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Serum Total Triiodothyronine versus Free Tetraiodothyronine and TSH in Patients with HCV Related Cirrhosis and Their Correlation to the Severity of Cirrhosis

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Abstract

Background and Aim: The levels of thyroid hormones and their binding proteins are altered in patient with cirrhosis. We aim to study the changes in triiodothyronine level in HCV related cirrhosis and its correlation to the severity of liver decompensation. Patients and Methods: This study included seventy two patients with HCV related cirrhosis in three groups Group I: 24 patients with Child A class Group II: 24 patients with Child B and C classes without hepatic encephalopathy Group III: 24 patients with Child B and C classes with hepatic encephalopathy. Results: T3 level was significantly lower in group III than group I and II (0.74 ng/ml vs 1 and 1.3 ng/ml in group II and I in succession). The correlation between Child's score and T3 level was highly significant (r = −0.64, P < 0.001). Conclusion: Triiodothyronine level is lower in cirrhosis and its level is correlated to the severity of decompensation.

Keywords

Free T4, TSH, Clinical Euthyroid, Cirrhosis, HCV

1. Introduction

Cirrhosis is the ninth leading cause of death in the United States and is responsible for 1.2% of all US deaths;

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about 35,000 deaths each year. Cirrhosis is often preceded by hepatitis and fatty liver (steatosis), independent of the cause. If the cause is treated at this stage, the changes are reversible. The pathological hallmark of cirrhosis is the development of fibrosis that replaces normal parenchyma. Damage to the hepatic parenchyma (due to inflammation) leads to activation of the stellate cell, which increases fibrosis (through production of myofibroblasts) and obstructs blood flow in the circulation [1]. In addition, it secretes TGF-β1, which leads to a fibrotic response and proliferation of connective tissue. Furthermore, it secretes TIMP 1 and 2, naturally occurring inhibitors of matrix metalloproteinases, which prevents them from breaking down fibrotic material in the extracellular matrix. The fibrous tissue bands (septa) separate hepatocyte nodules, which eventually replace the entire liver architecture [2].

The thyroid status depends not only on thyroxine secretion but also on normal thyroid hormone metabolism, delivery of T_3 to nuclear receptors and on receptor distribution and function. Normal thyroid function, which is essential for normal growth, development and the regulation of energy metabolism within cells, is dependent on a normally functioning thyroid and liver axis [3].

The liver performs important functions in the process of thyroid hormone transport and metabolism. The liver extracts 5% - 10% of plasma T_4 during a single passage, as shown by studies using [I^{131}] T_4 [4]. The liver also synthesizes a number of plasma proteins that bind the lipophilic thyroid hormones. More than ninety nine percent of the thyroid hormones are bound to thyroxine-binding globulin, thyroxine-binding prealbumin and albumin in plasma. This bound portion of the hormone works like a large reservoir of free circulating hormone. The free hormone component within plasma is in equilibrium with the protein-bound hormone, and it is this free fraction which accounts for the hormone's biological activities. The plasma concentrations of free T_4 and T_3 are at a steady concentration, so that the tissues are exposed to the same concentrations of the free hormone [5].

There are evidences showing an association between chronic liver diseases and changes in thyroid gland. Furthermore, it is demonstrated that levels of thyroid hormones and their binding proteins are altered in patient with hepatic disorders, especially cirrhosis [6]. Some studies even say that there's a significant increase in thyroid glandular volume in cirrhotic patients when compared with controls. However, almost all of them are clinically euthyroid [7].

On the other hand, some authors believe that the changes in thyroid hormones levels may be regarded as an adaptive hypothyroid state that helps to decrease the basal metabolic rate within hepatocytes and preserve liver function and total body protein stores [8]. This hypothesis is based on a study in cirrhotic patients which showed that the onset of hypothyroidism due to intrinsic thyroid disease during cirrhosis resulted in a biochemical improvement in liver function as compared to cirrhotic controls [9]. Hypothyroidism has also been associated with lesser degrees of decompensation in cirrhosis [10].

