THYROID FUNCTION ABNORMALITIES IN CHRONIC LIVER DISEASES

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ABSTRACT

BACKGROUND

A complex relationship exists between the thyroid gland and the liver in both health and disease. Many studies have been carried out on liver disease patients assessing their thyroid status, mostly in European countries. Most of these studies are limited by the number of patients in these studies. This study tries to find out the relationship between thyroid function and chronic liver disease in a tertiary care hospital in India.

Aim- To study the thyroid function abnormalities in chronic liver disease and its relationship with liver function.

MATERIALS AND METHODS

After obtaining clearance from the Institutional Review Board, this hospital-based cross-sectional study was conducted in patients admitted in the ward under the Department of General Medicine. A total of 150 subjects were selected after explaining the purpose of the study and the procedure in detail and after obtaining their consent in written format. Data collection was done by history, clinical examination and investigations. With physical examination aided by abdominal imaging, patients who had ascites were graded into mild, moderate and severe refractory ascites. Hepatic encephalopathy was graded into grade 0 to 4 according to West Haven criteria.

RESULTS

24.6% of the study population showed abnormalities in thyroid function tests. The commonest was sick euthyroid syndrome in 18% of patients. Subclinical hypothyroidism was present in 4.7% of patients. Thyroid hormone levels had significant correlation with various liver function indices. Serum levels of total T3 and free T3 had significant positive correlation with serum albumin level and negative correlation with serum bilirubin and INR value. Free T4 had a weak negative correlation with serum bilirubin. Serum T3 and Free T3 were found to be decreased in patients with hepatic encephalopathy and ascites according to the severity. When severity of liver dysfunction was assessed using Child-Pugh score, it was found that there was statistically significant decrease in serum T3 and FT3 levels as the severity of liver dysfunction increased.

CONCLUSION

Chronic liver diseases were associated with abnormalities in thyroid function tests, although most of the patients remained clinically euthyroid. Serum T3 and FT3 levels had an inverse correlation with the severity of liver dysfunction.

KEY WORDS

Chronic Liver Disease, Thyroid Function Abnormalities.

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BACKGROUND

Chronic liver disease represents a series of liver disorders of varying causes and severity, in which hepatic inflammation and necrosis continue for at least 6 months. Liver plays an important role in thyroid hormone metabolism. The association between chronic liver diseases and thyroid dysfunctions has often been reported. The most consistent ones reported in chronic liver disease is low serum T3 and free T3 level. This reflects a decreased type 1 deiodinase activity in hepatic tissue in chronic liver diseases, which converts T4 to T3. Different studies demonstrated that fall in T3 and free T3 level parallel with the severity of liver dysfunction.

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Thyroid hormone is associated with basal metabolic rate, and low total and free T3 levels may reflect adaptive hypothyroid state, which may help to preserve hepatocytes and liver function by reducing the basal metabolic rate. Occurrence of hypothyroidism in cirrhotic patients has been shown to be associated with a biochemical improvement in liver function and decreased rate of decompensation in cirrhosis.

Objectives

To study the thyroid function abnormalities in chronic liver diseases and its relation with liver function.

Study Design

A cross-sectional study.

Period and Duration of Study

12 months from 16/11/2015 to 15/11/2016

Study Location

This study was conducted in the Department of General Medicine, Kottayam Medical College, Kerala.

Study Population

The study population were the patients with chronic liver diseases admitted in the General Medicine Ward of Kottayam Medical College.

Sample Size

Sample size is calculated by the formula-

$$N = \frac{(Z_{1-\alpha/2})^2 P (1-P)}{d^2}$$

Where,

$Z_{1-\alpha/2} = 1.96$ for at 5% level of significance.

P = anticipated population proportion of factor under study

D = Absolute precision, 6

According to a study conducted by Sandeep Kharb et al, thyroid dysfunction was present in 16% of patients with liver disease.[1] Based on this fact 'p' was taken as 16%. Substituting these values in the above formula, N is calculated as 149.3 rounded off to 150 patients.

