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Correlation of Thyroid Function Test with Severity of Liver Dysfunction in Cirrhosis of Liver

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Abstract

Aims and Objectives: *To evaluate the Thyroid functions in patients with cirrhosis of liver and to assess the severity of liver dysfunction in relation with interpretation of thyroid functions.*

Material and Methods: *The present study was undertaken at Maharana Bhupal Govt. Hospital, attached to R.N.T. Medical College, Udaipur (Raj.).*

1) This study included total 50 patients admitted at Maharana Bhupal Govt. Hospital, attached to R.N.T. Medical College Udaipur (Raj.) with clinical, biochemical, and radiological evidence of cirrhosis of liver.

2) All patients were subjected to medical examination as per the fixed Performa.

Inclusion criteria-

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

2) Patients who himself or his/her relatives gave consent.

Exclusion criteria-

1) Patients with diabetes.

2) Pregnant subjects.

3) Patient with prior h/o thyroid disease.

4) Patient receiving drugs that may interfere with thyroid hormone metabolism and function.

5) Patient with any other chronic illness (except liver cirrhosis).

Sample Analysis-

-Fasting morning blood sample was collected.

Observations and Conclusion: *Prevalence of subclinical hypothyroidism with cirrhosis was 62%. 31 out of 50 patients had subclinical hypothyroidism. The study showed that prevalence of hypothyroidism in cirrhosis patients increases as the severity of cirrhosis increases and findings were statistically significant (p value 0.00).This study found association between serum T3 and severity of liver disease. As the severity of cirrhosis increases which is indicated by Child Pugh A to C, serum level of T3 reduces and findings were statistically significant (p value 0.00).All 50 patients of cirrhosis had their serum T4 level within normal limit and it does not change with severity of liver disease. This study found association between serum FT4 and severity of liver disease. As the severity of cirrhosis increases which is indicated by Child Pugh A to C, serum level of FT4 fall in low-normal or below normal value and findings were statistically significant (p value 0.00). This study found association between serum FT3 and severity of liver disease. As the severity of cirrhosis increases which is indicated by Child Pugh A to C, serum level of FT3 reduces. All patients of Child Pugh C had low FT3 level and the findings were statistically significant (p value 0.00). This study showed that serum bilirubin, prothombin time, INR, TSH level increases and serum albumin level, T3, FT3, and FT4 level reduces as the severity of cirrhosis increases.*

According to this study all cirrhotic patients should undergo thyroid function evaluation as these patients are definitely associated with development of hypothyroidism. There is significant inverse correlation between serum level of T3, FT3, and FT4 with severity of cirrhosis. These parameters can be used as markers to indicate the severity of cirrhosis.

Introduction

The liver plays the dominant role in the metabolism of thyroid hormones. It is here that 5'deiodinase enzyme act to convert part of T4 to T3. There are eight further circulating iodothyronines.The rT3, mainly derived from T4, appear to be a major inhibitor of T4 and T3. Thus if rT3 increases, the metabolic effect of T3 and T4 decreases. In the course of some chronic systemic disease (hepatic cirrhosis) rT3 increases simultaneously with the decrease of T3 level. Therefore one can describe particular alteration of thyroid pattern of chronic liver disease; low T3 syndrome, low T3 and T4 syndrome or high T4 syndrome mixed form.

T3 and T4 diminish due to inefficient hepatic deiodinization and defective hepatic cellular uptake. T4 level decreases, most likely because of an inefficient production of thyroid binding globulin or due to the action of peripheral binding inhibitors. During acute liver disease and primary biliary cirrhosis one can observe an increase of T4 and TBG together with an increase of the acute phase proteins. Such complex hormonal mechanisms are not influenced by TSH, which appear normal or inhibited, as the TRH stimulation test is normal. The explanation 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 of an organ in a catabolic state by reducing the circulating thyroid hormone T3. A relation has been found between circulating hormone level particularly the T3, rT3, and rT3/T3 ratio, and the hepatic functional insufficiency. In different types of liver diseases, similar processes may occur to those seen in the sick euthyroid syndrome, but in addition a number of changes specific to the type or stage of liver disease is also found.

