Section: Medicine

Original Research Article

THYROID DYSFUNCTION IN CHRONIC LIVER DISEASE AND IT'S CORRELATION WITH SEVERITY OF LIVER DISEASE, A STUDY AT TERTIARY CARE CENTRE IN UTTARAKHAND

Naveen Kumar Rajput[1], Reshma Kaushik[2], Shekhar Kushwaha[3]

[1]Assistant Professor, Department of Medicine, Himalayan Institute Of medical Science, SRHU, Dehradun, Uttarakhand, India
[2]Professor and Head, Department of Medicine, Himalayan Institute of Medical Science, SRHU, Dehradun, Uttarakhand, India
[3]Junior Resident, Department of Medicine, Himalayan Institute of Medical Science, SRHU, Dehradun, Uttarakhand, India

Received : 28/04/2023
Received in revised form : 02/06/2023
Accepted : 15/06/2023

Keywords:
Child-Turcotte-Pugh (CTP) scores, model for end-stage liver disease-sodium (MELD-Na) scores, Thyroid stimulating hormone (TSH), FT3, FT4.

Corresponding Author:
Dr. Naveen Kumar Rajput,
Email: naveenrajputmd@gmail.com

DOI: 10.47009/jamp.2023.5.3.479

Source of Support: Nil,
Conflict of Interest: None declared

Int J Acad Med Pharm
2023; 5 (3); 2440-2445

Abstract

Background: Chronic liver disease (CLD) and/or cirrhosis of liver represent different liver disorders of varing severity in which liver injury, inflammation, and fibrosis continue for more than 6 months. Various etiologies including drugs, toxins, alcohol abuse, infections, autoimmune disorders, genetic and metabolic diseases are implicated for CLD. In cirrhosis of liver thyroid hormone may be affected due to iodination defect. The aim is to study the thyroid dysfunction in CLD and its correlation with the severity of the disease. **Materials and Methods:** A prospective observational study was conducted on patients reporting to Himalayan Hospital in OPD and IPD between June 2021 to May 2022. A total 68 patients of CLD were recruited. All patients were examined with clinical history, physical examination, laboratory blood and biochemical and radiological investigations, Thyroid stimulating hormone (TSH), free T3 level, and free T4 level including. Child-Turcotte-Pugh (CTP) scores and model for end-stage liver disease-sodium (MELD-Na) scores were calculated to assess the severity of CLD. **Result:** The mean age of the patients was 48.52+/-10.12 years. Majority of patients 64/68(94.12%) were male. Most common etiology of CLD was alcoholism [44/68(64.7%)]. Majority of patients had normal TSH and FT4 level, and these were not changed significantly as the disease advances. There was strong negative correlation between low FT3 level and severity of CLD. As the severity of CLD increases which is indicated by CTP scores and MELD-Na scores, serum level of FT3 is reduced (p value 0.01 and 0.014 respectivally). **Conclusion:** According to study all CLD patients should undergo thyroid function evaluation. FT3 level can be an independent marker for severity of the disease.

INTRODUCTION

In metabolism of thyroid hormones, the liver play an important role. The most important site of the peripheral conversion of tetraiodothyronine (T4) to triiodothyronine(T3) by type 1 deiodinase is the liver.[1,2] About 30-40% of extrathyroidal production of triiodothyronine(T3) is occurred in the liver by or an enzyme type 1deiodinase. It can carry out both 5'-and 5 deiodination of T4 to T3. Moreover, the liver is involved in thyroid hormone conjugation excretion and synthesis of thyroid binding globulin.[1,3] Thyroid hormones regulate the basal metabolic rate of all cells, including hepatocytes, thereby they modulate liver function.Thyroid stimulating hormone (TSH) is metabolized in liver and liver also regulars it's systemic endocrine functions. Thyroid disease may disturb hepatic function, liver disease can cause alterations in thyroid hormone metabolism.[4] There are clinical and laboratory associations between thyroid and liver disease.

