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Original Research Article

TO EVALUATE THE THYROID PROFILE IN PATIENTS WITH CHRONIC LIVER DISEASE

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Abstract

Background: Aim: To evaluate the thyroid profile in patients with chronic liver disease. **Materials and Methods:** A total of 80 cases and 80 age/sex matched healthy controls were included in the study. A comprehensive medical history was obtained, which included a thorough investigation into the patient's past medical conditions such as hypothyroidism, hyperthyroidism, and liver cirrhosis. Following strict aseptic protocols, a 5 ml blood sample was obtained and sent for a comprehensive analysis including complete blood count, random blood sugar, liver function test (total bilirubin, direct bilirubin, alanine transaminase, aspartate aminotransferase, alkaline phosphatase, total protein, and albumin level), renal function test, hepatitis B surface antigen, hepatitis C virus antibodies, and thyroid function tests (free T3, free T4, and thyroid stimulating hormone). The classification of liver cirrhosis severity was determined using the Child Pugh score. **Results:** The mean age of the study group was 52.52±5.85, whereas the mean age of the control group was 53.11±3.69. The majority of patients (83.75%) were diagnosed with alcoholic liver cirrhosis, whereas a smaller proportion had non-alcoholic liver cirrhosis (12.5%) or chronic viral hepatitis (3.75%). The provided information corresponds to Table 1. According to the Child-Pugh Score, the majority of patients belonged to Child-Pugh B category (43.75%), followed by Child-Pugh C (31.25%) and Child-Pugh A (25%).Table 2. In this investigation, the levels of free T3, free T4, and TSH were compared between the study group and the control group. Abnormal values were seen in the patients, and a statistically significant difference was found. Abnormalities in the serum thyroid profile were seen in accordance with the progression of Child-Pugh Score Classes, and the difference was statistically significant for free T3 and free T4cx. **Conclusions:** Patients with liver cirrhosis had abnormalities in thyroid function tests, namely in the levels of circulating thyroid hormones, as compared to healthy individuals. Furthermore, it was shown that more severe abnormalities were linked to an advanced Child Pugh score.

INTRODUCTION

Chronic liver disease (CLD) is a range of illnesses marked by the gradual decline of liver functions over a duration of six months or more. These processes include the elimination of toxic metabolic byproducts, the production of clotting factors, other proteins, and the excretion of bile. The aetiology of this condition involves inflammation of the liver tissue, resulting in the destruction and subsequent regeneration of liver parenchyma. This process eventually leads to the development of fibrosis and cirrhosis, and in certain situations, it may advance to Hepatocellular carcinoma (HCC). The etiological spectrum for chronic liver disease (CLD) encompasses a range of variables including toxins, persistent alcohol consumption, infections such as hepatitis viruses, autoimmune illnesses, genetic abnormalities, and metabolic disorders. Chronic liver disease (CLD) is a commonly seen condition in clinical practice.[1,2]

The liver has a crucial function in the metabolic process of thyroid hormone. Thyroid function tests may reveal abnormal results in non-thyroidal diseases, such as chronic liver disease, even in the absence of any pre-existing dysfunction in the hypothalamic-pituitary and thyroid gland. The thyroid function test result returns to a state of total normalcy after the recovery of patients. The primary alterations seen are decreased levels of serum triiodothyronine (T3) and increased levels of reverse T3 (rT3). Hence, this illness is referred to as "low T3 syndrome" and alternatively as "euthyroid sick syndrome". The length and severity of the non-thyroidal illness (NTI) may impact the levels of TSH,

