Assessment of Thyroid Dysfunction in Patients with Chronic Hepatitis C Virus Related Liver Diseases

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Background and study aim: Hepatitis C virus is a hepatolymphotropic virus, which is abundant in liver and different body organs. It has a significant role in the metabolism of thyroid hormones, including peripheral conversion of T4 to T3.This research aimed to assess the thyroid dysfunction in patients with chronic hepatitis C (CHC) related liver diseases.

Methods: In this cross section study, we included 200 patients aged between 18-60 years. Patients were categorized into two groups: 50 patients with CHC infection without liver cirrhosis, and 150 patients had cirrhosis. The latter group were categorized based on Child-T-Pugh score into three subgroups; Child A, Child B, and Child C. Each group had 50 subjects. Patients were subjected to history taking, laboratory tests to assess liver and thyroid functions, in addition to abdominal ultrasound.

Results: The mean of TSH level in non-cirrhotic group was 2.57 while it was 2.81, 5.53, and 10.47 in child A, child B and C, respectively. FT3 mean values in non-cirrhotic group were 2.88 while it was 2.23, 1.42, and 1.01 in child A, B and C, respectively. The mean of FT4 level in non-cirrhotic group was 1.25 while it was 1.08, 0.84, and 0.77 in child A.B and C respectively.

Conclusion: Abnormalities in thyroid profile were higher among patient with cirrhosis than in those without cirrhosis. These abnormalities were strongly related to the severity of liver affection and advanced child T-Pugh scoring.

INTRODUCTION

HCV is one of the principal etiologies of chronic hepatitis and liver cirrhosis. Over half of HCV infected patients become chronic active develop fibrosis, cirrhosis, and potentially by decompensated cirrhosis and liver cancer **[1]**. The prevalence of HCV is high among the Egyptian population; the majrityof them (92.5%) are infected with genotype 4, 3.6% with genotype 1, 3.2% with multiple genotypes, and < 1% of patients with other genotypes **[2]**. In 2015, the latest Demographic Health Survey (DHS) reported a seroprevalence of 10% and viremic prevalence of 7%. Between 2008 and 2015, HCV burden markedly diminished to around 30% **[3]**. Cirrhosis is defined as a diffuse hepatic derangement that is characterized by fibrosis, and conversion of normal liver architecture into abnormal structure nodules. It represents the final histological pathway for a variety of liver diseases. The progression to cirrhosis is very variable among patients, and may occur over weeks or many years **[4]**. Apart from hepatic manifestations, HCV has extra-hepatic features in multiple organ systems such as dermatologic, hematologic, renal, rheumatologic and endocrinal. Of this most important endocrinal affection is thyroid abnormalities **[5]**. The liver has an essential role in the metabolism of

thyroid hormones; peripheral conversion of tetra-iodothyronine (T4) to tri-iodothyronine (T3) by type one deiodinase **[6]**. Previous studies claimed that levels of thyroid hormones, in addition to their binding proteins are disturbed among patients with hepatic disorders, especially cirrhotic. It is reported that the reduction in whole T3 and FT3 levels is the most frequent change in plasma levels of thyroid hormones, which is linked to the impact of hepatic derangement **[7]**. Unfortunately, most of those patients had genotypes other than genotype 4 which is the predominant one in Egypt. The present study was conducted to assess thyroid dysfunction in patients with hepatitis C related liver diseases; among Egyptian patients that infected mostly genotype 4

PATIENTS AND METHODS

Two hundred patients with chronic HCV infection who attended to endemic and infectious diseases department at Suez Canal University Hospital in Ismailia city and Communicable Diseases and Research Center in Suez city. We excluded patients with evidence of autoimmune diseases, previous thyroid operations, hepatic and extra-hepatic malignancy, on corticosteroid therapy or immuno-suppressive drugs, HBs Ag positive, on specific anti-HCV medications (DAAS) and those who refused to participate in this study.

The studied patients were divided into two main groups; Group I included 50 non cirrhotic chronic HCV patients and Group II included 150 HCV-related cirrhotic patients .The latter group was subdivided into three subgroups based on Child-T-Pugh scoring system into Child A,B and C; each group comprised 50 patients.