Egypt has the highest prevalence of hepatitis C virus (HCV) in the world it is estimated that about 15% of population are infected with hepatitis C. About 85% of patients infected with HCV develop chronic hepatitis C (CHC) and are at risk for fibrosis progression. About 20% - 30% of CHC patients will develop cirrhosis of the liver within years. Once cirrhosis is established the rate of HCC development is 1% - 4% per year [11]. Being a major health problem in Egypt, and due to its role in development of cirrhosis we chose post-HCV cirrhosis to evaluate the relation between thyroid functions and liver disease.

2. Aim of the Work

This study aims at exploring the changes in thyroid functions in patients with HCV related cirrhosis and the correlation between them and the severity of liver dysfunction.

3. Patients and Methods

This study had been carried out in Zagazig University Hospitals in the period between August 2014 and August 2015. The study design was approved by the Institutional Review Board (IRB) of Faculty of Medicine, Zagazig University. The study included 72 patients with liver cirrhosis due to chronic HCV infection, 40 males and 32 females and their ages ranged from 40 to 70 years old.

3.1. Inclusion Criteria

Patients with liver cirrhosis diagnosed by combination of clinical, ultrasonic and laboratory assessments due to chronic HCV hepatitis diagnosed by positive anti-HCVAb and PCR.

3.2. Exclusion Criteria

- Patients < 18 and > 60 years old
- Patients who refused to give written consent to be included in the study (the consent included description of the study and subsequent editing and publication)
- Patients suffering from previously known thyroid dysfunction
- Patients on medications that could affect thyroid functions e.g. Carbamazepine, Phenobarbitone, Phenytoin, Salicylates and Nonsteroidal anti-inflammatory drugs (NSAIDs)
- Patients with other etiology for liver cirrhosis e.g. history of significant alcohol consumption > 60 g/day, patients with positive HbsAg, patients with evidence of metabolic or autoimmune disease
- Patients under interferon therapy
- Patients admitted to the hospital in an acute event such as upper GI bleeding or sepsis.
- Patients with acute hepatitis and fulminant liver failure.

Patients were allocated to three groups

Group I: included 24 patients with compensated post-hepatitis C cirrhosis (Child's grade A)

Group II: included 24 Patients with decompensated post-hepatitis C cirrhosis (Child's grade B or C) without encephalopathy

Group III: included 24 Patients with decompensated post-hepatitis C cirrhosis (Child's grade B or C) with encephalopathy

All patients were subjected to:

- Thorough history taking regarding the duration of liver disease, history of alcohol intake
- Physical examination with special stress on manifestation of liver cirrhosis.
- Laboratory investigations including: Complete blood count (CBC) by Dyn 1700, Liver and kidney function tests including: Serum albumin, Total and direct bilirubin, Aspartate aminotransferase (AST), Alanine aminotransferase (ALT), serum creatinine and blood urea nitrogen by integra 400 analyser, coagulation profile, Prothrombin Time (PT) and (INR) by sysmex CA 1500, Serum antibodies to HCV and HbsAg by ELISA, auto immune markers (ANA, ALKM Ab, SMA) by slide immunoflorescence.
- Thyroid parameters including total T3, free T4 and TSH serum levels:
- T3 was measured using (Calbiotech, Inc. (CBI) total T3 ELISA kit). The assay was run fully automated. Normal level = (0.52 - 1.58 ng/ml).
- FT4 was measured using (Chemux BioScience, INC kit). The assay was run fully automated. Normal level = (0.65 - 1.97 ng/dl).
- TSH test done using (Chemux BioScience, INC kit). The assay was run fully automated. Normal level = (0.4 - 7.0 uIU/ml).
- Abdominal ultrasonography: examine patients for manifestations of liver cirrhosis and portal hypertension e.g. increased liver echogenicity, coarse echotexture, irregular borders, splenomegally, ascites, dilated portal vein.
- **The severity of the liver dysfunction** was graded according to Child-Pugh classification [12].

