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Original Research Paper

General Medicine

PREVALENCE OF THYROID DYSFUNCTION IN CHRONIC LIVER DISEASE

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ABSTRACT **Introduction:** Chronic Liver Disease affects most of the organs in the human body. Various studies have been done regarding chronic liver disease, but not many studies are done on the assessment of thyroid function in chronic liver disease. Present study thus aimed at assessing the thyroid functions in chronic liver disease patients. **Materials & Methods:** A hospital based cross-sectional study was conducted at a tertiary care hospital Study included 52 patients presenting with Chronic liver disease fulfilling the study criteria using purposive conservative sampling. Detailed examination was done for all cases including thyroid function tests. All analysis was carried out by using SPSS software version 21. **Results:** Overall prevalence of thyroid dysfunction among chronic liver disease patients was 36.5%. A significant positive correlation was observed between severity of chronic liver disease and TSH levels (r-0.60) while an inverse correlation was observed with T3 and T4 levels ($p<0.01$). A significant association was observed between presence of thyroid dysfunction among chronic liver disease patients who had hepatic encephalopathy (66.7% vs 32.6%; $p<0.05$). Also, a significant association was observed with severity of chronic liver disease. **Conclusion:** Present study observed that derangement in thyroid profile is common in patients with cirrhosis of liver. A statistically significant change was observed in serum T3 and T4 levels that tend to fall with progressive severity of chronic liver disease irrespective of aetiology. Thus all cirrhotic patients should undergo thyroid function evaluation as these patients are definitely associated with development of thyroid dysfunction.

KEYWORDS : Chronic Liver Disease, Cirrhosis, Hepatic encephalopathy, Hypothyroidism, Low thyroid syndrome.

INTRODUCTION

Chronic liver diseases (CLD) cause significant morbidity and mortality worldwide. Multiple etiological factors lead to a similar clinico-pathological syndrome (Cirrhosis) in CLDs, although the rates of progression and clinical course may be different [1,2]. Mortality data is most often used to assess the disease burden and there had been a 46% increase in CLD mortality in the world between period of 1980 to 2013, underscoring the emerging public health importance of CLD. Most of this increase in CLD mortality has been reported from the low and low-middle income countries of Asia and Africa [3].

Chronicity of liver disease is determined either by duration of liver disease (typically 3-6 months) or by physical stigmata of chronic liver disease (clubbing, spider telengiectasia and hepatosplenomegaly). The severity is variable; the affected adults may have only biochemical evidence of liver dysfunction, may have stigmata of chronic liver disease, or may present in hepatic failure. As a result of greater alcohol consumption, an epidemic of diabetes and obesity and hepatitis B and C infections, the incidence of chronic liver disease is increasing worldwide [4].

Etiology of chronic liver disease in adults include a broad spectrum of disorders. Overall, the most common causes of chronic liver disease world wide are alcohol, chronic hepatitis B and C and non-alcoholic fatty liver disease (NAFLD). Primary biliary cirrhosis and autoimmune hepatitis are commonly seen in females, while alcoholism, primary sclerosing cholangitis and hepatitis B are common in males. Genetic diseases such as alpha-1 antitrypsin deficiency, genetic cholestatic disease and wilson's disease are encountered predominantly in children [4-7].

Liver plays a vital role in thyroid hormone metabolism and circulation of thyroid hormone by producing thyroid binding globulin [8]. Liver also plays a role in the production of triiodothyronine (T3) by the action of selenium dependent 5' deiodinase. Moreover, another selenium independent deiodinase acts on the phenolic ring of thyroxine (T4) to produce the hormonally inactive reverse T3 (rT3) [9].

The levels of thyroid hormone and thyroid binding proteins are altered in patients of chronic liver disease. Low free T3 syndrome is frequently described in patients with cirrhosis of liver and is characterized by increased rT3, low T3 and decreased T3:T4 ratio [10]. Low T3 may be an adaptive thyroid response to reduce the basal metabolic rate of hepatocytes and preserve liver function [11].

Numerous clinicians have reported a sub clinical hypothyroidism in patients with chronic liver disease [12-17]. Although studies in different populations vary in their findings with respect to the type and degree of thyroid dysfunction in cirrhosis, but found to have consistently low FT3 in the face of a normal TSH and a clinical euthyroidism. Not only the free hormone level has been delineated as an indicator of thyroid dysfunction, but FT3 level has also been correlated with the degree of liver dysfunction.

MATERIALS AND METHODS

Present hospital based cross sectional study included 52 patients with Chronic liver disease. Patients on thyroid medications, terminally ill patients or admitted in ICU, cases of autoimmune hepatitis, primary biliary cirrhosis and those on drugs altering thyroid function (Lithium, amiodarone) were excluded.

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.

