ISSN2515-8260 Volume08, Issue 04, 2021

Thyroid Dysfunction Prevalence in Elderly Patients with Chronic Liver Disease in Zagazig University

Mohamed Mohamed Hassaan, Zeinab Maher Mohamed, Aya Hefny Ibrahem and Mayada Mohamed Mousa

Internal Medicine Department, Faculty of Medicine, Zagazig University, Egypt
Coressponding author: Aya Hefny Ibrahem, Email: ayabeder50@gmail.com

ABSTRACT

Background: Cirrhotic patients are more liable to thyroid dysfunction especially hypothyroidism and may have thyroiditis and hyperthyroidism. The aim of this work is the evaluation of thyroid dysfunction in elderly patients with chronic liver disease. Patients and methods: A cross-sectional study included 54 elderly patients with clinical, biochemical, and ultrasound evidence of cirrhosis of liver which was carried out in Internal Medicine Department, Faculty of Medicine, Zagazig University Hospitals. All subjects included in this study were elderly over 65 years and subjected to through clinical examination and full history taking with special stress on age, sex, comorbidities, medications, symptoms of hepatic decompensation and symptoms of hypothyroidism or hyperthyroidism. The technical part was done at Biochemistry Department in Zagazig University. We assessed complete blood count, serm bilirubin, serum albumin, serum ALT and AST, serum creatinine, serum urea, PT, PTT, INR, TSH, free T3, T4 and lipid profile. Results: There was a statistically significant positive correlation between serum TSH and weight, BMI, Child score, total, direct bilirubin, INR, serum cholesterol, LDL cholesterol and triglycerides. There is significant negative correlation between TSH and total leucocytic count, platelet count, serum albumin. There was a significant negative correlation between free T4 and both weight and BMI. There is significant positive correlation between free T3 and total leucocytic count, and platelet count. There is non-significant correlation between free T3 and neither weight, BMI, age, hemoglobin, serum albumin, serum creatinine, ALT, AST, INR, LDL or HDL cholesterol There was a significant negative correlation between child score and TSH while there is significant positive correlation between child score and both Ft4 and FT3. There is significant relation between presence and degree of ascites and all of free T4, free T3 and TSH. Conclusion: There is important relation between Child pough class and all of free T4, free T3 and TSH. There is significant relation between grade of hepatic encephalopathhy and all of free T4, free T3 and TSH.

Keywords: Liver Cirrhosis TSH; T3 ; T4; INR, LDL; Elderly Patients.

INTRODUCTION

Liver cirrhosis is defined as an advanced stage of liver fibrosis with conversion of normal liver vasculature and architecture. Regenerative nodules with fibrous tissues form in response to chronic injury and lead to cirrosis. So, distortion of the liver

architecture due to liver fibrosis and/or cirrhosis leads to hemodynamic instability and portal hypertension **(1).**

Long-term chronic exposure to toxic effects such as hepatitis viruses, alcohol or bile acids can stimulate hepatocyte damage and apoptosis. So, a repair reaction is triggered, which is characterized by extracellular matrix deposition and inflammation and results in liver fibrosis, when not only the exposure to toxic agents, but also the repair reaction is chronic **(2).** With progressive fibrosis and ongoing hepatocyte injury, disappearance of normal hepatocytes occurs resulting in a decrease in the functional metabolic capacity of the liver **(3).**

There is currently no standard therapy to treat liver cirrhosis, which is the final stage of these liver diseases and may be complicated with hepatocellular carcinoma. Therefore, management of the various symptoms of liver cirrhosis is very important, and aging-related parameters must be considered in the decision making for therapeutic strategies and dosage of the available medicine **(4).**

Thyroid function is precisely assessed by measurements of serum thyroid stimulating hormone (TSH) and thyrotropin. In the absence of pituitary disease, a precise inverse relationship between free thyroxine(FT4) and the logarithm of TSH can be derived across the spectrum of primary thyroid function and dysfunction. Given the logarithmic response of TSH to changes in FT4 levels, TSH measurement allows for more precise estimation of thyroid function than the thyroid hormones themselves **(5)**. However, it is presently difficult to consider a low TSH "physiologic" in the elderly. This is an aspect that will require further studies, considering the accumulating evidence suggesting adverse effects of mild hyperthyroidism in the older population **(6)**.