Child-T-Pugh scoring system is a scoring scale of five clinical features of liver disorder. These features are scored from one to three, with three denotes the highly severe derangement. The features include prothrombin time (PT), international normalized ratio (INR), serum albumin, total bilirubin, ascites, and hepatic encephalopathy.

Assessment of liver cirrhosis by abdominal ultrasound, Aspartate Aminotransferase-to-Platelet ratio index (APRI) and FIB-4). After signing the informed consent, all the studied patients were subjected to the following: Complete history taking was sought, via clinical examination confirming features of hepatic decompensation such as jaundice, encephalopathy and ascites; features of thyroid disorder or other systemic disease.

Investigations including abdominal sonography, liver function tests: aspartate transaminase (AST); alanine transaminase (ALT); prothrombin time; INR; serum bilirubin; serum albumin. In addition to complete blood count (CBC); HCV RNA PCR; serum anti-HCV antibody; Serum HBs-Ag; thyroid functions: FT3, FT4, and TSH. APRI and FIB-4 score was calculated for all patients according to the following equations **APRI** = [(AST level/ULN)/platelet count (10^9/L)] × 100. For detection of cirrhosis, a cutoff score of or more than 3.5 is diagnostic **[8]** The **FIB-4** score was determined using the following formula: **FIB-4** = [age × AST/platelet count (10^9/L) × √ALT] a threshold value of greater than 2.5 is diagnostic [9]. IRB approval written was obtained before starting the study.

Data was statistically analyzed with SPSS version 23. Statistically significant values considered when *P*-value < 0.05. Graphs were designed using Microsoft excel. For categorical variables, Chi-square test was used to compare two different groups. For normally distributed quantitative variables, Student t-test was used to compare two groups, while ANOVA test was used to compare between more than two groups. For abnormally distributed quantitative variables, Mann Whitney test was used to compare two groups, and.Kruskal Wallis test, to compare between more than two studied groups.

RESULTS

The study included 200 patients with a mean age of 45.96 years among patients in non-cirrhotic group, while it was 54.57 years in cirrhotic group. There was a male-gender predominance among all groups, while residence was indifferent among them. Both gender and residency were statistically insignificant between all groups (**Table 1)**. The mean of TSH in non-cirrhotic group was 2.57 while it was 2.81, 5.53 and 10.47 in child A, B and C respectively. The mean of FT3 in non-cirrhotic group was 2.88 while it was 2.23, 1.42, and 1.01 in child A, B and C respectively. The mean of FT4 in non-cirrhotic group was 1.25 while it was 1.08, 0.84, and 0.77 in child A, B and C respectively as shown in (**Table 2**).

Concerning the laboratory tests that affect TSH level, in a univariate analysis, we found that TSH is negatively and significantly correlated with CBC elements (WBCs, Hb, PLT) and serum Albumin while liver function tests (ALT, serum Bilirubin, PT), serum creatinine, presence of diabetes, duration of disease and age are dependent risk factors for it as shown in (**Table 3**). FT3 is negatively and significantly correlated with CBC elements (WBCs, Hb, PLT) and while liver function tests (ALT, serum Bilirubin, serum Albumin, PT), presence of diabetes, duration of disease and age are dependent risk factors for it as shown in (**Table 4**). FT4 correlates negatively and significantly correlated with CBC elements (Hb, PLT) and serum Albumin while liver function tests (ALT, serum Bilirubin, PT), duration of disease and age are dependent risk factors for it as shown in (**Table 5**).

Table (1): Demographic data of the studied groups.

	Non cirrhotic (n = 50)		Cirrhotic						Test of Sig.	p
			A (n = 50)		B (n = 50)		C (n = 50)			
	No.	%	No.	%	No.	%	No.	%		
Gender										
Male	32	64.0	33	66.0	34	68.0	33	66.0	χ^2= 0.178	0.981
Female	18	36.0	17	34.0	16	32.0	17	34.0		
Age (years)										
Min. – Max.	27.0 – 61.0		33.0 – 60.0		38.0 – 64.0		45.0 – 70.0		F= 25.243*	<0.001*
Mean ± SD.	45.96 ± 9.73		51.24 ± 7.03		53.50 ± 6.77		58.98 ± 6.39			
Median	48.0		52.50		54.50		59.0			
			p_2=0.447, p_3<0.001*, p_4=0.002*							
Residence										
Urban	23	46.0	24	48.0	26	52.0	26	52.0	χ^2= 0.540	0.910
Rural	27	54.0	26	52.0	24	48.0	24	48.0		

*: statistically significant p value, p_2: significance between group A and non-cirrhotic group, p_3: significance between group B and non-cirrhotic group, p_4: significance between group C and non-cirrhotic group, χ^2: chi squre test, F: ANOVA test.

