Free T3 as a Reliable Indicator of Thyroid Dysfunction in Cirrhosis

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Abstract - Liver cirrhosis is a common ailment afflicting a significant proportion of Pakistani population of all ages. Quite often, these patients require multi-system intervention, owing to the nature of this disease. This study was specifically conceived to objectively assess the level of thyroid dysfunction in cirrhotics of the urban population of Karachi, together with its relationship to the severity of liver malfunction as gauged by the Childs classification. Liver and thyroid hormones are intricately correlated so thyroid hormone abnormalities are seen in patients of liver diseases, although they are clinically euthyroid. The aim of this study is to correlate the abnormalities in thyroid hormones with the clinical staging of hepatic encephalopathy and to examine the role of thyroid hormone as a reliable prognostic indicator of encephalopathy. We assessed 50 patients of cirrhosis for the thyroid hormone levels (including thyroxine, triiodothyronine and TSH) by Enzyme Linked Immuno sorbent Assay (ELISA) technique. Patients were also examined clinically for gradings of Cirrhosis by The Childs Pugh classification. All procedures on patients were done in accordance with the Helsinki Declaration. Triiodothyronine (FT3) was found to be a useful indicator of thyroid dysfunctions and it parallels the grading of Childs classification, whereas thyroxine and TSH were not found to be significantly correlated. We proposed that triiodothyronine could act as a prognostic marker to predict severity of cirrhosis and for assessing minimal hepatic encephalopathy.
Keywords - Thyroid hormones, Cirrhosis, Childs classification, extra hepatic manifestations of liver disease.

INTRODUCTION

Cirrhosis becomes a multisystem disease owing to its several consequential complications, which are obviously due to liver's central role in body's metabolism. Its incidence is reportedly increased; Extra-hepatic manifestations of liver disease include involvement

of the lungs, central nervous system, the heart, and the kidneys, to name but a few. The involvement of these organ systems becomes manifest along the course of cirrhosis, and therefore, some of these complications are clinically relevant. Other less subtle and clinically non-manifest complications do occur, which are usually neglected in the management of cirrhosis but are present nonetheless (Ho JK, 2006). Several hormones may be affected, including insulin and glucagon due to a deamination defect, glucocorticoids and gonadal steroids due to a conjugation defect, and thyroid hormones due to an iodination defect (Burra P et al, 1992). Thyroid dysfunction is present in several chronic diseases like severe liver or kidney diseases, certain metabolic

disorders and infections. In patients with chronic illnesses fluctuation in thyroid hormones occur which may render routine thyroid hormone testing unreliable. Hormone testing is sometimes essential in cases where additional thyroid hormone deficiency is suspected and in patients who may benefit from thyroxin treatment (Chopra IJ 1997). Numerous clinicians have reported a sub clinical hypothyroidism in patients with chronic liver diseases (Sheridan P 1983). Although studies in different populations vary in their findings with respect to the type and degree of thyroid dysfunction in cirrhosis, but have consistently found low FT3 levels in the face of a normal TSH and a clinical euthyroidism (Chopra IJ, 1975). Not only has this free hormone level been delineated as indicator of thyroid dysfunction, but FT3 levels have also been correlated with the degree of liver dysfunction (Nomura S. et al, 1975).

Several methods are used to stage cirrhosis, including histological and clinical staging. A reliable and time tested system for assessing the clinical severity of cirrhosis is Child Pugh's classification. It includes serum biochemical tests, with serum albumen, bilirubin and prothrombin time, and two clinical criteria with ascites and encephalopathy (Ghany M and Hoofangle JH, 2008).

