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A study on thyroid functions in chronic liver disease: A one year prospective study

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***Abstract*---**In the present study, thyroid functions have been evaluated with all the clinically available indices and confirms the abnormalities in many parameters of thyroid function test in chronic liver disease patients. However euthyroid state is maintained virtually in all patients, probably as a result of low normal Free T3 and high normal FT4. Furthermore, serum T3 concentration appear to directly correlate with the severity of liver dysfunction.

***Keywords*---**thyroid functions, chronic liver disease, prospective study.

Introduction

Thyroid hormones, Thyroxine (T4) and triiodothyronine (T3) are essential for healthy organ development and function. These hormones regulate the basal

metabolic rate of cells of human body, including hepatocytes, and thereby modulate hepatic function.[1] The largest solid organ of our body, liver plays a significant role in thyroid hormone metabolism. It is involved in synthesis of thyroid binding globulin, conjugation, excretion and peripheral deiodination of thyroid hormones. Thyroid disorders may affect liver functions and similarly liver disease modulates thyroid hormone metabolism, and a variety of systemic diseases affect both organs. Although almost all patients with liver disease are clinically euthyroid, some abnormalities in the circulating hormone concentrations have been shown in previous studies. In liver disorders, the total and free thyroxine levels have been reported as normal, decreased or increased. There is also abnormality in thyroxine binding globulin serum levels and a reduced thyroid hormone binding capacity, because of a hypothetical circulating inhibitor.[2] Moreover, total, and free triiodothyronine concentrations are often decreased, sometimes profoundly and their levels correlate well with severity of liver dysfunction. To further evaluate the thyroid function in liver disease, this study measures T3, T4, FT3, FT4, TSH serum levels in patients with chronic liver disease and correlate thyroid hormone disturbances with severity of liver disease (assessed based on Child-Pugh score).

Method

We included a total of 100 patients in our study. Fifty patients with symptoms, signs with biochemical & radiological evidence of chronic liver disease and fifty controls, admitted at our institute. The patients were enrolled for this study after prior written and informed consent and after approval from ethical and research committee.

Period of study: One year from MAY 2017 – APRIL 2018
Inclusion criteria: Patients with symptoms, signs with biochemical and radiological evidence of chronic liver disease. Those patients willing to participate in the study
Exclusion criteria: Patients with upper gastrointestinal bleeding, renal failure, and patients already on thyroid medications.
As a control group 50 healthy subjects (40 men; 10 women) aged 25 – 75 years, matched for their age, sex was investigated All the patients were assessed for the duration of chronic liver disease and were also asked about past history of jaundice, blood transfusion, marital and sexual history and duration of alcoholism (if present). Physical examination in search of stigmata of chronic liver disease was routinely done in all patients. Ophthalmologic examination was done to look for KF ring. Detailed cardiovascular and neurological examination was done.

Blood investigations were done, CBC, ESR, Blood urea (urease-gldh), Serum creatinine (jaffe·s method), Total bilirubin (diazo), SGOT/SGPT (IFCC), lbumin. Ultrasound abdomen and pelvis, Portal vein Doppler, Serum T3, T4, TSH FT3, FT4, Serum T3, T4 was determined by standard radio immuno assay. Serum free T3 (FT3) and free T4 (FT4) were measured by direct radio immuno assay.

Child–Pugh score

The Child–Pugh score is used to assess the prognosis of chronic liver disease, mainly cirrhosis. Each patient was assigned a Child's grading (of A, B or C) to stratify the individual with regard to risk of death due to the procedure. Child's grade A patients were believed to have the best prognosis, and Child's grade C patients the worst. Five variables are considered: presence of ascites, encephalopathy, serum levels of albumin, total bilirubin, and prolongation of the prothrombin time. Each of these variables is assigned a score between 1 and 3 according to its severity or degree of abnormality. Following modification by Pugh, the scoring system was used to predict mortality of cirrhotic patients with regard to any type of surgery. Nowadays, the Child-Pugh score is used to assess prognosis of cirrhotic patients in general.