Table (2): Thyroid profile of the studied groups

Thyroid profile	Non cirrhotic (n = 50)				H	P
		Child A (n = 50)	Child B (n = 50)	Child C (n = 50)		
TSH						
Min. – Max.	0.30 – 4.90	0.30 – 4.90	0.30 – 15.70	0.90 – 41.80	105.859*	<0.001*
Mean ± SD.	2.57 ± 1.19	2.81 ± 1.34	5.53 ± 2.71	10.47 ± 7.82		
Median	2.45	3.15	5.55	7.75		
		p_2<0.001*,p_3<0.001*, p_4=0.001*				
FT3						
Min. – Max.	1.20 – 4.20	1.20 – 3.60	0.20 – 3.30	0.10 – 3.10	100.672*	<0.001*
Mean ± SD.	2.88 ± 0.90	2.23 ± 0.71	1.42 ± 0.93	1.01 ± 0.56		
Median	2.85	1.95	1.0	0.90		
		p_2<0.001*, p_3<0.001*, p_4=0.034*				
FT4						
Min. – Max.	0.80 – 1.90	0.60 – 1.80	0.30 – 1.50	0.10 – 1.30	54.851*	<0.001*
Mean ± SD.	1.25 ± 0.26	1.08 ± 0.37	0.84 ± 0.34	0.77 ± 0.29		
Median	1.20	1.05	0.80	0.75		
		p_2=0.002*, p_3<0.001*, p_4=0.448				

*: statistically significant p value, p_2: significance between group A and non-cirrhotic group, p_3: significance between group B and non-cirrhotic group, p_4: significance between group C and non-cirrhotic group, **H:** Kruskal Wallis test. Min: minimum, Max: maximum.

Table (3): Univariate and multivariate analysis for the parameters affecting TSH (n = 150) for group II

TSH	Univariate		Multivariate	
	B(95% CI)	p	B (95% CI)	P
WBCs (10^3)	-0.791(-1.13 – -0.449)	<0.001*	-0.337(-0.69 – 0.01)	0.059
HB	-1.199(-1.55 – -0.84)	<0.001*	-0.129(0.64 – 0.38)	0.621
PLT	-0.088(-0.127 – -0.05)	<0.001*	-0.002(-0.04 – 0.04)	0.937
PT	0.413(0.27 – 0.55)	<0.001*	0.075(-0.14 – 0.29)	0.485
ALT	0.056 (0.03 – 0.08)	<0.001*	-0.004(-0.03 – 0.03)	0.808
AST	0.025(0.0 – 0.05)	0.054	-	-
Bilirubin	1.871(1.38 – 2.36)	<0.001*	0.465(-0.37 – 1.30)	0.274
Albumin	-3.830(-4.98 – -2.68)	<0.001*	-0.828(-0.244 – 0.79)	0.313
S.cr	2.052(0.91 – 3.20)	0.001*	-0.157(-1.29 – 0.97)	0.783
AFP	0.042(-0.03 – 0.114)	0.242	-	-
RBS	-0.007(-0.02 – 0.004)	0.210	-	-
Gender (Female)	-0.093(-2.07 – 1.89)	0.926	-	-
Age (years)	0.351(0.239 – 0.463)	<0.001*	0.119(-0.03 – 0.27)	0.118
Diabetic	2.500(0.551 – 4.448)	0.012*	1.389(-0.27 – 3.05)	0.101
Duration of disease	0.544(0.40 – 0.68)	<0.001*	0.161(-0.06 – 0.38)	0.150

*Statistically significant p value. B: beta coefficient, CI: confidence interval, WBCs: white blood cells, HB: hemoglobin, PLT, platelets, ALT: alanine transaminase, AST: aspartate transaminase, S.cr: serum creatinine, AFP: alpha feto-protein, RBS, random blood sugar.