Till date, available studies showed that low plasma level of free T3 and total T3 concentration are the most frequent findings in liver disease. These changes in thyroid hormones levels are reported to be associated with severity of liver dysfunction. But very few studies clearly mentioned free T4 and TSH levels with the severity of chronic liver disease. Evidence regarding the correlation of thyroid dysfunction and severity of chronic liver disease is limited and needs to be future studied hence present study aimed to study the prevalence of thyroid

ISSN (O): 2687-5365; ISSN (P): 2753-6556

hormones dysfunction in chronic liver disease and it's correlation with the severity of the disease.

Aims and objectives: The aims of this study were

- Primary – to study thyroid hormones level (FT3,FT4, TSH) in chronic liver disease patient.
- Secondary – to find out the correlation of thyroid hormones dysfunction and severity of chronic liver disease.
- Design of study- An observational study in patients with established CLD or cirrhosis.

MATERIALS AND METHODS

Present Study included adults (age >18 to 80years) patients with investigation and or clinical evidence of chronic liver disease or cirrhosis presented to Himalayan hospital, HIMS, SRHU, Dehradun in OPD and IPD between June 2021 and May 2022. All patients diagnosed with CLD or cirrhosis were undergo detailed clinical history of patients, clinical examination and investigations that include full blood counts, blood sugar, serum creatinine, liver function test, urine analysis and serum electrolytes, serum TSH, FT4, FT3, ultasonography of abdomen. All patients were subjected to medical examination as per the fixed performa. Informed consent has been taken by all patients included in study. A convenience sampling technique was used for recruitment; patients with CLD reporting to OPD and IPD during this period were included.

Inclusion Criteria

Established case of chronic liver disease based on clinical, biochemical, and radiological findings, irrespective of etiology.

Exclusion Criteria

Patients having sepsis, thyroid disease, pregnancy, diabetes, cancer, with ongoing radio or chemotherapy, chronic kidney disease, patients receiving drugs that may affect thyroid hormones levels.

Identification of patients with chronic liver disease was done by reviewing the medical records manually. They were subjected to baseline liver function test, hormonal estimation along with routine biochemistry tests. All patients diagnosed with CLD were undergo detailed clinical examination and investigations that include full blood counts, blood sugar, serum creatinine, liver function test, INR, urine analysis and serum electrolytes, TSH, free T3 and free T4 level, ultrasonography of abdomen.

Baseline variables such as age and etiology of chronic liver disease were recorded. Baseline biochemistry including serum TSH, free T3 and free T4 level were measured and recorded. Recognized severity and prognostic markers were calculated and recorded including the model of end stage liver disease score(MELD score) and Child-Pugh scores(CTP score) and serum sodium (5,6).Severity of liver disease, as classified by the Child-Pugh score, with a scoring system of 5-15: scores of 5 and 6 represent Child-Pugh class A, scores of 7 -9 represents class B, and scores of 10-15 represent class C. MELD-Na was calculated from serum bilirubin level, prothrombin time(PT) with international normalized ratio(INR), serum sodium, and serum creatinine.

Diagnostic Tool

The diagnosis of chronic liver disease were based on case history, clinical examination, biochemical and radiological study. The Child –Pugh (CTP) and MELD-Na (model for end stage liver disease-sodium) scores were used to assess the severity. Thyroid function test (TFT)(7 5) was done by electrochemiluminescnce immunoassay. The normal range of thyroid profile as a following FT3 is (2.0-4.2 pg/ml) , FT4 is (0.6-1.7ng/dl), and TSH is (0.34-4.25 microIU/ml).

Statistical analysis: Continuos data were described using means and standard deviations; absolute and relative frequencies were used for categorical data. For bivariate analysis, we used the chi-squire test and the unpaired t test for continuous and categorical variables respectively. The Pearson's correlation coefficient was used to evaluate the correlation between TSH, free T3, free T4 and CTP and MELD-Na scores. Biochemical parameters, age, sex, etiology of CLD were entered as independent variables. Symptoms, variable organ dysfunctions, and other variables were analyzed. Statistical value ('p' value) <0.05 was considered as statistically significant. Student 't', chi-squire, and fisher's exact test were used to express the ratios, and proportions and to compare. As and others as appropriates. The correlation between Thyroid functions (TSH, FT3, and FT4) and severity of chronic liver disease were assessed by appropriate test. Data analysis was performed by using SPSS 22 (SPSS, Inc., Chicago, IL) software.

