

**Relationship between Thyroid hormone levels and severity of HBV and HCV related liver cirrhosis**Tarek E korah<sup>1</sup>, khaled M El-zorkany<sup>2</sup>, Rania M El-shazly<sup>1</sup> and Ahmed R El-ashmawy<sup>2</sup><sup>1</sup>Internal Medicine Department, Faculty of Medicine-Menoufia University, Egypt<sup>2</sup>Medical Biochemistry Department, Faculty of Medicine-Menoufia University, Egypt  
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**Abstract: Objectives:** To assess the levels of thyroid hormones and TSH in HBV and HCV related liver cirrhosis and their relation to the severity of cirrhosis. **Background:** Liver cirrhosis is a multisystem disease due to its several complications and Numerous clinicians have reported a subclinical hypothyroidism in patients of chronic liver diseases. **Patients and Methods:** sixty patients and twenty healthy subject as control group. Patients divided in to two groups **group 1:** thirty patients with chronic HCV related liver cirrhosis in different stages and **group II:** thirty patients with HBV related liver cirrhosis in different stages. All groups subjected to history taking, clinical examination, biochemical tests and thyroid hormones level. **Results:** free T3 lower than normal range significantly increased along with child score A,B,C. A negative correlation was found between child score and free T3 ( $P$  value < 0.05). **Conclusion:** In conclusion serum free T3 is a good indicator of hepatic function, decreasing by severity of liver damage.

[Tarek E korah, khaled M El-zorkany, Rania M El-shazly and Ahmed R El-ashmawy. **Relationship between Thyroid hormone levels and severity of HBV and HCV related liver cirrhosis.** *Nat Sci* 2014;12(12):89-94]. (ISSN: 1545-0740). <http://www.sciencepub.net/nature>. 13

**Key words:** Cirrhosis, thyroid hormones, thyroid dysfunction.

**1. Introduction**

Liver Cirrhosis is 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, The involvement of these organ systems become 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 (1).

Several hormones may be affected due to liver disease, including insulin and glucagon due to deamination defect, glucocorticoids and gonadal steroids due to a conjugation defect, and thyroid hormones due to iodination defect (2).

Thyroid dysfunction is present in several chronic disease 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(3). -Numerous clinicians have reported a subclinical hypothyroidism in patients of chronic liver diseases (4).

Although studies in different populations vary in their findings with respect to the type and degree of

thyroid dysfunctions in cirrhosis, but have consistently found low T3 levels in the face of a normal TSH (5).

Several methods are used to stage cirrhosis, including histological and clinical staging. A reliable and time tested system for assessing the clinical severity cirrhosis in Child Pugh's classification. It includes serum biochemical tests, with serum albumin, bilirubin and prothrombin time, and two clinical criteria with ascites and encephalopathy (6).

**2. Patients and methods:****Data collection and patients:**

This study was carried out at internal medicine department, faculty of medicine, Menoufia University. In the duration Between September 2013 and September 2014.sixty cirrhotic and twenty healthy subjects as a control, patients were included in this study aged from twenty and sixty. There were 44 male (63.8%) and 25 female (36.2%). All individuals were subjected to complete history taking and clinical examination.

**Microbiological laboratory methods:**

Two ml of venous blood was taken in EDTA tube for CBC.

Eight ml of venous blood was withdrawn into vacationer tube under aseptic condition.The sample was centrifuged and the clear supernatant serum was separated from the clot.The collected serum divided into:

a- The first was assayed for HBsAg, anti- HCV antibodies AST, ALT albumin, bilirubin, prothrombin time, urea, and creatinine.

b- The second was stored frozen at 20° C until assayed for serum freeT3, free T4, TSH,

### 1-Hepatitis C virus antibody (anti HCV) in serum:

Hepatitis C virus antibody detected by ELISA third generation, using kits from the Biochem. Immunosystem Inc(7).

### 2- Hepatitis B surface antigen (HBs Ag) in serum:

Based on Enzyme Linked Immuno sorbent Assay (ELISA) technique, by kit from Sorin Biomedica Co (8).

### Thyroid function tests:

#### -FREE T3, free T4, TSH Assay principle:

Determined using IMMULITE/IMMULITE is a solid-phase, competitive chemiluminescent enzyme immunoassay.

#### Statistical methods:

Data was analyzed by the SPSS version 11.0 statistical package.

The quantitative data were expressed as mean and standard deviation (mean+ or- SD).The quantitative data were expressed as number and percentage and analyzed by chi-square test and students test for the normally distributed variables and for the non normal distributed variables Mann Whitney test. All this tests were used as tests of significance at p value < 0.05.

### 3. Results:

The studied groups underwent free T3, free T4, TSH, CBC, HBs Ag, HCV Abs, serum albumin, bilirubin, prothrombin time, serum creatine, ultrasound. All patients and control groups were matched in terms of age, sex, BMI, thyroid function and viral markers.