The most consistent thyroid hormone profile in patients with cirrhosis are a low total and free T3 and an elevated rT3, probably reflecting a reduced deiodinase type 1 activity resulting in reduced conversion of T4 to T3. This results in an increase in conversion of T4 to rT3 by the deiodinase type 3 system and an increase in the rT3 to T3 ratio.

The plasma T3/rT3 ratio has a negative correlation with the severity of cirrhosis when assessed in non-alcoholic cirrhotic. Since T3 and rT3 bind to the same plasma proteins, the T3/rT3 ratio provides a parameter of liver function that is largely independent of protein binding. Both the T3/rT3 ratio and free T3 levels in plasma thus provide a correlation of liver function in cirrhosis, and are of prognostic value, albeit seldom used.

In cirrhosis of liver several hormones may be affected, including insulin and glucagon due to deamination defects, glucocorticoid and gonadal steroids due to a conjugation defects, and thyroid hormone due to an iodination defect.

Numerous clinicians have reported a sub clinical hypothyroidism in patients with chronic liver disease. Although studies in different populations vary in their findings with respect to the type and degree of thyroid dysfunction in cirrhosis, but found to have consistently low FT3 in the face of a normal TSH and a clinical euthyroidism. Not only the free hormone level has been delineated as an indicator of thyroid dysfunction, but FT3 level has also been correlated with the degree of liver dysfunction.

Material and Methods

The present study entitled "Correlation of Thyroid Function Test with Severity of Liver Dysfunction in Cirrhosis of Liver" was undertaken at Maharana Bhupal Govt. Hospital, attached to R.N.T. Medical College, Udaipur (Raj.).

A) Patients-

1) This study included total 50 patients admitted in Maharana Bhupal Govt. Hospital, attached to R.N.T. Medical College Udaipur (Raj.) with clinical, biochemical, and radiological evidence of cirrhosis of liver.
2) All patients were subjected to medical examination as per the fixed Performa.

B) Inclusion criteria-

1) Patients with clinical, biochemical, and radiological evidence of cirrhosis of liver.
2) Patients who himself or his/her relatives gave consent.

C) Exclusion criteria-

1) Patients with diabetes.
2) Pregnant subjects.
3) Patient with prior h/o thyroid disease.
4) Patient receiving drugs that may interfere with thyroid hormone metabolism and function.
5) Patient with any other chronic illness (except liver cirrhosis).

D) Sample analysis-

- Fasting morning blood sample was collected.

The samples of blood were allowed to stand to clot. Serum was separated by centrifugation and analyzed by following methods.

-Thyroid function test was measured with the COBAS e 411 ANALYSER which is an automated random-access; multi-channel analyzer for immunological assay (Roche Diagnostic Ltd).It is designed for both qualitative and quantitative in vitro determination of a wide range of chemicals by use of ELECTRO-CHEMILUMINESCENCE technology.

1) Estimation of T3, T4, and TSH by electro-chemiluminescence immunoassay (ECLIA)

a. Estimation of T3 & T4

The principle & procedure for estimation of FT3 & FT4 are similar.

Principle: (Competition principle). The T3 and T4 assay employs a competitive test principle with polyclonal antibodies specially directed against T3 and T4. Endogenous T3 and T4 released by the ion of 8 anilino-1- naphthalene sulphonic Acid (ANS) competes with the added biotinylated T3 and T4 derivative for the binding sites on the antibodies labeled with the ruthenium complex.

Procedure: Total duration of assay 18 min.

- **1st incubation:** 30 micro liter sample and a T3 specific antibody labeled with a ruthenium complex; bound T3 is released from the binding proteins in the sample by ANS.
- **2nd incubation:** After addition of streptavidin-coated micro particles and biotinylated T3, the still free binding sites of the labeled antibody become occupied with formation of an antibody-hapten complex. The entire complex bounds to the solid phase via interaction of biotin and streptavidin.
- The reaction mixture is aspirated into the measuring cell where the micro particles are magnetically captured onto the surface of the electrode. Unbound substances are then removed with procell. Application of a voltage to the electrode then induces chemiluminescent emission which is measured by a photo multiplier.
- Results are determined via a calibration curve which is instrument-specifically generated by 2-point calibration and a master curve provided via the reagent barcode.