RESULTS

A total of 68 patients with CLD or cirrhosis were selected. Mean age of the patients was 48.52 +/- 10.12 years. Majority of patients 64/68(94.12%) were male..Most common etiology of liver cirrhosis was alcoholism which comprised 44/68 (64.7%) of patients,13/68(19%) of patients had NASH related CLD,5/68 (7%) patients had HBV related CLD, and 3/68(4%) patients had HCV related disease. 34/68(50%) patients had low serum Free T3(<2.0pg/ml) and 1/68(1.47%) patients had high Free T3 level(>4.2pg/ml). Majority of patients60/68(88.23%) had normal FT4 level, 6/68(8.82%) had low FT4, and 2/68(2.94%) had high FT4 level. Normal TSH level was found in majority of CLD patients52/68(76.47%), only 8/68(11.76%) had low TSH and 8/68(11.76%) had high level. Severity of CLD was determined by Child-Pugh csoring system. 8(11.7%) patient had score between 5-6(grade A), 19(27.9%) patients had score between 7-9(gradeB), and 41(60.2%) patients

ISSN (O): 2687-5365; ISSN (P): 2753-6556

had scores more than 10(gradeC). Mean CTP score value of Patients having low FT3(<2.0pg/ml) was 10.88+/-2.63 (p value 0.003),and it was 9.12+/-2.23 in those who had normal FT3 level (2.0-4.2pg/ml). Mean CTP score value of patients with high FT3(>4.2pg/ml) was 5.00. Mean serum FT3 level in patients with CTP scores 5-6(grade A), 6-9(gradeB), and 10-15(gradeC) were 2.59+/-1.20, 2.07+/-0.82, and 1.80+/-0.56 respectively. Study demonstrate that as the severity of CLD increased from CTP score grading A to C, serum FT3 level decreased (p value 0.01). Mean value of MELD-Na score of patients having low FT3 was 26.58+/-7.73(p value 0.014), and it was 21.42+/-7.40 and 15 I those who had normal and high FT3 level respectively. Mean CTP score value in patients with low FT4 was 11.66+/-1.50, with normal FT4 level was 9.66+/-2.64, and in those who had high FT4 was 13.00 (p value0.05). Mean serum FT4 level in patients with CTP score grading A,B, and C were 0.98+/- 0.25, 0.98+/-0.21, and 0.0.96+/-0.35 respectivally (statistically insignificant). Mean value of MELD-Na was 30.33+/-5.53, 23.08+/-7.91, and 29.50+/-7.77 in patients with low, normal and high FT4 levels respectivally(p value0.061). Mean CTP socre value in patients with low TSHlevel was 10.75+/-2.05, with normal TSH was 9.96+/-2.68, and in those who had high TSH was 9.00+/-2.82 (p value 0.418).Mean serum TSH level in patients with CTP score A,B, and C were 2.50+/-1.84, 2.11+/-2.24, and 2.33+/-2.48 respectivally (statistically insignificant) Mean value of MELD-Na was 28.00+/-6.45, 23.21+/-8.25, and 24.37+/-6.90 in patients with low, normal and high TSH level respectivally(p value 0.286).

Table 1: Baseline characteristics of patients of CLD

Features	**All patients (n=68)**
	Mean ± SD Frequency
Age (years)	48.52±10.12
Gender (M:F)	64:4
Serum TSH(μIU/mL)	2.38±2.28
MELD Na points	23.91 ± 9.97
Child-Pugh (Class A,B,C)	8:19:41
Etiology of cirrhosis	
Alcohol	44(64.7%)
HBV	5(7%)
HCV	3(4%)
NASH- Cryptogenic	13(19%)
Autoimmune	3(4%)

HBV – Hepatitis B virus, HCV – Hepatitis C virus, NASH – Nonalcoholic steato hepatitis

Table 2: Distribution of patients according to Child Pugh score

Child Pugh score	**No. of patients**	**%**
A(5-6)	8	11.7
B(7-9)	19	27.9
C(10-15)	41	60.2
Total	68	68

Table 3: Mean value of thyroid function test in patients of cirrhosis of liver.