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FT4, FT3, and total T3 (TT3) in the bloodstream to varying extents. As the severity of the non-thyroidal illness (NTI) worsens, there is a reduction in the blood levels of T3 and T4. However, these levels eventually return to normal as the patient recovers.[3] Multiple theories exist about the abnormalities of thyroid hormone in chronic liver disease. The liver has a crucial function in the metabolism of thyroid hormones, namely in the processes of thyroid hormone conjugation and excretion. Liver disease may result in aberrant levels of thyroid hormones. In addition, individuals suffering from chronic liver illness may have thyroiditis, hyperthyroidism, or hypothyroidism.[3] However, the primary mechanism responsible for TFT (thyroid function test) abnormalities in the context of NTIS (non-thyroidal illness syndrome) is the defective conversion of T4 (thyroxine) to T3 (triiodothyronine) in the peripheral tissues, which is facilitated by the deiodinase enzyme. The liver plays a crucial role in the peripheral conversion of tetraiodothyronine (T4) to triiodothyronine (T3) via the action of Type 1 deiodinase. Type I deiodinase accounts for roughly 30%– 40% of T3 synthesis outside of the thyroid gland. As the activity of Type 1 and Type 2 deiodinase enzymes decreases, the conversion of T4 to T3 is reduced. The activation of Type III deiodinase occurs in muscle and liver, leading to a drop in T3 and T4 levels and, most notably, a rise in rT3.[1,2] Abnormalities in thyroid function tests can arise from alterations in thyroid hormone secretion by the thyroid gland, disruptions in the hypothalamic-pituitary-thyroid axis, changes in hormone metabolism in peripheral tissues, the inhibitory impact of thyroid hormone-protein binding, or a combination of these factors.[4]

Additionally, there exists another hypothesis. An inhibitor may exist in both the serum and bodily tissues, potentially impeding the binding of hormones to nuclear T3 receptors, hindering the binding of T4 to various binding proteins such as TBG, Transthyretin, and albumin, and obstructing the absorption of thyroid hormones by different cells. Therefore, the hormones are unable to function effectively. Additionally, it was suggested that cytokines had a significant impact on NTI. It has been shown that Pro-inflammatory cytokines are often elevated in non-thyroidal illness (NTI) and have been seen to have an inverse relationship with thyroid hormone levels in critically sick patients,[5,6] as well as in patients with chronic diseases.[7,8] According to a certain idea, serum factors including bilirubin, NEFA, furanoic acid, hippuric acid, and indoxyl sulphate, which are often seen in different non-thyroid illnesses (NTIs), hinder the transportation of thyroid hormones. This leads to an anomaly in the levels of thyroid hormones.[9,10] The liver is responsible for producing three binding proteins: TBG, TBPA, and albumin. Therefore, in the presence of liver illness, the synthesis of these binding proteins is impacted. Consequently, the transportation of thyroid hormone in the bloodstream is greatly impacted, which in turn adds to the abnormal thyroid function test (TFT). Systemic disorders that disrupt the metabolism of Thyroid hormone might exacerbate the situation when drugs that also impact TH metabolism are used.[11-13]

MATERIALS AND METHODS

The present investigation was a single-center, hospital-based, case-control study done in the department of general medicine. Prior to commencing the investigation, permission was obtained from the institutional ethics committee. All participants provided written informed consent. A total of 80 cases and 80 age/sex matched healthy controls were included in the study. The controls were randomly chosen from relatives who were visiting the outpatient department (OPD) with patients. This research covered patients who were above 18 years old and presented with liver cirrhosis or chronic liver disease. Patients with pregnancy, preexisting thyroid disease, diabetes, nephrotic syndrome, renal failure, or any other acute or chronic disorders. The patient is being administered medications such as amiodarone, phenytoin, beta blockers, steroids, oestrogen, and iodine-containing drugs/contrast, which have the potential to disrupt thyroid hormone metabolism and function. Patients who declined to provide consent. A comprehensive medical history was obtained, which included a thorough investigation into the patient's past medical conditions such as hypothyroidism, hyperthyroidism, and liver cirrhosis. This was followed by a detailed physical examination, which assessed various aspects such as pallor, icterus, edoema, hydration status, asterixis, and signs of chronic liver disease such as alopecia, spider naevi, parotid enlargement, palmar erythema, gynaecomastia, and testicular atrophy. Additionally, examinations of the thyroid, abdomen, and neurological system were also conducted. Subjects in both the experimental and control groups were instructed to abstain from eating or drinking anything for a period of 8-10 hours before to their morning follow-up. Following strict aseptic protocols, a 5 ml blood sample was obtained and sent for a comprehensive analysis including complete blood count, random blood sugar, liver function test (total bilirubin, direct bilirubin, alanine transaminase, aspartate aminotransferase, alkaline phosphatase, total protein, and albumin level), renal function test, hepatitis B surface antigen, hepatitis C virus antibodies, and thyroid function tests (free T3, free T4, and thyroid stimulating hormone). In addition, an ultrasound was performed on the abdomen and pelvis to assess the size and texture of the liver, diameter of the portal vein, existence of collaterals, condition of the gall bladder and common bile duct, size of the spleen, presence of any abdominal collections, size and texture of the kidneys, and distinction between the cortex and medulla. The classification of liver