Inclusion Criteria

All patients admitted in medicine wards with chronic liver diseases. Diagnosis of chronic liver disease was based on clinical grounds, impaired liver function tests and ultrasonographic features consistent with chronic liver disease.

Exclusion Criteria

1. Patients with preexisting thyroid disorder, chronic renal failure, congestive heart failure, malignancy.
2. Patients on medications known to cause TFT derangement.

MATERIALS AND METHODS

After obtaining clearance from the Institutional Review Board, this hospital-based cross-sectional study was conducted in inpatients of the Department of General Medicine. A total of 150 subjects were selected after explaining the purpose of the study and procedure in detail and after obtaining their consent. Data collection was done by history taking, clinical examination and investigations. With physical examination aided by imaging, patients who had ascites were graded into mild, moderate and severe refractory ascites. Hepatic encephalopathy was graded into grade 0 to 4 according to West Haven criteria.

Serum bilirubin, SGOT, SGPT, albumin, ALP, prothrombin time and value were estimated.

TFT including TSH, T3, T4, FT3 and FT4 were estimated using chemiluminescence method.

Statistical Analysis

Data from the study case sheets were entered in Microsoft Excel. SPSS version 20.0 was used for data analysis. Continuous variables were described by Mean, SD, Minimum and Maximum. Qualitative variables were described by percentage distribution between groups. Parametric data were expressed as mean values ± standard deviation (SD) and categorical variables as percentages. Categorical data were analysed by Chi-square tests for statistical significance. The Pearson's correlation coefficient was calculated for continuous variables to find out the relation between them. ANOVA was used to calculate P value in comparison of more than two continuous variables. A P value < 0.05 was considered statistically significant.

RESULTS

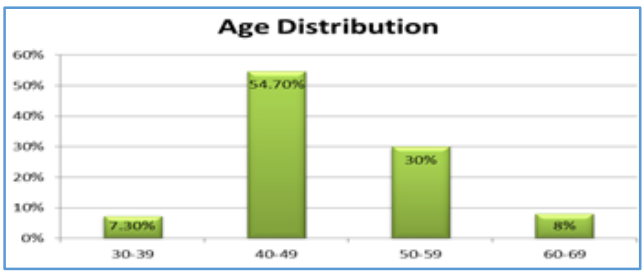
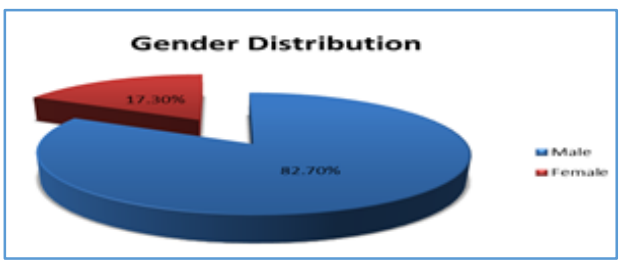


Figure 1



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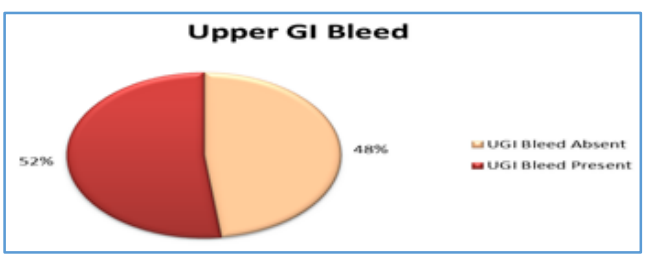

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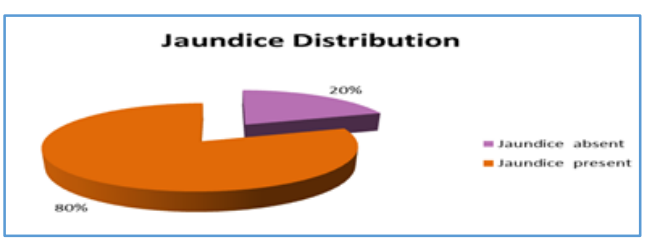