Comparing case and control group as regard age,sex,BMI no statistical significant difference(**p value >0.05**) ("Table1).

Comparing case and control groups as regards free T3,T4,TSH we found highly significant correlation between case and control groups as regards free T3(P value<0.001) but no statistical significant between studied groups as regards free T3 or TSH (P value> 0.05).(Table2).

Comparing between male and female cases as regards free T3,T4,TSH, we found no statistical significant difference(P value >0.05) between male and female.(Table 3).

Comparing between HBV and HCV cases as regards free T3,T4,TSH No significant statistical difference between hepatitis B and hepatitis C (P value >0.05).(table4).

Comparing between the HCV and HBV groups as regards Child push classification,no significant statistical difference between HBV and HCV as regard child classification(P value >0.05) and there is no statistical significant difference between HBV and HCV as regard compensated and decompensated liver cirrhosis (P value >0.05)(Table5).

We studied the Relationship between child classification (A,B,C)and thyroid functions(free T3,T4,TSH),we found shows highly significant negative correlation between child classification and Free T3 (P value <0.001) but no statistical difference between child classification andFT4 and TSH(P value >0.05).(table6).

We studied the Correlation between free T3 and different parameters among the studied group,we found highly significant positive correlation between free T3 and serum albumin(P value <0.001) and highly significant negative correlation between free T3 and (bilirubin,albumin) P value <0.001.also this table shows no significant statistical correlation between Free T3 Aand (age, BMI, HB,TLC, platelet count, s. Creatine) P value >0.05.

**Table 1:Comparison between the case and control groups as regards age, sex and BMI**

	The studied groups				Test of significance	P value
	Cases N = 69		Control N = 20			
Age/years						
X ± SD	45.13±9.97		48.65±7.23		t- test	0.15
Range	21 – 61		35 – 61		1.47	
BMI						
X ± SD	27.72±3.41		26.27±3.63		t- test	0.10
Range	20 – 35		20 – 33		1.66	
	No	%	No	%		
Sex					$\chi^2$	0.92 >0.05
Male	44	63.8	13	65.0	0.01	
Female	25	36.2	7	35.0		

X = mean SD = Standard Deviation  $\chi^2$ = Chi square test P value >0.05 = non significant

**Table 2: Comparison between the case and control groups as regards thyroid functions**

	The studied groups		Mann Whitney U	P value
	Cases N = 69	Control N = 20		
Free T3 X ± SD Range	2.15±0.66 1.07 – 3.28	3.01±0.45 2.31 – 3.71	6.73	<0.001
Free T4 X ± SD Range	1.25±0.17 1.09 – 2.2	1.30 ±0.07 1.14 – 1.38	1.83	0.07
TSH X ± SD Range	2.07±0.26 1.04 – 2.63	2.02±0.14 1.73 – 2.18	0.99	0.33

**Table 3: Comparison between male and female cases as regards thyroid functions**

	The studied cases		t- test	P value
	Male N = 44	Female N = 25		
Free T3 X ± SD Range	2.13±0.62 1.07 – 3.28	2.19±0.73 1.07 – 3.25	0.39	0.70
Free T4 X ± SD Range	1.24±0.16 1.09 – 2.17	1.27±0.20 1.1 – 2.17	0.66	0.51
TSH X ± SD Range	2.04±0.28 1.04 – 2.52	2.14 ±0.21 1.7 – 2.63	1.71	0.09

**Table 4: Comparison between HBV and HCV cases as regards thyroid functions**

	The studied cases		t- test	P value
	HBV N = 30	HCV N = 39		
Free T3 X ± SD Range	2.29±0.64 1.07 – 3.25	2.04±0.66 1.07 – 3.28	1.58	0.12
Free T4 X ± SD Range	1.27±0.26 1.09 – 2.2	1.24±0.05 1.12 – 1.32	0.78	0.44
TSH X ± SD Range	2.09±0.21 1.45 – 2.52	2.06±0.29 1.04 – 2.63	0.46	0.65

**Table 5: Comparison between the HBV and HCV as regards Child classification**

	The studied cases				χ <sup>2</sup>	P value
	HBV N = 30		HCV N = 39			
	No	%	No	%		
Child classification						
A	8	26.7	10	25.6	<b>0.09</b>	0.95
B	10	33.3	12	30.8		
C	12	40.0	17	43.6		
Compensated liver disease	16	53.3	20	51.3	<b>0.03</b>	0.87
Decompensated liver disease	14	46.7	19	48.7		