Thyroid function test	**Mean value in patients of cirrhosis of liver**	**Normal reference value**
Free T3 (pg/ml)	2.02±0.75	2.0-4.2
Free T4 (ng/dl)	0.97±0.30	0.6-1.7
TSH (mIU/mL)	2.38±2.28	0.34-4.25

Table 4: Comparison of TSH levels of patients with Child Pugh score

TSH (mIU/mL)	**N**	**Mean value of CTP**	**SD**	**P value**
<0.34	8	10.7500	2.05287	0.418
0.34-4.25	52	9.9615	2.68592	
>4.25	8	9.0000	2.82843	
Total	68	9.9412	2.63661	

Table 5: Comparison of FT3 levels of patients with Child Pugh score

FT3 (pg/ml)	**N**	**Mean value of CTP**	**SD**	**P value**
<2	34	10.8824	2.63732	0.003
2-4.2	33	9.1212	2.23268	
>4.2	1	5.0000	0	
Total	68	9.9412	2.63661	

Table 6: Comparison of FT4 levels of patients with Child Pugh score

FT4 (ng/dl)	**N**	**Mean value of CTP**	**SD**	**P value**
<0.6	6	11.6667	1.50555	0.05
0.6-1.7	60	9.6667	2.64682	
>1.7	2	13.0000	0	
Total	68	9.9412	2.63661	

ISSN (O): 2687-5365; ISSN (P): 2753-6556

Table 7: Comparison of TSH levels of patients with MELD sodium

TSH (mIU/mL)	N	Mean value of MELD sodium	SD	P value
<0.34	8	28.0000	6.45866	0.286
0.34-4.25	52	23.2115	8.25177	
>4.25	8	24.3750	6.90626	
Total	8	23.9118	7.97334	

Table 8: Comparison of FT3 levels of patients with MELD sodium

FT3 (pg/ml)	N	Mean value of MELD sodium	SD	P value
<2	34	26.5882	7.73860	0.014
2-4.2	33	21.4242	7.40789	
>4.2	1	15.0000	.	
Total	68	23.9118	7.97334	

Table 9: Comparison of FT4 levels of patients with MELD sodium

FT4 (ng/dl)	N	Mean value of MELD sodium	SD	P value
<0.6	6	30.3333	5.53775	0.061
0.6-1.7	60	23.0833	7.91328	
>1.7	2	29.5000	7.77817	
Total	68	23.9118	7.97334	

Table 10: Comparison of Serum fT3 of patients with Child Pugh score

CTP score	N	Mean value of fT3	SD	P value
A	8	2.59	1.20	0.15
B	19	2.07	0.82	
CTP score	N	Mean value of fT3	SD	P value
B	19	2.07	0.82	0.63
C	41	1.80	0.56	
CTP score	N	Mean value of fT3	SD	P value
A	8	2.59	1.20	0.01
C	41	1.80	0.56	

Table 11: Comparison of Serum fT4 of patients with Child Pugh score

CTP score	N	Mean value of fT4	SD	P value
A	8	0.98	0.25	0.56
B	19	0.98	0.21	
CTP score	N	Mean value of fT4	SD	P value
B	19	0.98	0.21	0.38
C	41	0.96	0.35	
CTP score	N	Mean value of fT4	SD	P value
A	8	0.98	0.25	0.85
C	41	0.96	0.35	

Table 12: Comparison of Serum TSH of patients with Child Pugh score

CTP score	N	Mean value of TSH	SD	P value
A	8	2.50	1.84	0.90
B	19	2.11	2.24	
CTP score	N	Mean value of TSH	SD	P value
B	19	2.11	2.24	0.75
C	41	2.33	2.48	
CTP score	N	Mean value of TSH	SD	P value
A	8	2.50	1.84	0.90
C	41	2.33	2.48	