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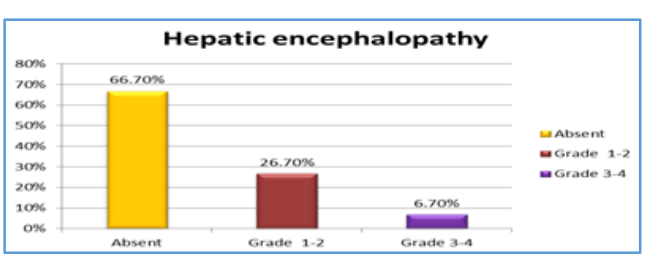

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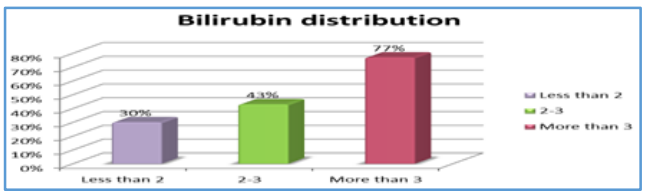

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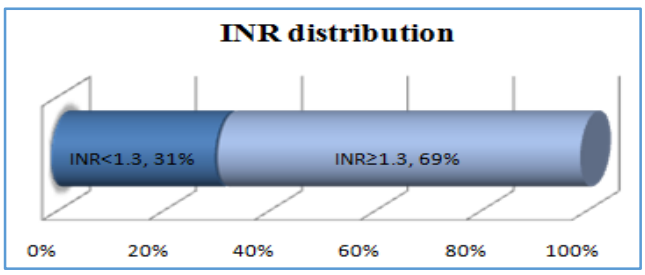

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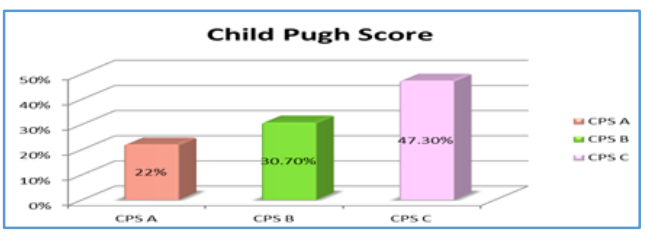

Figure 9

	Minimum	Maximum	Mean	Standard Deviation
TB	1.1	10.8	4.14	2.47
ALB	2.3	4.0	3.21	0.47
SGOT	22	280	60.94	38.42
SGPT	14	198	43.26	23.95
ALP	48	238	105.5	31.17
PT	14	36.2	22.6	5.41
INR	1.0	2.75	1.611	0.39

Table 1. Liver Function Tests

	Minimum	Maximum	Mean	Standard Deviation
TSH	0.20	18.6	2.78	2.05
T3	0.36	2.04	1.02	0.31
T4	3.07	10.80	7.69	1.45
FT3	1.52	4.26	2.78	0.52
FT4	0.56	2.14	0.99	0.20

Table 2. Thyroid Function Tests

	Liver Size	Spleen Size	Portal Vein Size
Mean	14.97 ± 1.28	11.03 ± 0.80	12.06 ± 1.01

Table 3. USG Findings

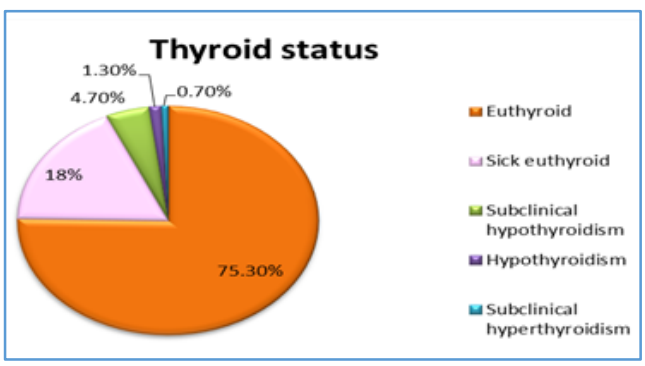

Figure 10

Correlation between Thyroid Function and Liver Function

The correlation between various thyroid function variables and liver function variables was calculated using Pearson's coefficient of correlation method.