Reagents

1. Streptavidin-coated micro particles contain 0.72mg/ml in preservative.
2. Anti T3-Ab & Anti T4-Ab (separate for both) contains polyclonal Anti -T3 & Anti T4 antibody (sheep) labeled with ruthenium complex 75 ng/ml for T3 & 100 ng/ml for T4; ANS 0.8 mg/ml for T3 & 1 mg/ml for T4; phosphate buffer 100 mmol/l, pH 7.4; preservative for both.
3. T3 or T4 – biotin: Contains biotinylated T3 3 ng/ml & biotinylated T4 20 ng/ml, phosphate buffer 100 mmol/l, pH 7.4; preservative.

b. Estimation of TSH

Principle: (Sandwich principle) The TSH assay employs monoclonal antibody specifically directed against human TSH. The antibodies labeled with ruthenium complex consist of chimeric construct from human & mouse specific

components. As a result interfering effects due to HAMA (human anti -mouse antibodies) are largely eliminated.

Procedure: Total duration, 18 min.

- **1st incubation:** 50 µl of sample, a biotinylated monoclonal TSH specific antibody and a monoclonal TSH specific antibody labeled with a ruthenium complex react to form a sandwich complex.
- **2nd incubation:** After addition of streptavidin coated micro particles, the complex becomes bound to the solid phase via interactions of biotin & streptavidin.
- The reaction mixture is aspirated in to the measuring cell where the micro particles are magnetically captured on to the surface of the electrode. Unbound substances are then removed with pro-cell. Application of voltage to the electrode then induces chemiluminescent emission which is measured by photomultiplier.
- Results are determined via calibration curve which is instrument specifically generated by 2 point calibration and a master curve provided via the reagent barcode.

Reagents:

1. Streptavidin-coated micro particles Contains 0.7 mg/ml in preservative.
2. Anti-TSH Ab- biotin, Contains- Biotinylated monoclonal anti-TSH-antibody (mouse) 2.0 mg/l; phosphate buffer 100 mmol/l pH 7.2 in preservative.
3. Anti-TSH-Ab Contains-monoclonal anti-TSH antibody (mouse/human) labeled with ruthenium complex 1-2 mg/l; phosphate buffer 100 mmol/l pH 7.2 in preservative.

Results

A total of 50 patients with cirrhosis of liver were selected. Majority of patients 36(72%) belonged to age group 41-60 yrs., 9 (18%) patients were below 40 yrs. of age and 5 (10%) patients were above 60 yrs. of age. 39(78%) patients were male, and 11(22%) were female. 26(52%) patients were from rural areas and 24 (48%) patients were from urban areas. Most common etiology of liver cirrhosis was Alcoholism which comprised 35(70%) patients, 13(26%) patients had HBV related cirrhosis, and 2(4%) patients had HCV related cirrhosis. 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. Normal Free T3 Level is 3.10-6.80 pmol/L. 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. Normal Free T4 Level is 12-22 pmol/L. 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. Normal TSH Level is 0.27-4.20 microIU/ml. Severity of cirrhosis of liver was determined by Child Pugh scoring system.13(26%) patients had score between 5-6 (grade A), 26(52%) patients had score between 7-9 (grade B), and 11(22%) patients had score more than 10 (grade C). 13(26%) patients who were categorized in Child Pugh A had serum Free T3 level more than 3.10 pmol/L. 26(52%) patients who were included in Child Pugh B, out of them 24 patients had serum Free T3 level more than 3.10 and 2 patients had Free T3 level below 3.10 pmol/L. Remaining 11(22%) patients who were categorized in Child Pugh C had serum free T3 level below 3.10 pmol/L. Study demonstrated that as the severity of cirrhosis increased from Child- Pugh A to C, serum Free T3 level decreased (p value 0.00). 13(26%) patients who were categorized in Child Pugh A and 26(52%) patients who were included in Child Pugh B had serum Free T4 level more than 12 pmol/L.11(22%) patients who were categorized in Child Pugh C, out of them 6 patients had serum Free T4 more than 12 pmol/L and 5 patients had serum Free T4 below 12 pmol/L(p value 0.00). 13(26%) patients who were categorized in Child Pugh A, out of them 11 patients had normal serum TSH level and 2