Each patients' complete history was recorded in a proforma. Every patient was investigated in the following order after the completion of physical examination: Hemoglobin Total WBC count; Differential count, ESR, Random blood sugar, blood urea, Serum creatinine, Liver function tests, Ultrasound abdomen, and T3, T4, TSH.

Serum T3, T4 was determined by Electrochemiluminescence immunoassay (ECLIA). The normal range for thyroid functions in our laboratory was: T3 : 0.8-2 ng / ml, T4 : 4.6 – 11 mcg / dl and; TSH: 0.4–4.2 μIU/ml. Any deviation from the normal value range of T3, T4, TSH was considered as thyroid dysfunction. Following operational definitions were used:

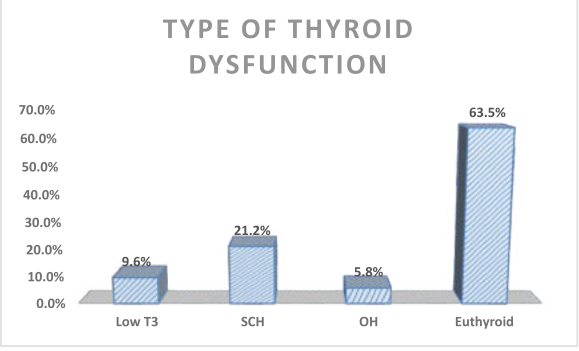
- Subclinical Hypothyroidism – TSH-4.2-10μIU/ml, T3, T4-within normal limits.
- Overt Hypothyroidism- TSH- above 10 μIU/ml, T3, T4-Normal or decreased.
- Low T3 syndrome- TSH- normal, Low T3.
- Subclinical Hyperthyroidism- TSH- decreased or undetectable,
  T3, T4- normal.
- Overt Hyperthyroidism- TSH- decreased, T3, T4-increased.

Severity of chronic liver disease was calculated by Child Pugh score and correlated with derangement of thyroid functions using Pearson's correlation coefficient. Quantitative data was represented as their mean ± SD. Categorical and nominal data was expressed in percentage. The t-test was used for analysing quantitative data and categorical data was analyzed by using chi-square test. The significance threshold of p-value was set at <0.05. All analysis was carried out by using SPSS software version 21.

RESULTS

Overall prevalence of thyroid dysfunction among chronic liver disease patients was 36.5%. Most common thyroid dysfunction seen in chronic liver disease patients was subclinical hypothyroidism (21.2%) followed by low T3 syndrome (9.6%). Overt hypothyroidism was seen in 5.8% cases (**Graph 1**).

Graph 1. Distribution of study cases as per presence of thyroid dysfunction



A significant positive correlation was observed between severity of chronic liver disease and TSH levels (r-0.60) while an inverse correlation was observed with T3 and T4 levels (p<0.01) (**Table 1**).

Table 1. Correlation between severity of chronic liver disease and thyroid functions

Pearson co-relation		
CP Grade	**r- value**	**p- value**
T3	-0.71	**<0.01**
T4	-0.72	**<0.01**
TSH	0.60	**<0.01**

No significant association was observed between age, gender or any specific etiology with presence of thyroid dysfunction (p>0.05). A significant association was observed between presence of thyroid dysfunction among chronic liver disease patients who had hepatic encephalopathy (66.7% vs 32.6%; p<0.05). Also, a significant association was observed with severity of chronic liver disease. Prevalence of thyroid dysfunction was 11.1%, 42.9% and 55% in child pugh grades A, B and C respectively (p<0.05) (**Table 2**).

Table 2. Association of thyroid dysfunction with study characteristics

Characteristics	Thyroid Dysfunction		p-value
	No	Yes	
Mean Age	44.94+/- 8.9	46.05 +/- 8.27	**0.65**
Female	11	4	**0.52**
	73.30%	26.70%	
Male	22	15	
	59.50%	40.50%	
Alcohol induced hepatitis (AIH)	18	11	**0.81**
	62.10%	37.90%	
Cryptogenic Cirrhosis	3	1	
	75.00%	25.00%	
Hep B	10	7	
	58.80%	41.20%	
Metastasis	1	0	
	100.00%	0.00%	
NASH	1	0	
	100.00%	0.00%	
Hepatic Encephalopathy	2	4	**<0.05**
	33.30%	66.70%	
CP grade A	16	2	**<0.05**
	88.90%	11.10%	
CP Grade B	8	6	
	57.10%	42.90%	
CP Grade C	9	11	
	45.00%	55.00%	

DISCUSSION

Present hospital based cross-sectional study was conducted to assess the thyroid functions in Chronic liver disease patients and to assess the relationship between thyroid function status and chronic liver disease.