The Results are shown in below table

	TB	ALB	SGOT	SGPT	ALP	INR	CPS
TSH	0.083 0.313	0.073 0.375	-0.076 0.353	0.006 0.939	0.076 0.354	-0.043 0.598	0.017 0.841
T3	-0.440** 0.001	0.581** 0.001	0.001 0.986	0.034 0.681	0.027 0.739	-0.348** 0.001	-0.556** 0.001
T4	-0.151 0.066	0.123 0.132	-0.063 0.443	-0.137 0.095	-0.051 0.538	-0.085 0.302	-0.104 0.205
FT3	-0.537** 0.001	0.596** 0.001	0.153 0.062	0.159 0.052	-0.039 0.631	-0.433** 0.001	-0.658** 0.001
FT4	-0.162* 0.048	0.076 0.356	-0.023 0.778	-0.044 0.591	-0.027 0.741	0.130 0.114	-0.077 0.347

Table 4

Correlation is significant at the 0.01 level (2-tailed).

Serum albumin showed a significant positive correlation with T3 and FT3. Bilirubin, prothrombin time and Child-Pugh score showed a significant negative correlation with T3 and FT3. FT4 showed a negative correlation with serum bilirubin. The best correlation was between FT3 and Child-Pugh score (-0.658). There is no significant correlation between thyroid function and level of liver enzymes (SGOT, SGPT, ALP). TSH did not show any correlation with liver function tests.

Relation between Hepatic Encephalopathy and T3						
	No HE	Grade 1-2	Grade 3-4	Total	χ^2	P value
T3≤0.8	10	13	4	27	13.31	0.001
T3>0.8	90	27	6	123		
Total	**100**	**40**	**10**	**150**		

Table 5

Study population was categorised into 3 groups according to the severity of hepatic encephalopathy. In each group, number of patients having T3 level lower than normal range (0.80 - 1.81 ng/mL) were found out. Out of the 100 patients who did not show any evidence of HE, 10 had T3 ≤ 0.8 while 90 patients had T3 > 0.8. Of the total of 40 patients with grade 1 - 2 HE, 13 patients (32.5%) had T3 ≤ 0.8 and 27 patients had T3 > 0.8 (67.5%), while 4 out of the 10 patients (40%) with grade 3 - 4 HE had T3 ≤ 0.8 and 6 patients had T3 > 0.8 (60%). T3 ≤ 0.8 was present in 10% of patients without HE and 32.5% of patients with grade 1 - 2 HE and 40% of patients with grade 3 - 4 HE. This difference was statistically significant with a P value of 0.001.

Relation between Hepatic Encephalopathy and Free T3						
	No HE	Grade 1-2	Grade 3-4	Total	χ^2	P value
FT3≤2.5	11	13	4	28	11.91	0.003
FT3>2.5	89	27	6	122		
Total	**100**	**40**	**10**	**150**		

Table 6

Similarly, in each of the above group, number of patients having Free T3 level lower than normal range (2.50 - 3.90 pg/mL) were also found out. Of the total 100 patients without HE, 11 (11%) had FT3 ≤ 2.5, while 89 (89%) had FT3 > 2.5. Out of the 40 patients with grade 1 - 2 HE, 13 patients (32.5%) had FT3 ≤ 2.5 and 27 patients had FT3 > 2.5 (67.5%) FT3 ≤ 2.5 was present in 4 patients (40%) with grade 3 - 4 HE and FT3 > 2.5 in 6 patients (60%) with grade 3 - 4 HE.

FT3 ≤ 2.5 was present in 11% of patients without HE and 32.5% of patients with grade 1 - 2 HE and 40% of patients with grade 3 - 4 HE. This difference was statistically significant with a P value of 0.003.