Table 1. Child-pugh classification of cirrhosis

Factor Units	1	2	3
Serum Bilirubin mg/dL	<2.0	2.0-3.0	>3.0
Serum Albumin g/dL	>3.5	3.0-3.5	<3.0
Prothrombin time Seconds prolonged	0-4	4-6	>6
Ascites	None	Easily controlled	Poorly controlled
Encephalopathy	None	Minimal	Advanced

(Ghany and Hoofangle, 2008)

Score 5 and 6 are designated as Child class A

Scores 7 to 9 indicate Child class B

Scores 10 to 15 are included in Child class C

This classification also serves as an indicator of survival and predicts the likelihood of complications in cirrhosis (Ghany M, Hoofangle JH. 2008). `In several studies done previously, the parameters of Child classification were found to be significantly linked with FT3 levels. This finding confirms the presence of abnormalities of thyroid dysfunction in patients with cirrhosis, despite clinical euthyroidism (Shimada T, 1988). Nonetheless, FT3 levels can be used as a useful marker and prognostic indicator of survival in cirrhotic patients along with other biochemical parameters of the Child Pugh classification (Van Theil DH

et al, 1985).
We tested thyroid hormone levels (FT3, FT4 and TSH) in 50 patients with varying degrees of severity of cirrhosis according to the Child Pugh scoring system. Our study suggested the prevalence of a low FT3 level and its inverse association with increasing severity of cirrhosis according to the Childs grading system. FT3 could be a significant predictor of thyroid dysfunction in cirrhotic patients. Results of both FT4 and TSH did not show any relationship with increasing severity according to Childs classification.
Chronic liver disease is classified into Child-Pugh class A to C, employing the added score from TABLE 1, and the relationship between the grading and years of survival are shown below.
Table 2. Child-pugh and years of survival

Points	Class	One year survival	Two year survival
5-6	A	100%	85%
7-9	B	81%	57%
10-15	C	45%	35%

http://en.wikipedia.org/wiki/Child-Pugh_score

MATERIALS AND METHODS

All patients with a known diagnosis of cirrhosis admitted to the medical unit II of Jinnah Postgraduate Medical Centre were initially recruited over a period of six months. They were further categorized

according to the Child classification as A, B or C. Of the 148 cases thus enrolled, 98 were later excluded according to the following criteria:
• Subjects with known, or with past or family history of thyroid disorders or any other autoimmune diseases or evidence of hypopituitarism
• Pregnant subjects
• Subjects with recent abdominal surgeries or any massive bleeds
• Subjects receiving drugs that may interfere with thyroid hormone metabolism or secretion
A total of 50 cirrhotic patients were then included in the final analysis. Their thyroid functions (FT3, FT4 and TSH) were determined by using a kit purchased from Immunotech, Bechman Coulter Company, Cat no1363. The radioimmunoassay was done utilizing the principle of ^{125}I-labeled antibody. The thyroid function tests were then associated with Child classes A, B and C.
Other biochemical tests commonly used in cirrhosis were also performed. Serum Alkaline phosphatase, alanine aminotransferase and bilirubin were done by colorimetric method, using commercial kits purchased from Human Gesellschaft fur und Diagnostica, Germany. Albumin was determined using Bromocresol green method, using a commercial kit by DiaSys Diagnostic systems GmbH, Germany. Prothrombin time was estimated by using a rabbit-brain thromboplastin reagent (Simplastin Excel), provided by BioMerieux Inc. USA.
These results were further compared to thyroid profiles of 50 normal subjects with no known co-morbidities.
Results were evaluated using SPSS 15. Students T-test was employed to compare variables between cases and controls. Correlation- coefficient (Pearson's product) was calculated for quantifying the association between the severity of hypothyroidism and that of cirrhosis.
Autonomy and confidentiality of all subjects was ensured. All clinical and biochemical evaluations were made subject to informed consent. All records were kept confidential, except from the patients

and subjects' doctors.

Local ethical committee in accordance with the Helsinki declaration approved all experimental procedures.

RESULTS AND DISCUSSION

FT3 emerged as a reliable indicator of thyroid dysfunction in cirrhosis. Results for both FT4 and TSH did not show variability with the increasing grades of cirrhosis. Table 1 and Figure 1 exhibit the thyroid function according to Child's grade. Patients with decompensate cirrhosis (Child's groups B and C) showed a significant decrease in FT3 levels (P<0.05) but no significant differences in FT4 and TSH levels.