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cirrhosis severity was determined using the Child Pugh score.

Data Analysis

The data was gathered and organised using Microsoft Excel, and then analysed using the SPSS 25.0 software. Frequency, percentage, averages, and standard deviations were computed for the continuous variables, while ratios and proportions were computed for the categorical variables. The chi-square test or Fisher exact test, if appropriate, were used to analyse the difference in proportions between qualitative variables. A P value below 0.5 was deemed statistically significant.

RESULTS

The current research examined 80 individuals with liver cirrhosis/chronic liver disease and compared them to 80 healthy controls. The mean age of the study group was 52.52±5.85, whereas the mean age of the control group was 53.11±3.69. The majority of individuals in study group were 81.25% males, whereas in the control group, 87.5% were males. The age and gender of the participants in the study group and control group were similar, and the observed difference was not statistically significant. The majority of patients (83.75%) were diagnosed with alcoholic liver cirrhosis, whereas a smaller proportion had non-alcoholic liver cirrhosis (12.5%) or chronic viral hepatitis (3.75%).The provided information corresponds to Table 1. According to the Child-Pugh Score, the majority of patients belonged to Child-Pugh B category (43.75%), followed by Child-Pugh C (31.25%) and Child-Pugh A (25%).Table 2. In this investigation, the levels of free T3, free T4, and TSH were compared between the study group and the control group. Abnormal values were seen in the patients, and a statistically significant difference was found. Abnormalities in the serum thyroid profile were seen in accordance with the progression of Child-Pugh Score Classes, and the difference was statistically significant for free T3 and free T4cx. (See Table 3 and 4).

Table 1: Basic profile of the participants

	Study Group		Control Group		P value
	Number =80	Percentage	Number=80	Percentage	
Gender					0.15
Male	65	81.25	70	87.5	
Female	15	18.75	10	12.5	
Age					0.22
below 30	2	2.5	5	6.25	
30-40	8	10	10	12.5	
40-50	39	48.75	40	50	
50-60	18	22.5	14	17.5	
Above 60	13	16.25	11	13.75	
Age Mean	52.52±5.85		53.11±3.69		
Diagnosis					
Alcoholic liver cirrhosis	67	83.75			
Non-alcoholic liver cirrhosis	10	12.5			
Chronic Viral Hepatitis (HBV/HCV)	3	3.75			

Table 2: Child-Pugh Score

	Number	Percentage
Classification according to Child-Pugh Score		
Child-Pugh A	20	25
Child-Pugh B	35	43.75
Child-Pugh C	25	31.25

Table 3: Comparison of Serum thyroid

	Reference range	Study Group	Controls Group	P-Value
Free T3 (pg/ml)	2.3 - 4.1	1.91 ± 0.44	2.92± 0.43	0.001
Free T4 (ng/dl)	0.9 - 1.7	0.65 ± 0.11	1.33 ± 0.31	0.001
TSH (mIU/ml)	0.3-4.5	0.95 ± 0.33	3.19 ± 0.59	0.001