	No Hepatic Encephalo-pathy	Grade 1-2 Hepatic Encephalo-pathy	Grade 3-4 Hepatic Encephalo-pathy	One-Way ANOVA P value
TSH	2.84 ± 2.37	2.67 ± 1.29	2.78 ± 0.76	0.90
T3	1.13±0.30	0.82±0.20	0.77 ± 019	0.001
T4	7.83 ± 1.48	7.46 ±1.32	7.17 ± 1.60	0.20
FT3	2.97 ± 1.43	2.46 ± 0.45	2.21 ± 0.55	0.001
FT4	1.02 ± 0.21	0.96 ± 0.20	0.93 ± 0.19	0.23

Table 7. Comparison between Thyroid Functions and Hepatic Encephalopathy

Thyroid function parameters in patients with no evidence of hepatic encephalopathy and those with grade 1 - 2 and grade 3 - 4 hepatic encephalopathy were compared using ANOVA. Means of T3 in no hepatic encephalopathy, grade 1 -2 hepatic encephalopathy and grade 3 - 4 hepatic encephalopathy were 1.13 ± 0.30, 0.82 ± 0.20 and 0.77 ± 0.19 respectively and the difference in means was statistically significant with a p value of 0.001. Means of FT3 in each above groups were 2.97 ± 1.43, 2.46 ± 0.45 and 2.21 ± 0.55 respectively and the difference in mean value was found to be significant with a p value of 0.001.

Relation between Ascites and T3						
	No Ascites	Mild	Moderate-to-Severe	Total	χ^2	P value
T3≤0.8	5	16	6	27	14.055	0.001
T3>0.8	69	45	9	123		
Total	**74**	**61**	**15**	**150**		

Table 8

Study population was grouped according to the severity of ascites. In each group number of patients having T3 level lower than normal range (0.80 - 1.81 ng/mL) were found out. Of the total 74 patients without ascites 5 (6.8%) had T3 ≤ 0.8, while 69 patients (93.2%) had T3 > 0.8. Out of the 61 patients with mild ascites, 16 patients (26.2%) had T3 ≤ 0.8 and 45 patients (73.8%) had T3 > 0.8, while of the 15 patients with moderate-to-severe ascites T3 ≤ 0.8 was present in 6 patients (40%) and T3 > 0.8 was present in 9 patients (60%).

T3 ≤ 0.8 was present in 6.8% of patients without ascites and 26.2% of patients with mild ascites and 40% of patients with moderate-to-severe ascites. This difference was statistically significant with a P value of 0.001.

Relation between Ascites and FT3						
	No Ascites	Mild	Moderate-to-Severe	Total	χ^2	P value
FT3≤2.5	5	17	6	28	14.81	0.001
FT3>2.5	69	44	9	122		
Total	**74**	**61**	**15**	**150**		

Table 9

Similarly, in each group number of patients having Free T3 level lower than normal range (2.50 - 3.90 pg/mL) were found out. Of the total 74 patients without ascites, 5 (6.8%) had FT3 ≤ 2.5, while 69 patients (93.2%) had FT3 > 2.5. Of the total 61 patients with mild ascites, 17 patients (27.9%) had FT3 ≤ 2.5 and 44 patients (72.1%) had FT3 > 2.5, while of the 15 patients with moderate-to-severe ascites FT3 ≤ 2.5 was present in 6 patients (40%) and FT3 > 2.5 in 9 patients (60%). FT3 ≤ 2.5 was present in 6.8% of patients without ascites and 27.9% of patients with mild ascites and 40% of patients with moderate-to-severe ascites. This difference was statistically significant with a p value of 0.001.