Overall prevalence of thyroid dysfunction among chronic liver disease patients was 36.5%. Most common thyroid dysfunction seen in chronic liver disease patients was subclinical hypothyroidism (21.2%) followed by low T3 syndrome (9.6%). Overt hypothyroidism was seen in 5.8% cases.

Kharb S et al. [18] studied thyroid function in subjects with liver pathologies. Thyroid dysfunction was present in 14 (16%) patients. The commonest thyroid dysfunction was sick euthyroid syndrome six (7%), followed by subclinical hypothyroidism in three patients (3.5%), subclinical hyperthyroidism and thyrotoxicosis in two patients each (2.3%) and overt hypothyroidism in one patient. Joeimon JL et al. [19] in their study observed hypothyroidism in 24 out of 111 patients (21.6%). Only serum TSH increase was seen in 12 patients (10.8%) and Serum TSH increase along with FT3 and FT4 decrease in 12 out of 111 patients (10.8%). Verma SK et al. [20] observed low free T3 and T4 in 72.5% and 26.47% of patients with cirrhosis of liver respectively. TSH towards the upper limit of normal range was observed in 52.3% of patients. Punekar P et al. [21] observed that cirrhotic patients had statistically significant lower level of FT3 (P < 0.0001) and FT4 (P < 0.0001) but had higher level of TSH (P < 0.0001) compared with the controls. Overall, the most common abnormality seen was low T3 (low FT3) syndrome (41%). Patira NK et al. [22] observed prevalence of subclinical hypothyroidism in cirrhosis as 62%.

In present study, a significant positive correlation was

observed between severity of chronic liver disease and TSH levels while an inverse correlation was observed with T3 and T4 levels (p<0.01). Prevalence of thyroid dysfunction was 11.1%, 42.9% and 55% in child pugh grades A, B and C respectively (p<0.05). A significant association was observed between presence of thyroid dysfunction and severity of liver disease and presence of hepatic encephalopathy.

Joeimon JL et al. [19] in their study observed that out of the 24 patients having hypothyroidism, 5 belonged to Child Pugh A (out of 28 i.e. 17.8%), 11 belonged to Child Pugh B (out of 53 i.e. 20.7%), and 8 belonged to Child Pugh C (out of 30 i.e. 26.6%). Verma SK et al. [20] in their study observed that Low free T3 and free T4 was found to be inversely related to the severity of liver disease. Punekar P et al. [21] observed that cirrhosis with Hepatic Encephalopathy (n = 38) had significantly lower lever of FT3 (P < 0.0001) compared with cirrhosis without Hepatic Encephalopathy (n = 62). FT3 level was significantly low in Hepatic Encephalopathy Grade 4 patients compared with Hepatic Encephalopathy Grade 1 patients (P = 0.0001). In all cirrhotic patients, FT3 and FT4 were negatively correlated, but TSH level was positively correlated with Child Pugh grade. Patira NK et al. [22] showed that prevalence of hypothyroidism in cirrhotic patients increases as the severity of cirrhosis increases (p value <0.01). As the severity of cirrhosis increases which is indicated by Child Pugh A to C, serum level of FT3 and FT4 reduces and TSH level increase (p value <0.01). Ray AC et al. [23] (2019) evaluated thyroid function tests in Chronic liver disease(CLD) patients and to find out whether the thyroid functions tests abnormalities if any correlate with the clinical severity or stage of CLD patients. The mean values of serum FT3 and FT4 showed a tendency to fall with progressive Chronic liver disease and was statistically significant, more marked with FT3 (Child A vs B, p-<0.001; A vs C, p-<0.001; CLD stage 1 vs stage 2,p <0.001) than with FT4 (Child A vs B, p 0.556; A vs C, p < 0.001, stage 1 vs stage 2, p 0.020).

Thus to summarize, present study observed that derangement in thyroid profile is common in patients with cirrhosis of liver. There is significant inverse correlation between serum level of T3 and T4 with severity of cirrhosis. According to our findings and of the authors supporting our results, all cirrhotic patients should undergo thyroid function evaluation as these patients have a tendency towards development of hypothyroidism.

There were some limitations in the present study. The present study was a cross-sectional study hence, it did not show a causal relationship between thyroid abnormalities and cirrhosis of liver. Moreover, it is 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. Detailed work up for thyroid profile like reverse T3 and thyroid antibodies [thyroperoxidase (TPO) antibody, thyroglobulin] were also not carried out.

CONCLUSION

Present study observed that derangement in thyroid profile is common in patients with cirrhosis of liver. A statistically significant change was observed in serum T3 and T4 levels that tend to fall with progressive severity of chronic liver disease irrespective of aetiology. Thus all cirrhotic patients should undergo thyroid function evaluation as these patients are definitely associated with development of thyroid dysfunction.

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