Table 3. Thyroid function in hepatic decompensation cirrhotics
(All values are expressed as Mean ± SE)

T h y r o i d Function	Child grade "A" (n=7)	Child grade "B" (n=26)	Child grade "C" (n=17)
	Mean ± SEM	Mean ± SEM	Mean ± SEM
FT3 (pg/ml)	2.58 ± 0.27	2.30 ± 0.13*	1.38 ± 0.25*
FT4 (ng/dl)	1.33 ± 0.11	1.26 ± 0.05	1.14 ± 0.11
TSH (mIU/L)	1.51 ± 0.61	2.52 ± 0.23	2.21 ± 0.32

* P<0.05 shows significant difference

Thyroid hormone levels according to Child's class A, B, C. Number of patients with Child's class A was 7 with B was 26, and C was 17. Childs class B and C exhibits significant decrease in FT3 (pg. /ml.)

Figure 2 shows frequencies of FT3 levels in cirrhotics, in terms of correlation coefficient, 12 out of 50 patients had an FT3 level less than

Fig. 1. Thyroid function tests in different stages of Childs class. FT3 expressed in pg/ml, FT4 in ng/dl and TSH in mIU/I. Patients with decompensated cirrhosis (childs class B and C showed a significant decrease in FT3 (p≤0.05) No significant difference found in FT4 and TSH.

Fig. 2. Histogram of FT3 Values in Cirrhotics.
Histogram showing FT3 in pg/ml on x axis and number of subjects on y axis 12 out of 50 subjects showing FT3 less than the lower limit of normal (i.e. less than 1.63)

the lower limit of normal (i.e.<1.63).Thus the prevalence of low FT3 levels in cirrhotic patients was 24%.

Figure 3 shows the clumping of values in the middle of regression line of FT3 against the Child's score, exhibiting a very high correlation between the two values.

Table 4 shows correlation coefficient of thyroid dysfunction versus Child's score. Only FT3 was observed to be significantly inversely correlated to Child's class and hence hepatic dysfunction .

Table 4. Correlation coefficient of thyroid function vs child's score

Parameters	Correlation Coefficient "r"
FT3	r = - 0.49 *
FT4	r = - 0.24
TSH	r = - 0.06

Table 5 shows correlation coefficients for individual thyroid function tests FT3, FT4 and TSH against albumen ,bilirubin, alkaline phosphatases, alanine amino transferase and prothrombin time. A

significant P value (<0.05) positive correlation was found between FT3 levels and albumen, and a negative correlation was found between FT3 and serum bilirubin levels. Also FT4 levels showed a significant

Fig. 3. Correlation of coefficient of thyroid function (FT3) and child score. Graph showing clumping of values about the regression line for FT3, expressed in pg/ml against child's score

positive correlation with serum albumin levels. Serum levels of alanine amino transferase and alkaline phosphatase correlated poorly with thyroid hormone levels. TSH showed no significant correlation with serum levels of any liver function markers. A significant negative correlation was found between prothrombin time of cirrhotic patients and their serum FT3 and FT4 levels.

Table 5. Relationship between liver function tests and thyroid function expressed as correlation coefficients

Thyroid Function	Liver Function Tests			
	Albumin	Bilirubin	Alkaline Phosphatase	Alanine amino transferase
PT				
FT3	0.48*	-0.30*	0.14	-0.26
FT4	0.32*	-0.05	0.08	-0.02
TSH	-0.02	-0.05	0.17	0.13
	-0.48*			
	-0.29*			
	0.02			

Correlation coefficients for FT3, FT4 and TSH against albumen, bilirubin, alkaline phosphatase and alanine aminotransferase. Table shows significant ($p \leq 0.05$) positive association between FT3 and albumen levels and a negative correlation between FT3, bilirubin, and prothrombin time (PT) levels.