Table 1: Assigning a Child-Pugh score (for an adult patient)

Parameter	Score		
	1	2	3
Ascites	None	Mild to moderate	Severe
Encephalopathy (grade)	None	1-2	3-4
Bilirubin (mg/dl) OR Bilirubin in Primary Biliary Cirrhosis (mg/dl)	<2 <4	2-3 4-10	>3 >10
Albumin (g/dl)	>3.5	2.8-3.5	<2.8
Prothrombin time	<4	4-6	>6

The sum of the five scores from the above table is used to assign a "Child-Pugh grade" (also known as a Child's grade) of A, B or C to the patient's clinical condition at that point in time. This grade is used to gauge mortality using the following table:

Table 2: Percentage survival in cirrhotic liver disease

Child-Pugh grade	Child-Pugh Score		1 Year Survival	5 year Survival	10 year Survival
A	5-6	Indicates a well-functioning liver	84 %	44 %	27 %
B	7-9	Indicates significant functional compromise	62 %	20 %	10 %
C	10-15	Indicates decompensation of the liver	42 %	21 %	0 %

Statistical analysis

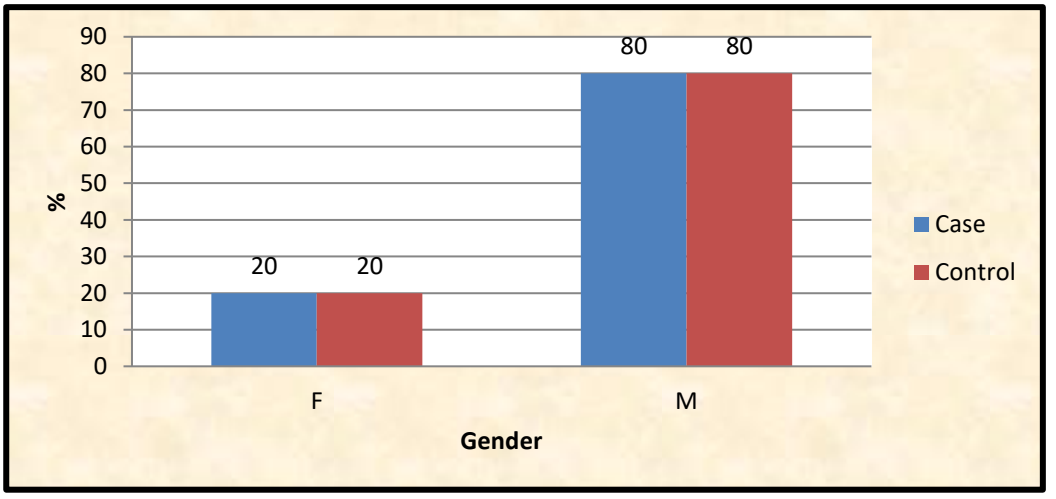
The data was coded and entered into Microsoft Excel spreadsheet. Analysis was done using SPSS version 20 (IBM SPSS Statistics Inc., Chicago, Illinois, USA).

Descriptive statistics included computation of percentages, means and standard deviations. The independent t test (for quantitative data within two groups) was used for quantitative data comparison of all clinical indicators. Chi-square test used for qualitative data whenever two or more than two groups were used to compare. Level of significance was set at $P \leq 0.05$. Pearson correlation test was also applied for multivariate comparison.

Results

In our study, out of 50 cases, 40 patients were males and 10 were females. Out of the 40 males, 32 had had alcohol related chronic liver disease and out of the remaining 8 had post viral chronic viral disease, Out of the 10 females, 5 had post viral chronic liver disease, 2 patients had alcoholic liver disease and remaining had cryptogenic cirrhosis. All subjects were hospitalized because of signs and symptoms of decompensated liver disease. The age range of cases was from 27yrs to 72 yrs (mean 46.52±9.4) whereas of control 28yrs to 70yrs (mean 45.34±9.62). 80% of patients were male and only 20% of patients were females. [Image 1]

Image 1: Gender wise comparison of groups



On investigations control group showed mean scores of thyroid profile greater as compared to case which showed statistically significant results. [Table 1] Bilirubin (2.48) and prothrombin time (16.34) were noted higher in case group as compared to control which showed statistically significant results. Albumin (2.58) was lower in case group as compared to control (4.106) which showed statistically significant results. [Table 4] In Case group hepatic encephalopathy score 1 was seen in 6 (12%) patients, score 2 in 4 (8%) patients, score 3 in 1 (2%) patient, whereas control group no patient showed signs of encephalopathy. The result showed statistical significance ($p < 0.006$). For ascites out of 50 (100%) cases subjects, 21 (42%) were found in mild ascities, 15 (30%) were found in moderate ascities and 8 (16%) were found in severe ascities. No ascites was found in control group. The result was statistically significant (P value=0.001) [Image 2]