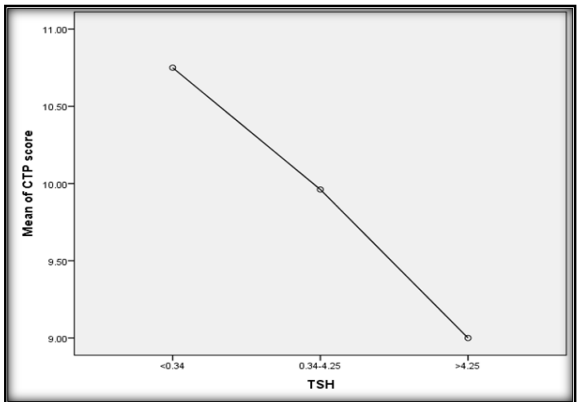

Figure 1:

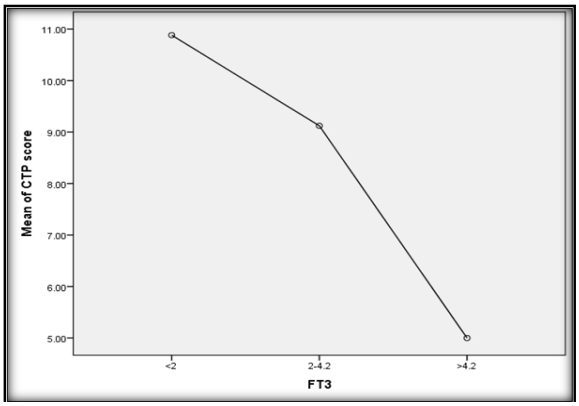

Figure 2:

ISSN (O): 2687-5365; ISSN (P): 2753-6556

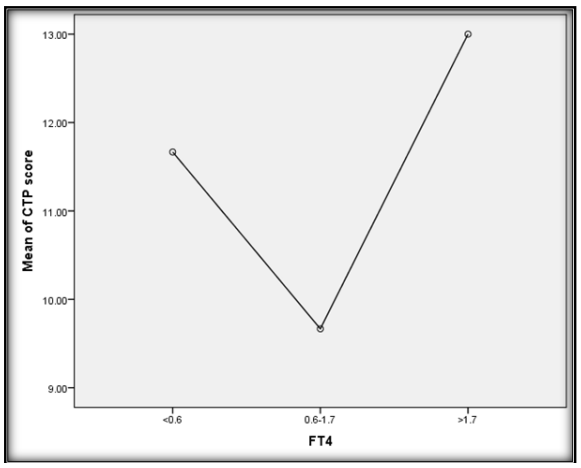

Figure 3:

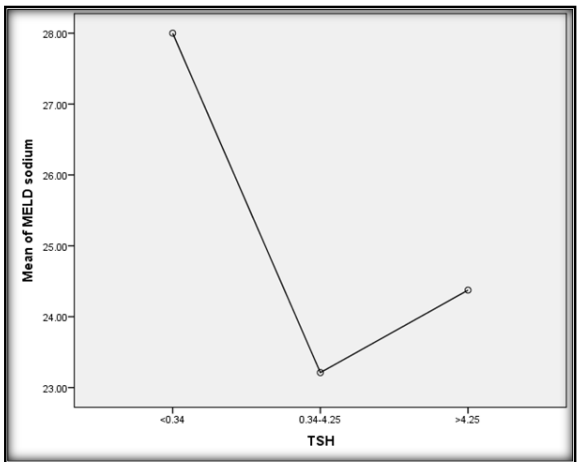

Figure 4:

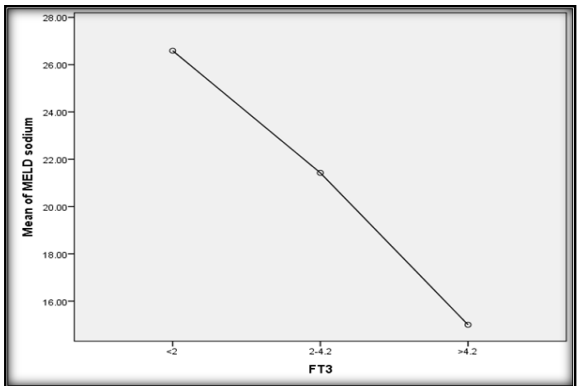

Figure 5:

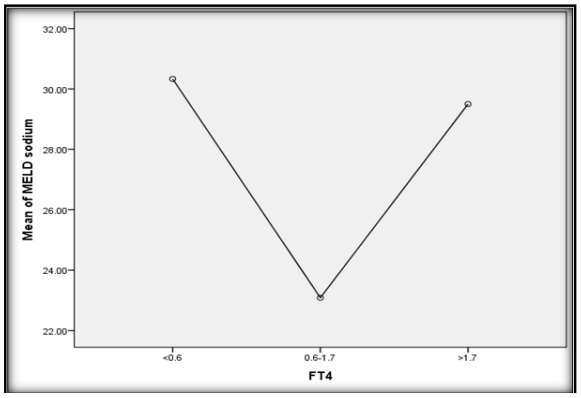

Figure 6:

DISCUSSION

Chronic liver disease/cirrhosis of liver is an important cause of morbidity and mortality worldwide. According to the World Health Organization (WHO), about 800,000 people die annually from cirrhosis.[7-9] CLD/cirrhoisis is one of the leading cause of death and it is responsible for majority of clinical burden of liver disease. Chronic liver injury is caused by various mechanisms, including activation of immunity (innate and adaptive both) and sterile inflammation.[8,10] Chronic liver disease is defined by chronic inflammation or injury of the liver and/or fibrosis occurring in the liver for more than 6 months.[1,9] Although the liver has a remarkable capacity to adapt to injury through tissue repair, chronic injury results in inflammation, matrix deposition, necrosis and angiogenesis, all of which lead to fibrosis. The key pathogenic feature of underlying liver fibrosis and cirrhosis is activation of hepatic stellate cells. The characterstic features of cirrhosis of liver is the diffuse process with nodule formation (regenerating nodules) and fibrosis as defined anatomically.[10,11] Clinically, patients may be asymptomatic(compensated) for long periods. The onset of symptoms may be insidious or less often, abrupt. Symptomatic patients present with nonspecific symptoms and signs such as fatigue, disturbed sleep, anorexia, malaise, weight loss, muscle waisting, and fever or with decompensation (jaundice, ascites, hepatic encephalopathy, or bleeding varices).Decompensation leads to unfavourable prognosis and poor quality of life in cirrhotic patients. Other complications, such as spontaneous bacterial peritonitis, hydrothorax, hepatorenal syndrome, hepatopulmonary syndrome, cirrhotic cardiomyopathy, portopulmonary hypertension, hepatocellular carcinoma, and portal vein thrombosis, and intercurrent infections may occur in these patients and can accelerate the clinical deterioration. Cirrhotic patients have low life expectancy and it further reduced in the presence of decompensation.[11,12] Median survival of compensated patient is about 12 years as compared to 2 years for decompensated patients.[12,13] Prognostic scoring systems for chronic liver disease include Child-Pugh score and MELD-Na score. Child-Pugh classification (which depends on serum bilirubin, ascites, hepatic encephalopathy, serum albumin and prothombin time-INR) is a reliable prognostic marker to predict the survival in many liver diseases and also predict major complications of cirrhosis, such as spontaneous bacterial peritonitis and variceal bleeding.[13,14] The MELD score is used to predict prognosis and determine the optimum timing for liver transplantation.[14,15] In previous sduty by Vincken et al. reorted that the mean FT3 and FT4 was significantly lower in cases as compared to controls, while the mean TSH was not significantly different(8=0 15). In another study, Punekar et al.

ISSN (O): 2687-5365; ISSN (P): 2753-6556

observed the mean FT3 and FT4 values of cases to be significantly lower while that of TSH to be significantly higher in cases as copared to that in controls. (9=0 16). Compared to he present study, Punekar et al. in their study had only 23% euthyoid cases. The most common thyroid dysfunction pattern was low FT3 (41%) followed by hypothyroidism (20%), normal thyroid illness syndrome with low FT4 (15%), and hyperthyroidism (1%) respectively (9=0 16). Patria et al. in their study found that all the three thyroid function hormone (FT3,FT4, and TSH) show a significant association with CTP classes (13=0 17). Regarding the etiology of CLD, our study found alcoholic cirrhosis is the most common etiology. Majority of the patient were male. Our study should that as the severity of liver disease increases indicated by CTP scores and MELD-Na scores the prevalence of reduced serum FT3 increased. In this study majority of patients had normal TSH and FT4 level, and these were not changed significantly as the disease advances. Alteration in serum ft3 levels correlate well with the disease severity and may be useful in assessing the course and prognosis in CLD patients.