	No Ascites	Mild Ascites	Moderate-to-Severe Ascites	One-Way ANOVA P value
TSH	2.52 ± 1.47	3.03 ± 2.70	3.15 ± 1.13	0.27
T3	1.18 ± 0.30	0.88 ± 0.23	0.79 ± 0.21	**0.001**
T4	7.95 ± 1.45	7.50 ± 1.37	7.15 ± 1.62	0.06
FT3	3.08 ± 0.40	2.55 ± 0.43	2.25 ± 0.50	**0.001**
FT4	1.03 ± 0.20	0.98 ± 0.21	0.90 ± 0.20	0.08

Table 10. Comparison between Thyroid Functions and Ascites

Thyroid function parameters in ascites were compared using ANOVA. Means of T3 in no ascites, mild ascites and moderate-to-severe ascites group were 1.18 ± 0.30, 0.88 ± 0.23 and 0.79 ± 0.21 respectively and the difference in means was statistically significant with a p value of 0.001. Means of FT3 in each of the above groups were 3.08 ± 0.40, 2.55 ± 0.43, 2.25 ± 0.50 respectively and the difference in mean value was found to be significant with a p value of 0.001.

T3 and Child-Pugh Score						
	CPSA	CPSB	CPSC	Total	χ^2	P value
T3≤0.8	1	6	20	27	10.75	0.005
T3>0.8	32	40	51	123		
Total	**33**	**46**	**71**	**150**		

Table 11

The study population was categorised according to the severity of liver dysfunction assessed by Child-Pugh score as CPS A, CPS B, CPS C and number of patients having T3 level lower than normal range (0.80 - 1.81 ng/mL) were found out. Of the total 33 patients with CPS A, 1 patient (3.03%) had T3≤0.8, while 32 patients (96.97%) had T3 > 0.8. Of the total of 46 patients with CPS B, 6 patients (13.04%) had T3 ≤ 0.8 and 40 patients (86.96%) had T3 > 0.8, while of the 71 patients with CPS C T3 ≤ 0.8 was present in 20 patients (28.2%) and T3 > 0.8 in 51 patients (71.8%).

T3 ≤ 0.8 was present in 3.03% of patients with CPS A and 13.04% of patients with CPS B and 28.2% of patients with CPS C. Number of patients with a T3 level lower than normal

range (0.80 - 1.81 ng/mL) significantly increased (p value of 0.005) along with Child-Pugh scores A, B and C.

Free T3 and Child-Pugh Score						
	CPSA	**CPSB**	**CPSC**	**Total**	χ^2	**P value**
FT3≤2.5	1	7	20	28	9.897	0.007
FT3>2.5	32	39	51	122		
Total	**33**	**46**	**71**	**150**		
Table 12						

Similarly, number of patients having Free T3 level lower than normal range (2.50 - 3.90 pg/mL) were found out in each CPS group and following observations were made of the total 33 patients in CPS A group. One patient (3.03%) had FT3≤2.5, while 32 patients (96.97%) had FT3 > 2.5. Of the total of 46 patients in CPS B group, 7 patients (15.2%) had FT3 ≤ 2.5 and 39 patients (84.8%) had FT3 > 2.5, while of the 71 patients with CPS C. FT3 ≤ 2.5 was present in 20 patients (28.2%) and FT3 > 2.5 was present in 51 patients (71.8%).

FT3 ≤ 2.5 was present in 3.03% of patients with CPS A and 15.2 % of patients with CPS B and 28.2% of patients with CPS C. Number of patients with a Free T3 level lower than normal range significantly increased (p value of 0.007) along with Child-Pugh scores A, B and C.

	CPS A	**CPS B**	**CPS C**	**One-Way ANOVA P value**
TSH	3.37 ± 1.46	2.13 ± 12.67	2.94 ± 1.70	0.18
T3	1.26 ± 0.26	1.06 ± 0.27	0.87 ± 0.27	0.001
T4	7.98 ± 1.33	7.78 ± 1.53	7.69 ± 1.45	0.24
FT3	3.17± 0.35	2.94 ± 0.43	2.78 ± 0.52	0.001
FT4	0.99 ± 0.11	1.04 ± 0.25	0.99 ± 0.20	0.195
Table 13. Comparison between Thyroid Functions and Child-Pugh Score				

Thyroid function parameters in each Child-Pugh group were compared using ANOVA. Means of T3 in CPS A, CPS B and CPS C were 1.26 ± 0.26, 1.06 ± 0.27 and 0.87 ± 0.27 respectively and the difference in means was statistically significant with a p value of 0.001. Means of FT3 in CPS A, CPS B and CPS C were 3.17 ± 0.35, 2.94 ± 0.43, 2.78 ± 0.52 respectively and the difference in mean value was found to be significant with a p value of 0.001.