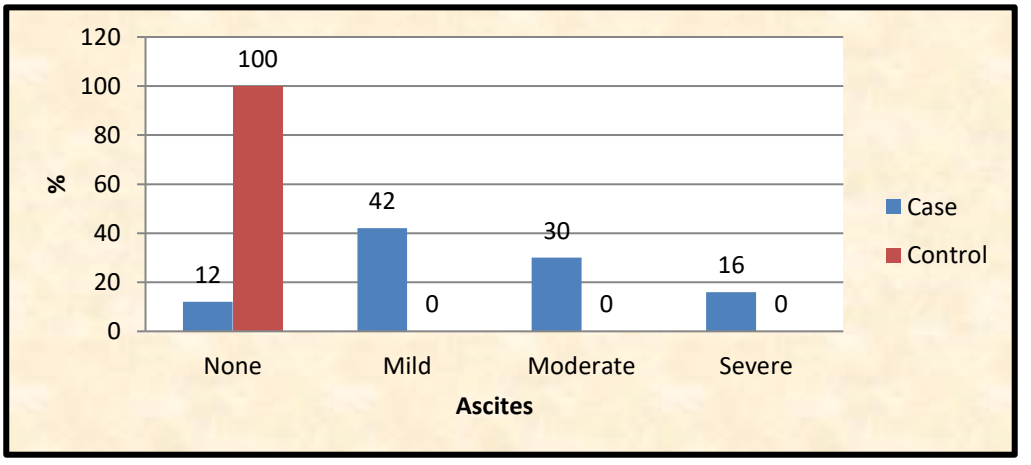
Table 3: Thyroid functional test wise comparison of groups

		Mean	S.D.	Minimum	Maximum	P value
T3	Case	83.88	8.69	76.00	114.00	0.001 (S)
	Control	92.87	7.34	82.00	118.00	
T4	Case	6.28	1.19	3.60	9.70	0.001 (S)
	Control	7.15	1.32	4.60	10.20	
FT3	Case	3.61	0.83	2.55	6.10	0.001 (S)
	Control	4.21	0.59	2.80	6.40	
FT4	Case	11.83	2.66	6.30	16.40	0.03 (S)
	Control	12.88	2.16	8.75	16.40	
TSH	Case	3.09	0.87	1.73	5.40	0.003 (S)
	Control	3.63	0.93	2.00	5.50	

Table 4: Blood tests wise comparison of groups

		Mean	S.D.	Minimum	Maximum	P value
Bilirubin	Case	2.48	0.61	1.30	3.80	0.001 (S)
	Control	0.94	0.17	0.60	1.30	
Albumin	Case	2.58	0.406	1.90	3.30	0.001 (S)
	Control	4.106	0.52	3.5	5.00	
PT	Case	16.34	1.94	14.00	22.00	0.001 (S)
	Control	12.94	0.79	12.00	14.00	

Image 2: Ascites wise comparison of groups



Cases (9.6) showed higher mean CP score as compared to controls (5) which showed statistically significant results. [Table 5]

Table 5: Child pugh score wise comparison of groups

	Mean	S.D.	Minimum	Maximum	P value
Case	9.6	1.91	6.00	13.00	0.001 (S)
Control	5.0	0.00	5.00	5.00	

Table 6: comparison of CP score classification among thyroid functional test

		N	Mean	S.D.	Minimum	Maximum	P value
T3	Group A	1	112.2	.	112.20	112.20	0.001 (S)
	Group B	25	84.74	9.71	76.00	114.00	
	Group C	24	81.81	4.74	76.00	98.20	
	Total	50	83.88	8.69	76.00	114.00	
T4	Group A	1	9.7	.	9.70	9.70	0.01 (S)
	Group B	25	6.16	1.25	3.60	8.20	
	Group C	24	6.26	0.92	3.70	7.50	
	Total	50	6.28	1.19	3.60	9.70	
FT3	Group A	1	4.8	.	4.80	4.80	0.16
	Group B	25	3.73	0.85	2.60	6.10	
	Group C	24	3.44	0.78	2.55	6.00	
	Total	50	3.61	0.83	2.55	6.10	
FT4	Group A	1	15.2	.	15.20	15.20	0.45
	Group B	25	11.72	2.46	6.90	16.40	
	Group C	24	11.808	2.87	6.30	15.80	
	Total	50	11.83	2.66	6.30	16.40	
TSH	Group A	1	5.3	.	5.30	5.30	0.03 (S)
	Group B	25	3.03	0.903	1.82	5.40	
	Group C	24	3.06	0.74	1.73	5.20	
	Total	50	3.09	0.87	1.73	5.40	