Thyroid illness is very much a disease of the elderly and that it often goes undiagnosed. Although the incidence of thyroid problems increases with age, it is sometimes difficult to diagnose as symptoms are not always as widespread or obvious as those in younger patients **(7)**.

Liver is one of the main sites of deiodinase enzyme activity for T3 production from T4. And other biological pathways for T4, T3 metabolism and their transportation in the liver and the blood circulation that is role responsibility of the liver function. Other reason is liver can play an important role for transport thyroid hormones within circulation and in target tissue intracellular due to thyroid transport system which mediated through Thyroxine-Binding Globulin (TBG) and albumin, all are synthesized within liver **(8).** Therefore, the aim of the present study is the evaluation of thyroid dysfunction in elderly patients with chronic liver disease.

Therefore, the aim of the present study is the evaluation of thyroid dysfunction in elderly patients with chronic liver disease.

Patients and Methods:

A cross-sectional study included 54 elderly patients with clinical, biochemical, and ultrasound evidence of cirrhosis of liver which was carried out in Internal Medicine Department, Faculty of Medicine, Zagazig University Hospitals and the technical part was done at Biochemistry Department in Zagazig University in the period from March 2019 to October 2019.

Written Informed consent was taken from the patient to participate in the study. Approval for performing the study was obtained from Internal Medicine and Medical Biochemistry Departments, Zagazig University Hospitals after taking Institutional Review Board (IRB) approval.

Inclusion criteria:

Patients with symptoms, signs, biochemical and ultrasound features of chronic liver disease irrespective of cause. Their age: ≥ 65 years, female and male.

Exclusion criteria:

Patients with known thyroid disorder hypo- or hyper-thyroidism on eltroxine or antithyroid medications already.Patients with history of organ failure, cancer, radio or chemotherapy and individual with active infection such as bone and muscle disease, cardiac, pancreatic (diabetes), nephrotic syndrome.

Methods:

All patients were subjected to full history taking and general examination thorough physical examination was done especially signs of hepatic decompensation like ascites, hepatic encephalopathy, internal bleeding from large blood vessels in the esophagus (varices), Yellowing of eyes and skin (jaundice) and neck examination for goiter.

Blood sample collection:

From peripheral fasting venous blood (10 ml) were taken from each subject under complete aseptic conditions, the venous blood samples were collected and divided for measurement of kidney function test and liver function test. 1 ml blood collected on 3.8% trisodium citrate anticoagulant in a 9:1 ratio, which is centrifuged to produce platelet poor plasma. Coagulation profile (PT, INR and PTT) were calculated from these sample according to the manufacture instructions. Serum sample s and kept frozen until the time of assay of thyroid function (TSH, FT3 and FT4).

Laboratory investigations:

The laboratory investigations included any investigations that verify inclusion and exclusion criteria. Complete blood count, liver function tests [serum bilirubin (total and direct), serum albumin, serum alanine transaminase (ALT) and aspartate transferase (AST), Kidney function tests (serum creatinine and serum urea), Bleeding

profile [Prothromine Time (PT), Partial Thromboplastin Time (PTT) and INR], TSH, free T3 and free T4.

Human thyroid stimulating hormone ELISA kit, Inteco Diagnostics UK Ltd, 62 Beechwood Road, E8 3DY England, used for estimation of TSH. The mean TSH values based on 160 random normal adult blood samples are 0.4-4.2 μIU/mL. Human Free Triiodothyronine (F-T3) ELISA kit, Catalog No. E1004. AUTOBIO Diagnostics Co., LTD, Zhengzhou, China, used for estimation of F-T3. Human Free thyroxine (F-T4) ELISA kit, Catalog No. E1005. AUTOBIO Diagnostics Co., LTD, Zhengzhou, China, used for estimation of F-T4 (Normal Range (±2σ, pmol/l): 9.0 - 23.0).

Statistical analysis:

Data analysis was performed using the software SPSS (version 20 (IBM corp.Released 2011.IBM SPSS statistics for windows, Version20.0.Armonk, NY: IBM Corp.). Quantitative variables were described using their means and standard deviations. Kolmogorov-Smirnov and Levene tests were used to verify assumptions for use in parametric tests. Mann whitnet test and Kruskal Wallis test were used. One way ANOVA test was used. Pearson correlation and Spearman rank correlation coefficients were used to assess strength and direction of a linear relationship between two variables. The level statistical significance was set at 5% ($P<0.05$). Highly significant difference was present if $p\leq0.001$.