Table (4): Univariate and multivariate analysis for the parameters affecting FT3 (n = 150) for group II

FT3	Univariate		#Multivariate	
	B (95% CI)	p	B (95% CI)	P
WBCs (10^3)	0.098 (0.043 – 0.152)	0.001*	0.018(-0.040 – 0.075)	0.546
HB	0.180 (0.123 – 0.237)	<0.001*	0.070(-0.015 – 0.154)	0.106
PLT	0.013 (0.007 – 0.019)	<0.001*	0.002(-0.005 – 0.009)	0.569
PT	-0.053 (-0.075 – -0.030)	<0.001*	0.012(-0.022 – 0.046)	0.478
ALT	-0.007 (-0.12 – -0.003)	0.002*	0.0(-0.005 – 0.005)	0.890
AST	0.0 (-0.004 – 0.004)	0.953	-	-
Bilirubin	-0.268 (-0.347 – -0.188)	<0.001*	-0.106(-0.244 – 0.032)	0.132
Albumin	0.544 (0.360 – 0.728)	<0.001*	0.111(-0.155 – 0.378)	0.409
S.cr	-0.167 (-0.352 – 0.017)	0.075	-	-
AFP	-0.011 (-0.022 – 0.001)	0.061	-	-
RBS	0.0 (-0.002 – 0.002)	0.849	-	-
Gender (Female)	-0.249 (-0.556 – 0.058)	0.111	-	-
Age (years)	-0.040 (-0.059 – -0.022)	<0.001*	0.009(-0.016 – 0.033)	0.474
Diabetic	-0.244 (-0.552 – 0.065)	0.120	-	-
Duration of disease	-0.078 (-0.101 – -0.056)	<0.001*	-0.042(-0.078 – -0.006)	0.022*

*Statistically significant p value. B: beta coefficient, CI: confidence interval, WBCs: white blood cells, HB: hemoglobin, PLT, platelets, ALT: alanine transaminase, AST: aspartate transaminase, S.cr: serum creatinine, AFP: alpha feto-protein, RBS, random blood sugar.

Table (5): Univariate and multivariate analysis for the parameters affecting FT4 (n = 150) for group II

FT4	Univariate		#Multivariate	
	B (95%CI)	P	B (95%CI)	P
WBCs (10^3)	0.020(-0.003 – 0.042)	0.084	-	-
HB	0.049 (0.025 – 0.073)	<0.001*	0.031(-0.006 – 0.068)	0.101
PLT	0.003 (0.0 – 0.005)	0.031*	0.0 (-0.003 – 0.003)	0.937
PT	-0.011 (-0.020 – -0.001)	0.024*	0.009 (-0.005 – 0.024)	0.211
ALT	-0.002 (-0.004 – 0.0)	0.048*	0.0 (-0.002 – 0.002)	0.890
AST	0.0 (-0.002 – 0.001)	0.619	-	-
Bilirubin	-0.067 (-0.101 – -0.032)	<0.001*	-0.025 (-0.085 – 0.034)	0.402
Albumin	-0.153 (0.076 – 0.230)	<0.001*	0.054 (-0.062 – 0.170)	0.360
S.cr	-0.064 (-0.137 – 0.010)	0.089	-	-
AFP	-0.001 (-0.006 – 0.003)	0.556	-	-
RBS	-005 (-0.001 – 0.001)	0.826	-	-
Gender (Female)	0.027 (-0.096 – 0.150)	0.434	-	-
Age (years)	-0.010 (-0.017 – -0.002)	0.015*	0.007 (-0.004 – 0.017)	0.196
Diabetic	-0.091 (-0.214 – 0.032)	0.145	-	-
Duration of disease	-0.022 (-0.031 – -0.012)	<0.001*	-0.017 (-0.032 – -0.001)	0.037*

*Statistically significant p value. B: beta coefficient, CI: confidence interval, WBCs: white blood cells, HB: hemoglobin, PLT, platelets, ALT: alanine transaminase, AST: aspartate transaminase, S.cr: serum creatinine, AFP: alpha feto-protein, RBS, random blood sugar.