	1	2	3
Bilirubin Total	<2 mg/dl	2 - 3 mg/dl	>3 mg/dl
Serum albumin	>3.5 g/dl	2.8 - 3.5 g/dl	<2.8 g/dl
INR	<1.7	1.71 - 2.20	>2.20
Ascites	None	Suppressed with medication	Refractory
Hepatic encephalopathy	None	Grade I-II (or suppressed with medication)	Grade III-IV (or refractory)

Points	Class
5 - 6	A
7 - 9	B
10 - 15	C

4. Statistical Analysis

Data were analyzed using SPSS (Statistical Package for the Social Sciences) version 15 for data processing and statistics. Numbers and percentages were used for qualitative data while mean ± standard deviation (SD) was used for quantitative ones. Chai square test X^2 was used to compare categorical data and ANOVA was used to compare numerical data. KW test was used for numerical data when normal distribution is lacking. Linear regression was used to test the correlation between variables. P value < 0.05 was considered significant.

5. Results

Comparison between the three studied groups as regards their demographic data shows that there were no significant differences as regards age and gender distribution as shown in **Table 1**. **Table 2** represents comparison between the three studied groups as regards all the laboratory parameters. It shows that group I had significantly higher hemoglobin concentration, WBC's count and albumin concentration than the other two groups. Group I also had significantly lower bilirubin level, liver enzymes, PT, INR, urea and creatinine than the other two groups. When it comes to thyroid functions **Table 2** shows that group I had significantly higher level of serum total T3 than the other two groups and group II had significantly higher level of serum total T3 than group III. Comparing the level of free T4 revealed no significant difference between the studied groups while the level of TSH was significantly higher in group II. **Table 3** shows that most of the patients included in the study had normal thyroid function tests. Comparing the three studied groups as regards the prevalence of subnormal levels of the studied thyroid parameters shows that group III had statistically higher incidence of subnormal total T3 level than the other two groups and group II shows significantly higher incidence of subnormal total T3 than group I as shown in **Table 3**. **Table 3** also shows that the prevalence of subnormal serum level of free T4 is not significantly different among the three groups. Also the level of TSH was within normal range in all patients of the three groups. **Table 4** shows that there's highly significant negative correlation between total T3 and the Child's score while TSH has significant positive correlation with it.

6. Discussion

This work aims to study the relation between serum levels of some thyroid parameters specially total T3 and HCV related cirrhosis and their relation to the severity of decompensation. The three groups of patients in this study represented three degrees of hepatic decompensation to evaluate the relation between thyroid and liver functions. There were no significant differences between the three studied groups in this study as regard age and gender distribution.

There was a statistically significant difference between different studied groups regarding the mean value of serum total T3 and serum TSH. We found that, the mean value of serum total T3 was the lowest among decompensated cirrhotic patients with hepatic encephalopathy (group III) (0.74 ± 0.3 ng/ml) and Kayacetin *et al.*, 2003 agrees with this finding in is study on patients with hepatic encephalopathy, followed by decompensated cirrhotic patients without hepatic encephalopathy (group II) (1.0 ± 0.3 ng/ml) but the highest mean value was seen among compensated cirrhotic patients (group I) (1.33 ± 0.3 ng/ml) [13]. This means that mean level of total T3 in groups II and III was higher than in group I. These results come in agreement with most of the previous studies dealing with this topic (Yamanaka *et al.*, 1980, Brozio *et al.*, 1983, Shimada *et al.*, 1988, Agha *et al.*, 1989, Antonelli *et al.*, 2006, Spadaro *et al.*, 2004, Elkabbany *et al.*, 2012, Mansour-Ghanaei *et al.*, 2012 and Dehghani *et al.*, 2013) [6] [14]-[21]. this finding is explained by the fact that liver plays a central role in the peripheral

Table 1. Demographic data.

		Group I No = 24		Group II No = 24		Group III No = 24		Test value	P	Signif.
Age (years) Mean ± SD		53.2 ± 5.1		58.5 ± 8.1		61.5 ± 7.2		8.89*	<0.001	HS
		No	%	No	%	No	%			
Gender	**Male**	14	58.3	9	37.5	17	70.8	5.51#	0.06	NS
	Female	10	41.7	15	62.5	7	29.2			

*ANOVA, #X^2.

Table 2. Comparison between the three groups as regards all laboratory parameters.