RESULTS:

The present study included Fifty four elderly patients with clinical, biochemical, and ultrasound evidence of cirrhosis of liver. There was a statistically significant positive correlation between serum TSH and weight, BMI, Child score, total, direct bilirubin, INR, serum cholesterol, LDL cholesterol and triglycerides. There is significant negative correlation between TSH and total leucocytic count, platelet count, serum albumin. There is non-significant correlation between TSH and neither age, hemoglobin, serum creatinine, ALT, AST, or HDL cholesterol **(Table 1)**. There was a significant negative correlation between free T4 and both weight and BMI **(Figure 1)**. There is statistically significant negative correlation between free T3 and Child score, total, direct bilirubin, INR, serum cholesterol, and triglycerides. There is significant positive correlation between free T3 and total leucocytic count, and platelet count. There is non-significant correlation between free T3 and neither weight, BMI, age, hemoglobin, serum albumin, serum creatinine, ALT, AST, INR, LDL or HDL cholesterol **(Table 2)**.

There was a significant negative correlation between child score and TSH while there is significant positive correlation between child score and both Ft4 and FT3 **(Figure 2)**. There is significant relation between presence and degree of ascites and all of free T4, free T3 and TSH. On pair wise comparison for TSH, the difference is significant between groups with no and tense ascites. However, on LSD comparison for free T4, the difference is significant between group with no ascites and both groups with moderate and marked ascites. On LSD comparison for free T3, the

difference is significant between groups with no ascites and each of minimal and moderate ascites groups **(Table 3)**.

Table (1): Correlation between TSH and the studied demographic, anthropometric and laboratory parameters:

Parameters	TSH	
	R	P
Age	-0.124	0.371
Weight	0.323	0.017*
BMI	0.296	0.03*
Child score	0.507	<0.001**
TLC (10^3/mm^3)	-0.447	0.001**
Hemoglobin (g/dl)	-0.17	0.208
Platelet count (10^3/mm^3)	-0.384	0.004*
Serum creatinine	-0.128	0.356
Serum albumin	-0.271	0.047*
Total bilirubin	0.455	0.001**
Direct bilirubin	0.437	0.001**
ALT	0.126	0.363
AST	0.118	0.394
INR	0.271	0.047*
Serum cholesterol	0.377	0.005*
Serum triglycerides	0.497	<0.001**
HDL	-0.17	0.22
LDL	0.389	0.004*

r Spearman correlation coefficient *p<0.05 is statistically significant **p≤0.001 is statistically highly significant

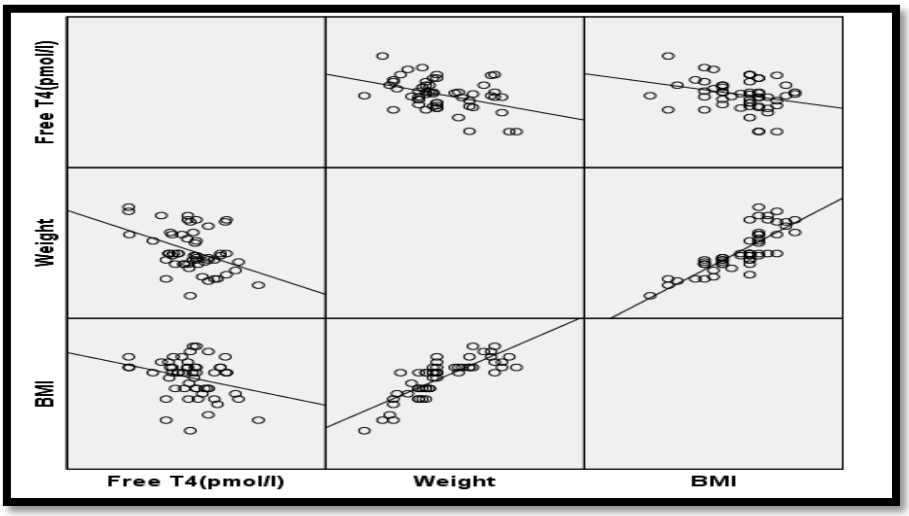

Figure (1): Matrix dot graph showing correlation between free T4 and both weight and BMI.