χ<sup>2</sup>= Chi square test P value >0.05 = non significant

Table 6: Relationship between child classification and thyroid functions

	Child classification			t- test	P value
	A N = 18	B N = 22	C N = 29		
Free T3				6.84	<0.001 <sup>1</sup>
X ± SD	2.87±0.25	2.36±0.22	1.54±0.47	11.14	<0.001 <sup>2</sup>
Range	2.45 – 3.28	1.87 – 2.73	1.07 – 3.25	7.65	<0.001 <sup>3</sup>
Free T4				0.16	0.86 <sup>1</sup>
X ± SD	1.27±0.04	1.26±0.21	1.23±0.20	0.83	0.41 <sup>2</sup>
Range	1.18 – 1.22	1.13 – 2.17	1.09 – 2.2	0.55	0.58 <sup>3</sup>
TSH				0.92	0.36 <sup>1</sup>
X ± SD	2.01±0.12	2.07±0.27	2.12±0.30	1.54	0.13 <sup>2</sup>
Range	1.82 – 2.72	1.58 – 2.63	1.04 – 2.52	0.62	0.64 <sup>3</sup>

1 = relation between child A and child B classes 2 = relation between child A and child C classes

3 = relation between child B and child C classes

Table 7: Correlation between T3 and different parameters among the studied group

	T3		T4		TSH	
	Correlation coefficient (r)	P value	Correlation coefficient (r)	P value	Correlation coefficient (r)	P value
Age	- 0.18	0.09	- 0.08	0.44	+ 0.05	0.63
BMI	- 0.20	0.07	- 0.001	0.99	- 0.003	0.98
PT	- 0.72	<0.001	- 0.23	0.06	+ 0.15	0.23
Albumin	+ 0.87	<0.001	+ 0.06	0.62	- 0.14	0.26
Bilirubin	- 0.67	<0.001	- 0.08	0.52	+ 0.15	0.22
Hb	+ 0.20	0.10	- 0.15	0.21	+ 0.11	0.39
TLC	+ 0.21	0.09	+ 0.02	0.87	- 0.18	0.15
Platlets	+ 0.21	0.08	- 0.12	0.31	+ 0.11	0.39
Child classification	- 0.83	<0.001	- 0.22	0.18	+ 0.12	0.33
S. creatinin	- 0.19	0.12	- 0.10	0.42	+ 0.16	0.19

P value < 0.05 = significant P value < 0.001 = highly significant P value > 0.05 = non significant

Table 8: The relationship between compensated and decompensated liver cirrhosis ass regard thyroid function.

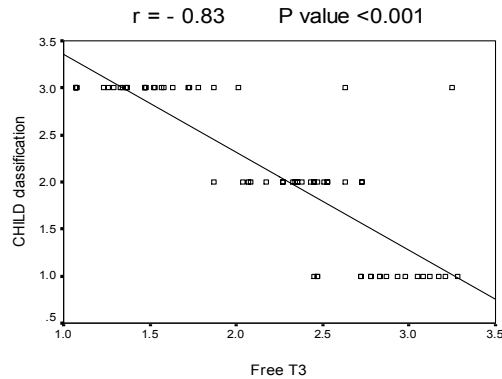
	The studied cases		t- test	P value
	Compensated N = 36	De-compensated N = 33		
Free T3				
X ± SD	2.61±0.36	1.64±0.53	9.02	<0.001
Range	1.37 – 3.28	1.07 – 3.25		
Free T4				
X ± SD	1.25±0.05	1.26±0.25	0.23	0.82
Range	1.13 – 1.32	1.09 – 2.2		
TSH				
X ± SD	2.04±0.22	2.11±0.29	1.04	0.30
Range	1.58 – 2.63	1.04 – 2.52		

This table showing significant statistical difference between free T3 and (compensated and decompensated liver cirrhosis) *p* value < 0.001 and non-statistical significant difference between free T4, TSH and (compensated, decompensated) liver cirrhosis *p* value > 0.05.

This table shows also no significant statistical correlation between (F T4, TSH) and (age, BMI, PT, albumin, bilirubin, platelet count, TLC, s. creatine, HB) *P* value > 0.05. (Table 7).

We studied the relationship between compensated and de compensated liver cirrhosis ass

regard thyroid function (free T3, T4, TSH), There were significant statistical difference between free T3 and (compensated and decompensated liver cirrhosis) *p* value < 0.001 and non statistical significant difference between (free T4, TSH) and (compensated, decompensated) liver cirrhosis *p* value > 0.05 (Table 8).



#### 4. Discussion:

Liver has a key role in thyroid hormones metabolism and their serum level is very important for normal hepatic function and bilirubin metabolism. Besides the associations between the thyroid and liver diseases of an autoimmune nature, such as primary biliary cirrhosis and thyrotoxicosis. Thyroid diseases are frequently associated with liver injuries and biochemical test abnormalities like elevation of ALT, AST and ALP. These thyroid liver association may cause diagnostic confusions and neglect of these facts may result in over or under diagnosis of associated liver or thyroid disease.(9)

Thyroid hormones are essential for normal growth, development and function of all tissues on the body by regulating BMR of all cells, including hepatocytes. The liver in turn metabolize thyroid hormones and regulates their systemic endocrine effects. Therefore thyroid dysfunction may disturb liver function and liver diseases modulates thyroid hormone metabolism (10). Numerous clinicians have reported a subclinical hypothyroidism in patients of chronic liver diseases (4).