	Group I No = 24	Group II No = 24	Group III No = 24	F	P	Signif.
HB(g/dl) Mean ± SD	12.1 ± 2.0	10.1 ± 2.4	11.1 ± 2.2	4.9	0.009	S
WBC's(cells x10^3/ml) Mean ± SD	6.1 ± 2.1	7.1 ± 3.5	9.9 ± 5.8	5.29	0.007	S
Platelet(cellsx10^3/ml) Mean ± SD	94.6 ± 28.2	91.3 ± 30	110.3 ± 38.9	2.3	0.1	NS
Total Bilirubin (mg/dl) Mean ± SD	0.9 ± 0.4	2.6 ± 1.4	3.7 ± 2.5	16.7	<0.001	HS
Direct Bilirubin(mg/dl) Mean ± SD	0.3 ± 0.2	1.1 ± 0.8	1.8 ± 1.5	12.5	<0.001	HS
Albumin (g/dl) Mean ± SD	3.6 ± 0.5	2.4 ± 0.3	2.5 ± 0.5	53.2	<0.001	HS
ALT (IU/ml) Mean ± SD	47.8 ± 32.5	46.2 ± 28.3	80.4 ± 126	KW = 1.16	0.55	NS
AST(IU/ml) Mean ± SD	51.4 ± 25.4	63 ± 45.9	131.7 ± 214.7	KW = 5.2	0.07	NS
INR Mean ± SD	1.16 ± 0.14	1.7 ± 0.5	1.6 ± 0.4	12.3	<0.001	HS
PT(sec) Mean ± SD	13.5 ± 0.7	16.3 ± 3.8	16.1 ± 2.7	7.68	<0.001	HS
Blood Urea (mg/dl) Mean ± SD	33.8 ± 17.6	59.9 ± 43.8	102 ± 37.1	11.2	<0.001	HS
Creatinine (mg/dl) Mean ± SD	0.8 ± 0.2	1.1 ± 0.6	1.6 ± 1.2	5.6	0.005	S
Child's Score(Points) Mean ± SD	5.4 ± 0.5	10.2 ± 1.5	11.2 ± 2.1	99.03	<0.001	HS
Total T3(ng/ml) Mean ± SD	1.33 ± 0.3	1.0 ± 0.3	0.74 ± 0.3	19.56	<0.001	HS
Free T4(ng/dl) Mean ± SD	1.46 ± 0.5	1.47 ± 0.8	1.69 ± 1.1	0.56	0.58	NS
TSH (uIU/ml) Mean ± SD	0.86 ± 0.57	1.36 ± 1.0	0.81 ± 0.6	KW = 6.5	0.03	S

Table 3. Comparison between the studied groups as regards the prevalence of hypothyroidism.

	<Lower Limit N = 72(%)	Normal Range N = 72(%)	>Upper Limit N = 72(%)			
Total T3	14 (19.4%)	57 (79.2%)	1 (1.4%)			
Free T4	10 (13.9%)	56 (77.8%)	6 (8.3%)			
TSH	8 (11.1%)	64 (88.9%)	0 (0.0%)			
	Group I No = 24	**Group II No = 24**	**Group III No = 24**	**X^2**	**P**	**Signif.**
Total T3 **Normal 0.52 - 1.58 ng/ml**	24 (100%)	20 (83.3%)	14 (58.3%)	13.48	0.001	HS
<Lower Limit	0 (0%)	4 (16.7%)	10 (41.7%)			
Free T4 **Normal 0.65 - 1.97 ng/dl**	22 (91.7%)	19 (79.2%)	21 (87.5%)	1.63	0.4	NS
<Lower Limit	2 (8.3%)	5 (20.8%)	3 (12.5%)			
TSH **Normal 0.4 - 7.0 uIU/ml**	24 (100%)	24 (100%)	24 (100%)	0.0	1	NS
>Upper Limit	0 (0%)	0 (0%)	0 (0%)			

Table 4. Correlation between thyroid function tests and Child's score.