Table (2): Correlation between free T3 and the studied demographic, anthropometric and laboratory parameters:

Parameters	Free T3	
	R	P
Age	0.108	0.436
Weight	-0.078	0.576
BMI	0.003	0.986
Child score	-0.494	<0.001**
TLC (10^3/mm^3)	0.332	0.014*
Hemoglobin (g/dl)	0.103	0.457
Platelet count (10^3/mm^3)	0.347	0.01*
Serum creatinine	-0.231	0.093
Serum albumin	0.23	0.094
Total bilirubin	-0.291	0.033*
Direct bilirubin	-0.287	0.035*
ALT	-0.137	0.323
AST	-0.119	0.339
INR	-0.32	0.018*
Serum cholesterol	-0.342	0.011*
Serum triglycerides	-0.396	0.003*
HDL	-0.052	0.71
LDL	-0.224	0.103

r Spearman correlation coefficient *p<0.05 is statistically significant **p≤0.001 is statistically highly significant

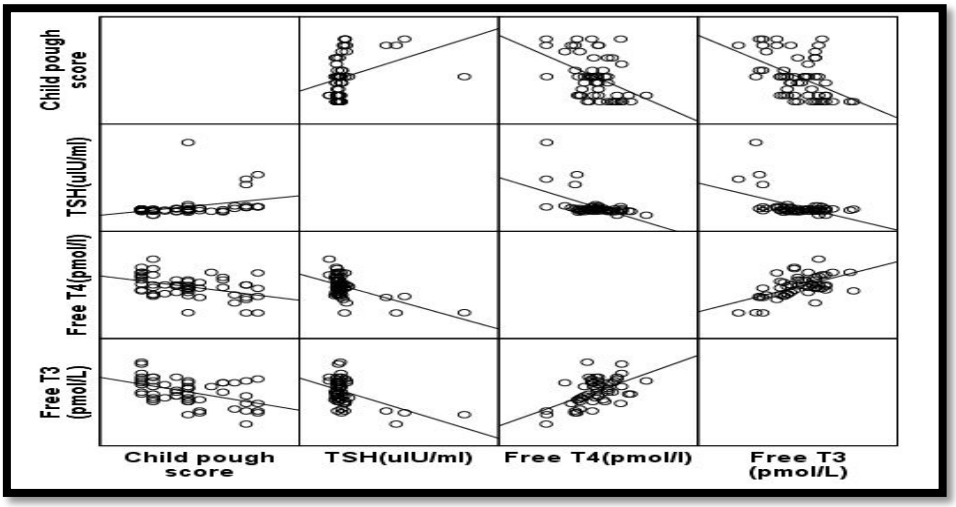

Figure (2): Matrix dot graph showing correlation between child score and TSH and FT4 and FT3.

Table (3): Relation between presence and degree of ascites and thyroid profile among the studied patients:

Ascites	TSH		Free T4		Free T3	
	Mean ± SD	Median (Range)	Mean ± SD	Range	Mean ± SD	Range
No	3.07 ± 1.19	3.3 (0.01 – 4.4)^{g0,4}	16.38 ± 4.11	10.5 :25.3 ^{g0,2,4}	3.39± 0.59^{g0,1,2}	2.5 – 4.6
Minimal	3.78 ± 1.37	3.6 (2 – 7)	14.08 ± 2.19	10.7 – 17	2.87 ±0.51 ^{g0,1}	2 – 3.6
Moderate	12.82 ± 15.62	4.4 (2.2 – 48.4)	11.21± 5.7	3.8 – 20 ^{g0,2}	2.61 ± 0.88^{g0,2}	1.3 – 3.8
Marked	9.86 ± 9.6	5.7 (5.3 – 7)	14.96 ± 3.43	10.4 – 19.8	2.84 ± 0.78	1.9 – 3.7
Tense	4.46 ± 1.2	5.7(2.6 – 5.5) ^{g0,4}	11.36 ± 4.84	3.8 – 15^{g0,4}	2.78 ± 0.6	2 – 3.5
KW/F	19.477		3.405		3.134	
p	0.001**		0.016*		0.023*	

F One Way ANOVA KW Kruskal Wallis test *p<0.05 is statistically significant

****p≤0.001 is statistically highly significant**

DISCUSSION

Chronic liver failure are leading cause of morbidity and mortality in the whole world; with the majority of preventable cases attributed to excessive alcohol consumption, viral hepatitis or nonalcoholic fatty liver disease. Chronic liver disease often is an indolent disease. Most patients remain asymptomatic until the occurrence of decomposition, characterized by ascites, Spontaneous bacterial peritonitis, hepatic encephalopathy or variceal bleeding from portal hypertension **(9)**. In patients with chronic liver disease are decreased total and fT3 levels. Liver injury caused by thyrotoxicosis is relatively common, and can be conveniently divided into hepatitic or cholestatic types **(10)**.

