT3 level was lower among cases (3.63 ± 0.97pmol/L) as compared to controls (5.24 ± 0.82 pmol/L) and the difference was found to be statistically significant ($p<0.001$). Serum fT4 level was also significantly lower ($p<0.001$) among cirrhotic cases (14.67 ± 2.12 pmol/L) as compared to controls (16.28 ± 1.74 pmol/L). Mean serum TSH level was found to be higher among cirrhotic cases (4.16 ± 0.61µIU/ml) as compared to controls (2.10 ± 1.04 µIU/ml), this difference was also found to be statistically significant ($p<0.001$).



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**Table 3: Distribution of cases according to CTP Class**

| CTP Class | Cases | |
|---|---|---|
| | N | % |
| A | 24 | 48 |
| B | 11 | 22 |
| C | 15 | 30 |
| Total | 50 | 100 |

This table showed that most of the cirrhotic cases belonged to CTP class A (48%). 11 (22%) of cirrhotic cases belonged to class B and 15 (30%) of the cirrhotic cases belonged to CTP class C.

**Table 4: Comparison of fT3 among different severity class of cirrhosis**

| Class | Mean | Std. deviation | P value |
|---|---|---|---|
| A | 4.18 | 0.84 | <0.001(S) |
| B | 3.82 | 0.54 | |
| C | 2.60 | 0.51 | |

| Multiple comparison | A vs. B | A vs. C | B vs. C |
|---|---|---|---|
| P value | 0.309(NS) | <0.001(S) | <0.001(S) |

This table showed that mean serum fT3 level was higher among cirrhotic patients of CTP class A (4.18 pmol/L) followed by class B (3.82 pmol/L) and was lowest among class C patients (2.60 pmol/L), this difference in fT3 among different severity class cirrhotic patients was found to be statistically significant. Post hoc analysis show that significant difference was seen between class A and class C and between class B and Class C (p<0.001).

**Table 5: Comparison of fT4 among different severity class of cirrhosis**

| Class | Mean | Std. deviation | P value |
|---|---|---|---|
| A | 15.43 | 1.63 | <0.001(S) |
| B | 15.84 | 1.34 | |
| C | 12.58 | 1.83 | |

| Multiple comparison | A vs. B | A vs. C | B vs. C |
|---|---|---|---|
| P value | 0.721(NS) | <0.001(S) | <0.001(S) |

This table showed that mean serum fT4 level was higher among cirrhotic patients of CTP class B (15.84 pmol/L) followed by class A (15.43 pmol/L) and was lowest among class C patients 12.58 pmol/L), this difference in fT4 among different severity class cirrhotic patients was found to be statistically significant (p<0.001). Post hoc analysis show that significant difference was seen between class A and class C and between class B and ClassC (p<0.001).

**Table 6: Comparison of TSH among different severity class of cirrhosis**

| Class | Mean | Std. deviation | P value |
|---|---|---|---|



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| | | | |
|---|---|---|---|
| A | 3.70 | 0.45 | <0.001(S) |
| B | 4.48 | 0.46 | |
| C | 4.68 | 0.34 | |

| Multiple comparison | A vs. B | A vs. C | B vs. C |
|---|---|---|---|
| P value | <0.001(S) | <0.001(S) | 0.472(NS) |

This table showed that mean serum TSH level was raised among cirrhotic patients of CTP class C (4.68µIU/ml) followed by class B (4.48 µIU/ml) and was lowest among class A patients (3.70 µIU/ml), this difference in TSH among different severity class cirrhotic patients was found to be statistically significant (p<0.001). Post hoc analysis show that significant difference was seen between class A and class B and between class A and Class C (p<0.001).

**Discussion**

Our case control study included 50 patients diagnosed with cirrhosis of liver and 50 age sex matched healthy individuals. All patients subjected to routine laboratory investigations such as complete blood count, renal function test, liver function test, PT/INR, USG abdomen, color doppler, endoscopy, fT3, fT4, TSH. Patients of cirrhosis of liver were classified on the basis of Child- Pugh score in different classes. Both cases and controls groups were compared with different parameters of thyroid dysfunction. In our study we found that most of the subjects in both the cirrhotic cases group 24(48%) as well as control group 25(50%) were aged 40 to 59 years. 11 (22%) subjects in both cases and controls belonged to ≥60 years age group. Mean age of cirrhotic cases was 47.18 ± 13.04 years, while that of control group was 47.20 ± 13.03 years. No significant difference was observed in age composition of the groups (p>0.05).