DISCUSSION

Following Observations were made in this Study

i. Age Group

In this study, majority of patients with chronic liver disease were among the age group of 41 to 49 years (54.7%). mean age was 48.27 ± 6.57 years. This was comparable to the study done by Mansour-Ghanaei F et al,[1] in which mean age was 55.03 ± 12.05 years.

ii. Gender

In this study, 124 patients (83%) were males and 26 were females (17%). The study conducted by Borzio et al had 87% male population.[2]

iii. Thyroid Dysfunction in Study Population

37 patients (24.6%) showed abnormal thyroid function parameters. 113 patients were euthyroid. Commonest thyroid dysfunction was sick euthyroid syndrome in 27 patients (18%) followed by subclinical hypothyroidism in 7 patients (4.7%). These results were comparable to the study conducted by Sandeep Kharb[3] et al, which showed that 16% of patients with liver disease had thyroid dysfunction in which 7% had sick euthyroidism, 3.5% had subclinical hyperthyroidism.

iv. Correlation between Thyroid Function Parameters and Liver Function Indices

In this study, serum T3 and FT3 levels showed significant positive correlation with serum albumin level (p value < 0.05) and significant negative correlation with serum bilirubin level, INR value and Child-Pugh score (p value <0.05). FT3 showed highest correlation between liver function indices, maximum with Child-Pugh score. Borzio et al in their study observed that serum T3 is significantly correlated with serum bilirubin, albumin, prothrombin time and serum T3 levels appear parallel to the severity of liver dysfunction. Sandeep Kharb et al showed a significant decrease in T3 and FT3 in liver disease according to severity assessed by the Child-Pugh staging.[3] Novis et al also observed a positive relationship between the low serum levels of T3 with the degree of hepatic dysfunction according to the Child-Pugh classification.[4] Green JR et al observed an increased TSH response in hepatic cirrhosis patients.[5]

v. Thyroid Function and Ascites

In this study, T3 and FT3 levels were significantly reduced in patients who had ascites.

vi. Thyroid Function Abnormalities and Hepatic Encephalopathy

In this study, T3 and FT3 were significantly reduced (p value <0.01) in those patients with hepatic encephalopathy. Kayacetin et al found a significant reduction in serum FT3 in non-alcoholic cirrhotic patients compared with a control group.[6] El-Sawy et al also demonstrated a significant reduction of FT3 level in patients with hepatic encephalopathy in patients with chronic hepatitis C related liver cirrhosis.[7] These results suggest that serum T3 and FT3 may be considered a sensitive index of hepatic function in liver disease.

According to Oren R et al, hypothyroidism in cirrhotic patients has been shown to be associated with a biochemical improvement in liver function and a decreased rate of decompensation in chronic liver disease.[8]

CONCLUSION

1. Chronic liver diseases were associated with abnormalities in thyroid function tests, although most of the patients remained clinically euthyroid.
2. Serum T3 and FT3 levels had an inverse correlation with the severity of liver dysfunction.

Limitations of the Study

1. It was a cross-sectional study without follow-up of the patients. A cohort study would have been better for assessing the prognosis of patients with chronic liver diseases with regard thyroid function tests.
2. Assessment of liver disease was limited by lack of histological diagnosis.

Recommendations

- Serum T3 and FT3 concentrations may be considered as a sensitive index of hepatic function in chronic liver disease.
- Thyroid hormone is an important determinant of basal metabolic rate, low total and free T3 levels in chronic liver diseases may reflect the adaptive hypothyroid state which reduces the basal metabolic rate and helps to preserve hepatocytes and liver function. Hence, treatment indication of hypothyroidism in chronic liver disease has to be redefined.

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