Our study included Fifty four patients with chronic liver disease of different aetiologies were referred to the Internal Medicine Department, Faculty of Medicine, Zagazig University Hospitals after excluded patients with known thyroid disorder hypo- or hyper-thyroidism, liver disease with antiviral B or C treatment, steroid or drugs that affect thyroid function.

In our study there is significant relation between presence and Child pough class and all of free T4, free T3 and TSH. On pairwise comparison for TSH, the difference is significant between groups with Child A and C. However, on LSD comparison for free T4 and FT3, the patients with Child A class had the most significant high level.

Regarding individual parameter of thyroid function, **Mobin et al. (11)** reported that in all decompensated cirrhotic patients (sample size n = 76), 76.3% had low serum T3 levels, 14.47% had low serum T4 levels, and 2.63% had raised TSH levels. **Verma et al. (12)** found low free T3 and free T4 in 72.5% and 26.47% in patients of cirrhosis of liver respectively. TSH towards the upper limit of normal range was observed in 52.3% of patients. Also, **Punekar et al. (13)** reported that most abnormality seen with was low free T3 level (71%), low free T4 (21%), and high TSH level (20%).

Our results showed statistically significant positive correlation between serum TSH and weight, BMI, Child score, total bilirubin, INR, serum cholesterol, LDL cholesterol and triglycerides. **Yadav et al. (14)** determined whether liver function is associated with subclinical and overt hypothyroidism. Thyroid and liver function tests were evaluated in 47 patients with overt (TSH ≥10.0 mIU/L) and 77 patients with subclinical hypothyroidism (TSH 6.0-9.9mIU/L) and compared with 120 age-matched euthyroid controls. They reported that TSH showed significant positive correlation with AST and ALP values. Thus, overt hypothyroid state is associated with significant derangement in biochemical parameters of liver function. Hence, liver function should be regularly monitored in hypothyroid patients.

Similarly, **Chin et al. (15)** found the association between thyroid hormones and thyroid-stimulating hormone (TSH) with lipid profile in a euthyroid male population in a total of 708 men aged 20 years and above. Their blood was collected for the determination of total cholesterol, LDL-C, HDL-C, TG, FT4, FT3and TSH levels. The association was analyzed using multiple regression and logistic regression models with adjustment for age, ethnicity, body mass index and FT4/FT3/TSH levels. They documented that there is a significant and independent relationship between TSH and thyroid hormones and BMI.

Zhang et al. (16) found that TSH was significantly associated with TC and LDL-C, even in a partial correlation analysis multiple linear regression analysis, TSH was positively associated with TC and LDL-C. Also, **Verma et al. (2017)** found statistically no significant difference between TSH levels. They saw no significant correlation between TSH and various biochemical parameters.

Several mechanisms have been postulated for this occurrence of lower free T3 levels in patients with cirrhosis of liver and its inverse correlation with the severity of liver injury. Most common hypothesis states that loss of peripheral deiodination as the primary cause of decreased free T3 levels, the so called sick euthyroid syndrome **(18)**.

In our study, there is significant relation between Child Pugh class and all of free T4, free T3 and TSH. On pairwise comparison for TSH, the difference is significant between groups with Child A and C. However, on LSD comparison for free T4 and FT3, the patients with Child A class had the most significant high level. These results were consistent with **El-Feki et al. (18)** who found significant relation between Child Pugh class and thyroid hormones.

Punekar et al. (13) concluded that the mean FT3 and FT4 levels were significantly decrease and mean TSH levels were significantly increase in liver

cirrhosis patients compared to healthy controls. Level of FT3, FT4, and TSH also correlate with the severity of liver disease, level of FT3 can be used as prognostic marker for liver cirrhosis patients.

Conclusion:

There is important relation between Child pough class and all of free T4, free T3 and TSH. On comparison for TSH, the difference is significant between groups with Child A and C. However, on comparison for free T4 and FT3, the patients with Child A class had the most significant high level. There is significant relation between grade of hepatic encephalopathhy and all of free T4, free T3 and TSH.

NO conflict of interest.

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