Our study observed that mean Serum fT3 level was lower among cases (3.63 ± 0.97 pmol/L) as compared to controls (5.24 ± 0.82 pmol/L) and the difference was found to be statistically significant (p<0.001). Serum fT4 level was also significantly lower (p<0.001) among cirrhotic cases (14.67 ± 2.12 pmol/L) as compared to controls (16.28 ± 1.74 pmol/L). Mean serum TSH level was found to be higher among cirrhotic cases (4.16 ± 0.61µIU/ml) as compared to controls (2.10 ± 1.04 µIU/ml), this difference was also found to be statistically significant (p<0.001). Sudhir Kumar Verma et al [10] found that mean value of free T3 was 2.32±0.17; free T4 was 12.5±0.38 & TSH was 4.12±0.32 in enrolled patients. Low free T3 and free T4 was found in 72.5% and 26.47% in patients of cirrhosis of liver respectively. TSH towards the upper limit of normal range was observed in 52.3% of patients. Punekar P et al [11] found that mean fT3 was 1.95±0.57; mean fT4 was 1.27±0.54 and mean TSH was 4.09±1.70 in case group (100 patients) while in control group (100 individuals) mean fT3 was 3.13±0.59; mean fT4 was 1.86±0.36 and mean TSH was 3.15±1.20.

In our study we observed that mean serum fT3 level was higher among cirrhotic patients of CTP class A (4.18 pmol/L) followed by class B (3.82 pmol/L) and was lowest among class C patients (2.60 pmol/L), this difference in fT3 among different severity class cirrhotic patients was found to be statistically significant. Post hoc analysis show that significant difference was seen between class A and class C and between class B and Class C (p<0.001). Further mean serum fT4 level was higher among cirrhotic patients of CTP class B (15.84 pmol/L) followed by class A (15.43 pmol/L) and was lowest among class C patients (12.58 pmol/L), this difference in fT4 among different severity class cirrhotic patients was found to be statistically significant (p<0.001). Post hoc analysis show that significant difference was seen between class A and class C and between class B and class C (p<0.001). Also mean serum TSH level was raised among cirrhotic patients of CTP class C (4.68µIU/ml) followed by class B (4.48 µIU/ml) and was lowest among class A patients (3.70 µIU/ml), this difference in TSH among different severity class cirrhotic patients was found to be statistically significant (p<0.001). Post hoc analysis show that significant difference was seen between class A and class B and between class A and Class C



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(p<0.001). We found association between serum fT3 level and severity of cirrhosis of liver. Our study is concordant with other studies done by Patira NK et al.[12] found statistically significant association between serum T3, fT3, fT4 and severity of liver disease, as the severity of cirrhosis increased which is indicated by Child Pugh A to C, serum levels of T3, fT3 and fT4 were reduced while serum level of TSH was increased. Sudhir Kumar Verma et al[10] observed that Low free T3 and free T4 was found to be inversely related to the severity of liver disease. Punekar P et al[11] found that Cirrhosis patients had statistically significant lower level of fT3 (P < 0.0001) and fT4 (P < 0.0001) but had higher level of TSH (P < 0.0001) compared with the controls and levels of fT3, fT4, and TSH were also correlated with the severity of liver disease.

Our study showed that lower free T3 level (<3.1 pmol/L) was found in 15 (30%) of the cases and none of the control patients, this difference in free T3 level among cirrhotic cases and controls was found to be statistically significant (p<0.001). Our study also showed that lower free T4 level (<12 pmol/L) was reduced in 7 (14%) of the cases and none of the control patients, this difference inT4 level among cirrhotic cases and controls was found to be statistically significant (p<0.05). Our study showed that raised TSH level (>5µIU/ml) was reported in 2 (4%) of the cases and none of the control patients, this difference inTSH level among cirrhotic cases and controls was however not found to be statistically significant (p=0.475). Similar study done by Patira NK et al.[12] demonstrated that –(1) 37(74%) patients had serum free T3 level more than 3.10 pmol/L and 13(26%) patients had serum Free T3 level below 3.10 pmol/L. (2) 45(90%) patients had serum free T4 level more than 12 pmol/L and 5(10%) patients had serum free T4 level below 12 pmol/L. (3) 31(62%) patients had serum TSH level more than 4.20 microIU/ml and 19(38%) patients had serum TSH level between 0.27-4.20 microIU/ml.

## Conclusion

1. Overall serum fT3 and fT4 levels were significantly lower in all cases irrespective of age and sex as compared to age and sex matched controls.
2. Irrespective of age and sex of the patients, serum fT3 level was higher among cirrhotic patients of Child Turcotte Pugh (CTP) class A followed by class B and was lowest among class C patients.
3. Irrespective of age and sex of the patients, lower serum fT4 level was more common among cirrhosis patients of CTP class C as compared to CTP class B and CTP class A.
4. Our study clearly established the fact that level of serum fT3 inversely correlated with severity of cirrhosis, it can be used as prognostic indicator for cirrhosis of liver.
5. Our study clearly established the fact that incidence of low serum fT3, low serum fT4 with normal TSH are significantly associated with severity of cirrhosis.

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