patients had TSH level more than 4.20µIU/ml. 26(52%) patients who were included in Child Pugh B, out of them 8 patients had normal TSH level and 18 patients had TSH level more than 4.20 µIU/ml. 11(22%) patients who were categorized in Child Pugh C, all of them had TSH level more than 4.20 µIU/ml. Study demonstrated that as the severity of cirrhosis increased from Child- Pugh A to C serum level of TSH started to rise above normal level (p value 0.00).

Table 1 Distribution of patients according to FT3 levels

FT3 levels (pmol/L)	No. of patients	%
> 3.10	37	74.00
< 3.10	13	26.00
Total	50	100

Table 2 Distribution of patients according to FT4 levels

FT4 levels (pmol/L)	No. of patients	%
> 12	45	90.0
< 12	5	10.0
Total	50	100

Table 3 Distribution of patients according to TSH levels

TSH levels (µIU/ml)	No. of patients	%
< 0.27	0	0
0.27-4.20	19	38.0
> 4.20	31	62.0
Total	50	100

Table 4 Distribution of patients according to Child Pugh score

Child Pugh Score	No. of patients	%
A(5-6)	13	26.0
B(7-9)	26	52.0
C(10-15)	11	22.0
Total	50	100

Table 5 Comparison of Child Pugh score with FT3 levels

FT3 levels (pmol/L)	Child Pugh score			p value
	5-6	7-9	10-15	
> 3.10	13	24	0	0.000
< 3.10	0	2	11	

Table 6 Comparison of Child Pugh score with FT4 levels

FT4 levels (pmol/L)	Child Pugh score			p value
	5-6	7-9	10-15	
> 12	13	26	6	0.000
< 12	0	0	5	

Table 7 Comparison of Child Pugh score with TSH levels

TSH levels (µIU/ml)	Child Pugh score			P value
	5-6	7-9	10-15	
< 0.27	0	0	0	0.000
0.27-4.20	11	8	0	
> 4.20	2	18	11	

Discussion

In this cross sectional study it was seen that prevalence of hypothyroidism in cirrhosis patient was 62% i.e. 31 out of 50 cirrhotic patients had increased TSH level. The prevalence of hypothyroidism increases as the severity of liver cirrhosis increases. All 31 patients did not have clinical signs of hypothyroidism and there TSH level was also in subclinical range of hypothyroidism. 23(46%) out of 31 patients with hypothyroidism were male indicating that hypo-thyroidism is more common in male cirrhotic.

Regarding the etiology of cirrhosis in those with hypothyroidism our study found alcoholic cirrhosis to be the most common etiology. Our study showed that as the severity of liver disease increases indicated by Child Pugh grade A to C the prevalence of reduced serum T3 increased.

The study showed that all the cirrhotic patients had their serum T4 level within normal limit. This was in contrast to Kayacetin E, Kisakol G, Kaya A et al study which showed there is reduced total T4 level in non-alcoholic hepatic encephalopathy patients.

In this study it was shown that as the severity of liver disease increases indicated by Child Pugh grade A to C the prevalence of reduced serum FT4 level increased. This was in contrast to study by *Borzio M, Caldara R, Borzio F, Piepoli V, Rampini P, Ferrari C* which showed the existence of several abnormalities of thyroid function tests in patients 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.

Study showed that as the severity of liver disease increases indicated by Child Pugh grade A to C the prevalence of reduced serum FT3 level increased (p value<0.00).This study was supported by Agha F et al study which confirms the presence of abnormalities in serum thyroid hormone levels in cirrhosis of liver. Alteration in serum T3 and FT3 levels correlate well with the disease severity and may be useful in assessing the course and prognosis in cirrhotic patients.

Conclusion

According to this study all cirrhotic patients should undergo thyroid function evaluation as these patients are definitely associated with development of hypothyroidism. As the study suggest significant inverse correlation between serum level of FT3, FT4 and TSH with severity of cirrhosis. These parameters can be used as markers of severity of cirrhosis.

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