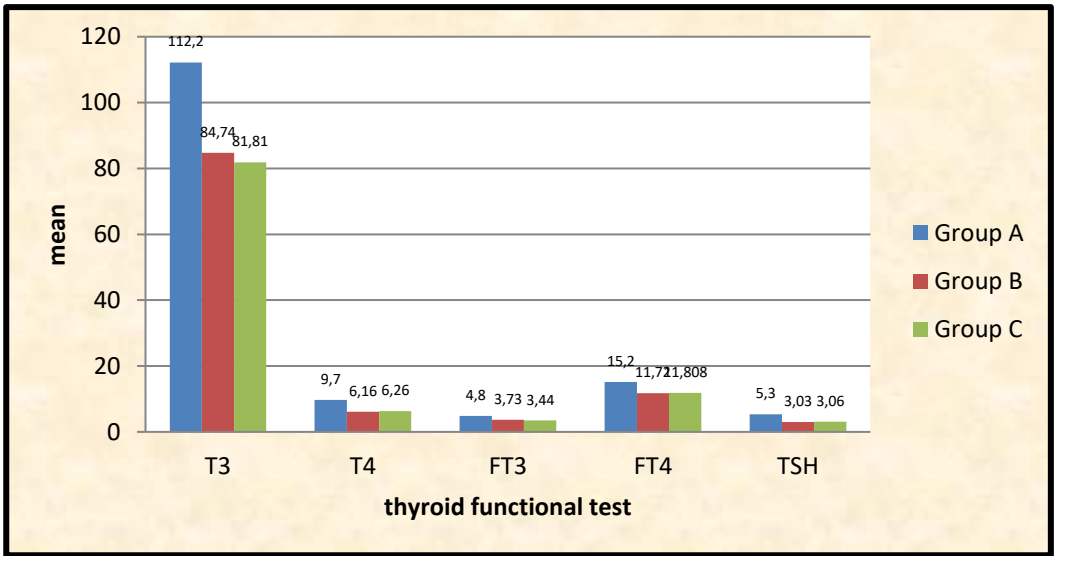
Based on Child-Pugh SCORE out of 50 cases one patient (2%) was classified as Child-Pugh class A, 25 patients (50%) were classified as Child-Pugh class B, 24 patients (48%) were classified as Child-Pugh class C, out of 50 control all (100%) were classified as Child-Pugh class A. The comparison of various parameters between Child Pugh Group A, B and C are shown in Table 6. T3 value in patients with Chronic Liver Disease varies as severity of disease (child pugh score) progresses. A mean value of T3 in patient with child pugh A is 112.2, that of CP B is 84.74 and CP C is 81.81. Hence T3 level shows a downtrend (but within the normal limit) with progression of severity of disease.

T4 value in patients, shows a mean value of T4 in patient with child pugh A is 9.7, that of CP B is 6.16 and CP C is 6.26. Hence T4 level shows a reading within lower side of normal limit and does not strictly follow a pattern with progression

of severity of disease (child pugh score), because T4 level in the patient with CP score B is slightly higher than that of CP score C. It is important to notice that the values of T4 are within normal limit (near towards lower normal limit). FT3 (free T3) shows a mean value of FT3 in patient with child pugh score A is 4.8, that of CP score B is 3.73 and CP score C is 3.44. Hence FT3 level shows a downtrend (but within the normal limit) with progression of severity of disease.

FT4 (free T4) shows a mean value of FT4 in patient with child pugh A is 15.2,that of CP B is 11.72 and CP C is 11.80. Hence FT4 level shows reading within the lower side of normal limit and does not strictly follows a pattern with progression of severity of disease (child pugh score), because FT4 level in the patient with cp score B is slightly higher than that of cp score C. It is important notice values of FT4 are within normal limit. TSH value shows a mean value of TSH in patient with child pugh A is 5.3, that of CP B is 3.03 and CP C is 3.06. Hence TSH level shows a downtrend, but does not strictly follow the with progression of severity of disease (child pugh score), because TSH level in the patient with CP score B is slightly higher than that of cp score C. It is important notice values of TSH are within normal limit.