Thyroid hormone abnormalities are seen in liver diseases like acute and chronic hepatitis and cirrhosis and are known to parallel the severity of liver diseases (Malik R. and Hodgson H, 2002). Cirrhotic patients may exhibit abnormalities of thyroid hormone levels while being clinically euthyroid (Faber J, et al 1981) .Several abnormalities of thyroid function tests may be seen including derangements in free T3 and free T4 levels as well as those of Thyroxin-binding globulin [TBG] (Huang J, Liaw F, 1995)

Out of these the finding of low free T3 was a more persistent conclusion (L'age M, 1980 and Georgia Kostopanagiotou et al, 2009) which is consistent with our results in Pakistani population. Thyroid function has again been evaluated as marker of prognosis of liver disease [Kano T et al, 1987 and Güven K et al 1993) as thyroid function

abnormalities usually get reversed on improvement in liver function (Kabadi UM and Premachandra BN, 1983).

Our study, therefore, emphasizes on assessing FT3 levels along with other biochemical parameters of Child's classification, as it may be used as a prognostic, rather than diagnostic tool for patients awaiting liver transplantation.

Although the relationship between liver and thyroid has been discussed several times in context of non-thyroidal illnesses, measurement of thyroid hormones is generally considered unreliable in severe illnesses. However, when dysfunction needs to be assessed in such patients, thyroid hormone must be measured. We have linked the FT3 levels with degree of liver dysfunction, and were able to exhibit significant relationship.

Our study has exhibited the presence of a low FT3 level and its inverse relationship with increasing severity of liver dysfunction in the local population of Karachi, Pakistan. A negative correlation between FT3 levels and increasing severity of liver dysfunction was also demonstrated by (Green et.al 1977). They specifically correlated the FT3 levels with serum albumen and had found lower FT3 levels corresponding to lower serum albumen levels. This finding is consistent with ours, and this study in Pakistani population has further expanded the scope of liver dysfunction tests in addition to the correlates of other assessments of liver function including Child Pugh scoring, by emphasizing the importance of FT3 as a prognostic marker. Our results are also in concordance with a French study (Schlienger, 1979) in which thyroid profile was done on 50 alcoholic cirrhotics using a clinical and biological index to score the severity of the disease. They also related decreased levels of FT3 with the degree of liver dysfunction as a result of alcoholism.

Another study conducted in Pakistan, (Agha F et al, 1989), also concluded that FT3 correlates with the disease severity hence could be used as a prognostic tool for assessing the course and prognosis of cirrhosis though the comparison has different perspective. Our study also strongly agrees with the study conducted by Takahashi and Yamada 1989 who has considered FT3 as a sensitive index of liver damage.

Literature also indicated that low FT3 plays a protective role in the catabolic state (Gallo V, et al 1990). Similarly, Borzio et al (1983)

who studied 55 patients of chronic hepatitis found low FT3 levels despite the presence of clinical euthyroidism. Walfish et al (1979) have correlated FT3 levels with worsening liver function, and since they were able to follow up on their patients, they had demonstrated that mortality rates in patients with low FT3 on admission may in fact be greater as compare to higher FT3 levels.

The findings of low FT3 in cirrhotics, its association with worsening liver function by Child Pugh class, and absence of correlation between FT4 and TSH levels are all in agreement with the results of Kayacetin et al. (2003). Hepner and Chopra, in 1979, also found a similar decrease in FT3 levels in 29 patients with alcoholic cirrhosis, although they did not correlate it with the severity of the disease. Burra et al (1992) found low FT3 levels in 31 alcoholic cirrhotic patients and also demonstrated that the changes in FT3 reflected the severity of underlying liver disease.

CONCLUSIONS

In conclusion, we found significant correlation of FT3 with the indicators for detecting Childs score, while other signs commonly used for diagnosis of cirrhosis did not have any correlation. This effect suggests that FT3 could be used as a marker for grading severity of liver dysfunction.

We propose a further qualification of FT3 as a prognostic marker to predict severity and progression of cirrhosis by undertaking a largescale follow-up study of early cirrhotic patients.

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