DISCUSSION

Since there is an alteration in thyroid profile was noticed among patients with CHC, we aimed to assess the thyroid profile among them. In this cross section study, we included 200 patients with CHC. We classified patients into two groups: cirrhotic and non-cirrhotic. The former group was subdivided into three more groups based on Child-T-Pugh scoring system among those patients we evaluated the thyroid profile, liver and kidney function tests, and CBC.

The result of this research revealed a decrease in the level of FT3 in cirrhotic patients (Group II) and it was statistically significant. When the serum levels of FT3 in different subgroups were compared, Child A group was within the normal range meanwhile child C patients had the lowest levels. This result is in agreement with Kharb **[6]**, Mansour **[9],** El-Kabbany **[11]**, Eshraghian **[12]** who documented that dysregulation and dysfunction of thyroid hormones were in cirrhotic patients. Furthermore, our results are also in agreement with Malik **[13]** who reported that the level of FT3 was significantly low in patients with chronic hepatitis C in comparison to control.

Our results also revealed that the level of FT4 was statistically significant lower in cirrhotic patients (Group II). When comparing the mean serum level of FT4 among different subgroups; A, B, and C we found that the lowest levels were in Child C group, followed by the Child B group, meanwhile Child A group was within the normal range. These results are in agreement with Kabadi **[14]** who reported that there was low levels of T3 and T4 in patients with advanced liver cirrhosis. In addition, our study was in line with Kayacetin **[15]** and Antonelli et al **[10]** who reported that FT4 level was significantly lower in cirrhotic patients. They proposed that the previous findings might be reliant on the severity of hepatocellular damage and might be reversed on improvement of liver functions, so that we can consider T4 and T3 levels as useful prognostic indices.

Conversely, our previous outcomes were in disagreement with Malik **[13]** who recorded that most of chronic hepatitis C had normal thyroid function; normal TSH and FT4 levels. Moreover, they were in disagreement with Huang **[16]** who reported that levels of FT4 and TSH were within normal range in chronic liver disease patients. They also were in disagreement with Antonelli et al **[10]** who recorded a marked reduction in FT3 and increase in the level of FT4 in both cirrhotic and non-cirrhotic chronic hepatitis C patients. These controversial results might be due to the difference in genetic background of patients, geographic distribution, and different environmental factors; like iodine intake and presence of other infectious agents.

Our study revealed a highly significant level of TSH in cirrhotic patients (Group II) when compared to non-cirrhotic (Group I). When comparing the mean TSH serum level in different subgroups; A, B, and C we found that Child C group had the highest level followed by the Child B group, meanwhile normal range was found in Child A group.

This result was in agreement with Antonelli et al. **[10]**, Moustafa **[17]** and Mansour **[9]**, who found that serum TSH level was higher in decompensated cirrhotic hepatitis C patients than both chronic hepatitis and compensated cirrhotic patients. However, that result were in disagreement with Kharb **[6]** who found that TSH level was lower in patients with chronic liver disease than control; they proposed an explanation for that finding that the increased level of inflammatory cytokines in chronic liver disease patients might negatively affect the hypothalamic-thyroid axis. These results also were in disagreement with Kayacetin **[15]** who reported that the level of TSH had no significant difference between cirrhotic and non-cirrhotic chronic hepatitis C patients. These different results as mentioned before might be due to differences in HCV genotyping, environmental factors, geographic distribution, and genetic background.

The present study showed that serum albumin level , serum bilirubin, prothrombin time and Child -T-Pugh score are dependent risk factor for FT3 and FT4 abnormalities. These results are similar to those of Borzio **[18]** who observed that serum FT3 was significantly correlated with serum bilirubin, serum albumin, and Prothrombin time.

CONCLUSION

Cirrhotic hepatitis C patients have thyroid abnormalities higher than non-cirrhotic patients do. It is intensely related to the severity of liver affection and the advancing of child score. S.Bilirubin, Prothrombin time, duration of disease and degree of liver cirrhosis are dependent risk factor for TSH abnormalities**.** We can consider TSH**,** FreeT4 and Free T3 to be useful prognostic indices.

Ethical approval: Consent was taken from each participant, who was assured about the confidentiality of his information. The Faculty of Medicine, Suez Canal University Research Ethics Committee approved the study.

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Conflicts of interest: There are no conflicts of interest.

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