Image 3: Comparison of CP score classification among thyroid functional test

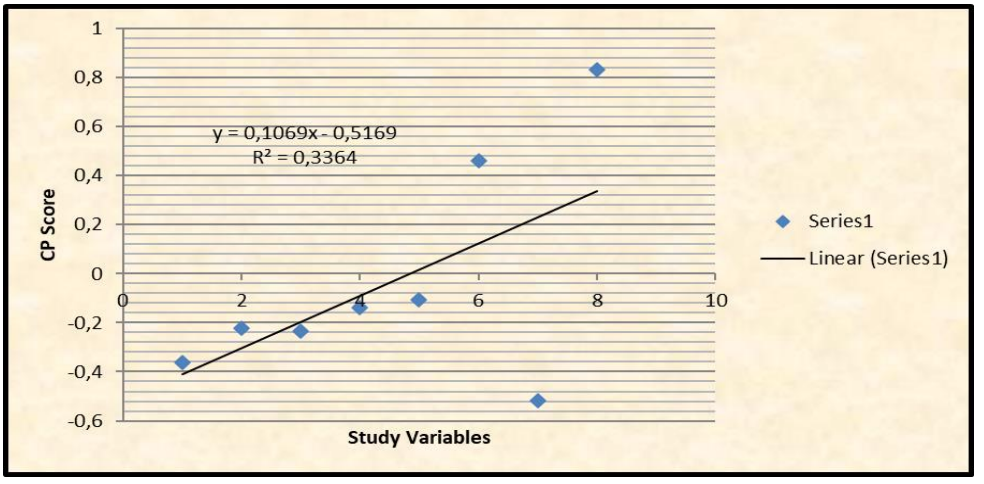


T3 and albumin showed negative correlation with CP score. CP score increased with slowdown of T3 and albumin level and also vice-versa. Bilirubin and PT showed positive correlation with CP score. CP score increased with slowdown of Bilirubin and PT level and also vice-versa.[Table 7]

Table 7: Correlation of CP score with study variables

		CP score
T3	Pearson Correlation	-0.361
	P value	0.01 (S)
T4	Pearson Correlation	-0.222
	P value	0.121
FT3	Pearson Correlation	-0.233
	P value	0.104
FT4	Pearson Correlation	-0.138
	P value	0.339
TSH	Pearson Correlation	-0.108
	P value	0.456
Bilirubin	Pearson Correlation	0.462
	P value	0.001 (S)
Albumin	Pearson Correlation	-0.518
	P value	0.000 (S)
PT	Pearson Correlation	0.831
	P value	0.000 (S)

Image 4: Correlation of CP score with study variables



Discussion

Low T3 syndrome i.e., low total T3 with normal total T4 in the absence of clinical hypothyroidism has been frequently reported in patients with chronic liver disease and it has been shown to depend on impaired liver conversion of T4 to T3.[3] Our study confirms a highly significant decrease in T3 serum concentration in liver disease, the lowest values correlate with severe disease. We found that T3

and free T3 levels were inversely correlated with the Child-Pugh class and previous studies done by Patira N K et. al.[4], Dehghani SM et. al.[5] and Taş A et. al.[6] also suggested similar results. 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 is sick euthyroid syndrome which states that loss of peripheral deiodination as the primary cause of decreased T3 and free T3 levels.[5-11] Poor nutrition in cases of liver cirrhosis has also been linked to decrease in T3 and free T3. Release of cytokines such as Interleukin-6 (IL-6) might also be responsible for the sick euthyroid syndrome. Further, alcohol intake has been associated directly with impaired hepatic deiodinase activity.[12] Free T4 levels and TSH levels were not found to be significantly related to Child-Pugh class in our study, which is in concordance with previous studies.[3-7]

In their study on a large group of alcoholic patients, Israel et al[13] reported a significant correlation between serum T3 concentration and severity of liver dysfunction as well as progressive T3 increase in those subjects eventually displaying favorable outcome suggesting that T3 concentration in patients with advanced liver disease may be considered as helpful prognostic indicator. Sudhir kumar et al[14] found that free T3 levels were inversely correlated with the Child-Pugh class.

The coagulation parameters were also significantly deranged in patients with low T3 and free T3 levels as compared to patients with normal T3 and free T3 and similar findings were also observed by Dehghani SM et al.[5]. This study found a good correlation between T3 concentration and serum albumin, bilirubin, prothrombin time, ascites & hepatic encephalopathy. This result suggests that T3 concentration should be considered as a sensitive index of hepatic function in liver disease. Many studies performed on equilibrium dialysis, showed decreased FT3 and normal or frequently increased FT4 concentration. These findings are confirmed by present study with direct radioimmunoassay of FT3 and FT4 in chronic liver disease. These data suggest that in a different group of patient with chronic liver disease divided on the basis of child pugh score, euthyroid state is maintained by a subtle equilibrium between low FT3 and increased FT4 concentrations.

Limitations

There were some limitations in the present study. The present study was a single-centred study. In future, we need multi centric study involving patients of different geographical areas. As sample size was not adequate, so we need a study involving larger sample size to support our findings. Another limitation was lack of a liver biopsy to confirm cirrhosis. We avoided liver biopsy as it is an invasive procedure.

Conclusion

In the present study, thyroid functions have been evaluated with all the clinically available indices and confirms the abnormalities in many parameters of thyroid function test in chronic liver disease patients. However euthyroid state is

maintained virtually in all patients, probably as a result of low normal Free T3 and high normal FT4. Furthermore, serum T3 concentration appear to directly correlate with the severity of liver dysfunction.

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