The diagnosis of liver cirrhosis in our study was based on clinical features, ultrasonographic findings as well as laboratory investigations "These findings were supported by previous reports. Clinical diagnosis of liver cirrhosis may include signs and symptoms that may occur in the presence of cirrhosis or as a result of the complications of cirrhosis. Many are nonspecific and may occur in other diseases and do not necessarily point to cirrhosis. Likewise, the absence of any does not rule out the possibility of cirrhosis. These features include weakness, fatigue, anorexia, weight loss, spider nevi, gynecomastia, palmar erythema, hypertrophic osteoarthropathy, etc(11). As regard laboratory diagnosis of cirrhosis. (12) clarified that no serological test can diagnose cirrhosis accurately but when a liver abnormality is suspected or identified, a liver panel, a complete blood count with prothrombin time should be performed. Moreover, imaging study of patients with cirrhosis revealed the following characteristic ultrasonographic features of liver

cirrhosis: liver modularity & irregularity, regenerating nodules, etc (13). Ghany and Hoofangle (6) reported that chronic HCV is the most common cause of chronic liver disease, accounting for 40% to 60% of cases. Of patients exposed to HCV, about 80% develop chronic HCV, and of those about 20-30% will develop cirrhosis over 20-30 years.

This study to evaluate the relationship between thyroid hormones and TSH in HBV and HCV related liver cirrhosis and their relation to the severity of liver cirrhosis.

This study had been conducted on a 60 patients and 20 healthy subjects as a control group. All subjects were divided in to three groups.

Group1: thirty patient with chronic hepatitis c related liver cirrhosis.

Group 11: trirty patient with chronic hepatitis b related liver cirrhosis.

Group 111: twenty healthy subject age and sex matched to patient group as control group.

In our study, it was confirmed that more severe liver status was inversely associated with free T3 using child score such a negative correlation was observed. Categorizing patients according to child score A, B, C, we found that the number of patients with free T3 below normal range significantly increase with child score. However free T4 and TSH are reported to be at steady levels despite all alteration in free T3.

Our study also confirmed that no significant difference was found according to viral etiology of liver cirrhosis (HBV, HCV).

Our study also confirmed that there is a significant positive correlation between freeT3 and serum albumin and significant negative correlation between free T3 and serum bilirubin and prothrombin time. And no significant relationship between freeT3 and age, BMI, HB, TLC, platelet count and serum creatine among studied groups.

Two main enzymes acting in the liver as a part of iodothyronine seleno-deiodinase enzyme system are type 1 and type3 deiodinases responsible for extra thyroidal production of free T3(14). So respectively decrease in free T3 Probably reflects decrease in deiodinase 1 activity in the liver of cirrhotic patients.

However, serum TSH and free T4 are reported to be at steady levels in spite alteration in free T3, indicating adaptive mechanisms by which the body reduces basal metabolic rate within hepatocytes and the resultant preservation oh liver function and total body protein storage(15). This experimental study showed sub clinical hypo thyroidism in rats has benefit in both protecting the liver from further damage and regression of establish fibrosis in induced liver fibrosis. it's also suggested that liver function in hypothyroid patients tend to be better than euthyroid.



Some studies show also a controlled hypothyroidism might be beneficial for euthyroid cirrhotic patients (16).

These studies could be suggestive of a protective mechanism in the body in which lower circulating free T3 in the body contributes to protection of liver from further fibrosis and helps the liver reverse the damage.

Hepatitis C is reported to be more associated with hypothyroidism rather than hepatitis B(17). However we did not find any significant relation between etiology of hepatitis and thyroid hormones level.

Our results were similar to that found by (18) who conduct their study on 50 patients with varying degrees of cirrhosis according to child push scoring system. This study suggested the prevalence of low free T3 level and its inverse association with increase severity of cirrhosis according to child score and free T3 could be a significant predictor of thyroid dysfunction in cirrhotic patients.

Another study was similar to our results by (19) which was done on 72 patients with different severity according to child score and different etiology (HBV and HCV). This study had found that serum T3 concentration is reported to be a good indicator of hepatic function and no difference was observed in thyroid hormones regarding etiology of viral hepatitis.

#### Conclusions:

Our results confirm other studies in which serum free T3 is reported to be a good indicator of liver function. No difference was observed in thyroid hormones regarding etiology of viral hepatitis.

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11/28/2014