CONCLUSION

According to this study all CLD patients should undergo thyroid function evaluation. As the study suggest significant inverse correlation between serum level of FT3 and severity of CLD, this parameter can be used as a marker of the severity of disease.

REFERENCES

1. Sorvillo F, Mazziotti G, carbone A, Morisco F, Cioffi M,Rotondi M, et al. Increased serum reverse triiodothyronine levels at diagnosis of hepato cellular carcinoma in patients with compensated HCV- related liver cirrhosis . clin Endocrionl (oxf) 2003;58:207-12.
2. Kharb s. Garg MK, Puri P, Brar KS, pandit A, Srivastav S, at al. Assessment of thyroid and gonadal function in liver diseases . Indian J endocrinol Metab. 2015;19:89-94.
3. Kayacetin E, Kisakol G, kaya A. Low serum total thyroxine and free triiodothyronine in patients with hepatic encephalopathy due to non-alcoholic cirrhosis . Swiss Med Wkly.2003;133:210-3.
4. Malik R, Hodgson H. The relationship between the thyroid gland and the liver . QJM.2002;95:559-69.
5. Pugh RNH, Muray-Lyon IM, Dawson JL, et al. Transsection of the esophagus in the bleeding esophageal varies. Br J Surg. 1973;60:648-652.
6. Kim WR, Biggins SW, Kremers WK, Wiesner RH, Kamath PS, Benson JT, Edward E, Therneau TM. Hyponatremia and mortality among patients on the liver-transplant waiting list. New England Journal of Medicine. 2008 Sep 4;359(10):1018-26.
7. Garcia- Tsao G. Cirrhosis and its sequelae. In: Goldman L, Schafer AI, eds. Goldman's Cecil medicine. 25th ed. Philadelphia: Elsevier Saunders; 2016.
8. Firth JD, Conlon CP, Cox TM. Oxford Textbook of Medicine. Oxford, United Kingdom; New York, NY, United States of America: Oxford University Press; 2020.
9. Penman ID, Ralston SH, J. SMW, Hobson RP, Davidson LS. Davidson's principles and practice of medicine. London ; New York ; Oxford ; Philadelphia ; St. Louis ; Sydney: Elsevier; 2023.
10. Poynard T, Bedossa P, Opolon P,. Natural history of liver fibrosis progression in patients with chronic hepatitis C. The Lancet. 1997 Mar 22; 349(9055):825-32.
11. Dooley J, F. LAS, Garcia- Tsao G, Pinzani M. Sherlock's diseases of the liver and biliary system. Hoboken, NJ: Wiley; 2018.
12. D' Amico G, Garcia- Tsao G, Pagliaro L. Natural history and prognostic indicators of survival in cirrhosis: a systematic review of 118 studies. J Hapatol2006;44:217-231.
13. Loscalzo J, Kasper DL, Longo DL, Fauci AS, Hauser SL, Jamson JL, et al. Harrison's principles of internal medicine. New York: McGraw Hill; 2022.
14. Lawrence S. Friedman, Paul Martin. Handbook of liver diseases; 4th ed; Elsevier; 2018
15. Vincken S, Reynaert H, Schiettecatte J, Kaufman L, Velkeniers B, Liver cirrhosis and thyroid function: Friend or foe? Acta Clin Belg 2017;72:85-90. (8=0)
16. P punekar, AK Sharma , A. Jain . A study of thyroid dysfunction in cirrhosis of liver and correlation with severity of liver disease. Indian Journal of Endocrinology and metabolism 2018 sep-oct:;22 (5) : 645-650.
17. Patira NK, Salgiya N, Agarwal D.Correlation of thyroid function test with severity of liver dysfunction in cirrhosis of liver , J Med Sci Clin Res. 2017;5:21921-7.

ISSN (O): 2687-5365; ISSN (P): 2753-6556