	R	P	Signif.
Total T3	−0.64	<0.001	HS
Free T4	0.15	>0.05	NS
TSH	0.25	<0.05	S

conversion of T4 to T3 and that in conditions of liver cirrhosis the enzyme system of the diseased liver converts T4 to reverse T3b which is less active than T3 [8]. This finding was also explained by Novis *et al.*, 2001 that found that the lower T3 level was accompanied by a higher reverse T3 level which is a less active form of the hormone that appear due to peripheral conversion of T4 [22]. This finding is also emphasized by Tas *et al.*, 2012 in a study that linked this lower T3 levels to higher mortality in critically ill cirrhotic patients [23]. The level of free T4 showed no significant differences between the three groups, this agrees with Spadaro *et al*, 2004 and Elkabbany *et al.*, 2012 [19] [20]. This finding disagrees with Yamanaka *et al.*, 1980, Shimada *et al.*, 1988, Agha *et al.*, 1989, Kayacetin *et al.*, 2003, Antonelli *et al.*, 2006 and Dehghani *et al.*, 2013 who said that the level of F T4 was also lower than non-cirrhotic patients [13] [14] [16]-[18] [21]. This also disagrees with Brozio *et al.*, 1983 who found that free T4 was higher than non-cirrhotic patients [15]. The authors who say that the free T4 is lower in cirrhotic patients though they are clinically euthyroid explain this by the fact that there are some changes in the thyroid gland itself [19]. Comparing the three studied groups as regards TSH level revealed that group II had significantly higher TSH, this agrees with Aizawa *et al.*, 1980, Schlienger *et al.*, 1980 and Antonelli *et al.*, 2006 [18] [24] [25]. This finding agrees also with Atalav *et al.*, 2015 that said that cirrhotic patients have lower levels of TSH especially at night [26]. This finding disagrees with Spadaro *et al.*, 2004 and Elkabbany *et al.*, 2012 that found that there was no change in TSH level [19] [20].

A highly significant negative correlation was observed, between total T3 and Child's score and a significant positive correlation between TSH and Child's score and non significant correlation as regard serum free T4. This relatively comes in the same line with Mansour-Ghanaei *et al*. (2012) who found that only for serum total T3, its level decreased with advancing Child-Pugh score [6].

Comparing the three groups as regards prevalence of subnormal thyroid function levels, we found that the incidence of low serum total T3 (below the lower limit) was the highest in decompensated cirrhotic patients with hepatic encephalopathy (group III) (41.7%), followed by decompensated cirrhotic patients without hepatic encephalopathy (group II) (16.7%) versus none of the compensated cirrhotic patients (group I). This difference was statistically highly significant when compare compensated group I with other two decompensated groups (II, III), which means, in other words that the frequency of patients with serum total T3 level below the lower limit significantly increased with severity of liver cirrhosis. This finding agrees with Tas *et al.*, 2012 who found that T3 level is correlated to MELD and Child's score of the patients. As regard serum FT4 level, in our study, we found that, There is no statistically significant correlation with the Child's score this also agrees with Tas *et al.*, 2012. The study by Tas *et al*. disagrees with our study as regards the fact that the level of TSH is also correlated to the Child's score. Tas *et al.* believe that TSH isn't significantly correlated to the severity of liver disease [23].

In our study, it was found that 11.1% (8 patients) of all patients with liver cirrhosis had serum TSH level below the lower limit, serum TSH level was normal in most cases. With a closer look at these abnormalities, patients with low serum TSH level included 3 patients with compensated liver cirrhosis (group I) and 5 patients with decompensated liver cirrhosis with hepatic encephalopathy (group III). This can be explained by the fact that late alteration in thyroid metabolism is a decrease in the pituitary secretion of TSH. Such changes may be a self-protective adaptation to illness, as the body attempts to conserve energy [27].

Such thyroid function derangements sought in this study may be attributed either to a true thyroid dysfunction associated with liver disease or the well-established entity of non-thyroidal illness syndrome (NTIS) formerly known as sick euthyroid syndrome. These findings agree with previous studies that analyzed thyroid dysfunction during critical illness as Fliers *et al*. study that reported a significant inverse correlation between serum total T3 concentrations and the severity of liver dysfunction. Also, Borzio *et al*. study that compared cirrhotic with normal subjects and chronic hepatitis patients. They found that serum total and free T3 levels inversely paralleled severity of liver dysfunction. TSH levels are described to be commonly within the normal range in NTIS but may decrease in prolonged illness [15] [28].

7. Conclusion

Patients with chronic liver disease may have lower serum total T3 level than normal though clinically euthyroid. The decline in thyroid function is correlated to the severity of liver disease.

Conflict of Interests

The research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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