Table 4: Comparison of Serum thyroid profile among Child-Pugh Score Classes

Thyroid function	CPS categories			Total	P-value
	CPS A	CPS B	CPS C		
Free T3	1.89 ± 0.25	1.41± 0.33	1.11 ± 0.45	1.61 ± 0.29	0.003
Free T4	0.87 ± 0.19	0.69 ± 0.22	0.49 ± 0.12	0.66 ± 0.18	0.005
TSH	1.87 ± 0.29	1.31 ± 0.37	0.97 ± 0.16	0.96 ± 0.27	0.15

DISCUSSION

The liver has a crucial function in the metabolism, transportation, and elimination of thyroid hormones. It does this by generating thyroid binding globulin, albumin, and transthyretin.[14] Alcohol is the most prevalent factor leading to cirrhosis in India, accounting for 34.3% of cases. Additionally, about 20% of all liver disease patients and a notable fraction

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of liver-related deaths with unexplained causes may be linked to alcohol consumption.[15] Non-alcoholic fatty liver disease (NAFLD) is characterised by the buildup of fat in the liver, without being caused by genetic or autoimmune disorders, drug-related liver damage, alcohol intake, or viral infections. The incidence of non-alcoholic fatty liver disease (NAFLD) has significantly risen in recent decades, with variables such as heredity, obesity, unhealthy lifestyle, and other metabolic risk factors potentially contributing to its rapid growth.[16,17] The low total and FT3 levels might be considered as an adaptive hypothyroid condition, which helps decrease the baseline BMR in hepatocytes and maintain liver function and total body protein reserves.

The average age of the research group was 52.52±5.85, whereas the control group had an average age of 53.11±3.69. The majority of individuals in study group were 81.25% males, whereas in the control group, 87.5% were males. The age and gender of the study group and control group were similar, and the observed difference was not statistically significant. The majority of patients (83.75%) were diagnosed with alcoholic liver cirrhosis, whereas a smaller proportion had non-alcoholic liver cirrhosis (12.5%) or chronic viral hepatitis (3.75%). Patira NK et al. observed that the majority of patients (72%) were between the ages of 41 -60, with a higher percentage of males (78%).[13] Punekar et al. observed that men (71%) were more often interested than females.[2]

In this research, the distribution of patients according to the Child-Pugh Score was as follows: the majority of patients belonged to Child-Pugh B category (43.75%), followed by Child-Pugh C category (31.25%), and Child-Pugh A category (25%). In this investigation, the levels of free T3, free T4, and TSH were compared between the study group and the control group. Abnormal values were seen in the patients, and a statistically significant difference was found. Abnormalities in the serum thyroid profile were seen in accordance with the progression of Child-Pugh Score Classes. The difference was statistically significant for free T3 and free T4cx.

Ashish Kumar et al,[18] conducted a study on 50 patients diagnosed with liver cirrhosis, consisting of 35 men and 15 females, resulting in a male to female ratio of 2.33. There were 21 cases of alcoholic liver disease, 20 cases of Hepatitis C, 5 cases of hepatitis B, and 4 cases of cryptogenic cirrhosis among the patients. Upon evaluating the degree of cirrhosis, it was found that 26 patients were classified as CTP A, 19 as CTP B, and 5 as CTP C. Among the 50 patients, 5 individuals (10%) had subclinical hypothyroidism, whereas hyperthyroidism was seen in 2 instances (4%). Out of the patients diagnosed with hypothyroidism, 3 individuals had liver cirrhosis attributable to ethanol use, 1 had Hepatitis C, and 1 had cryptogenic cirrhosis. Both patients diagnosed with hyperthyroidism were classified as CTP A. One patient had cryptogenic cirrhosis while the other had hepatitis C. A significant prevalence of anomalies in the levels of thyroid hormones, namely hypothyroidism, is seen particularly in individuals with liver cirrhosis caused by ethanol use. This condition is closely linked to the progression of liver disease.

Agha et al discovered a substantial drop in the average blood levels of T3, FT3, and FT4 in individuals with cirrhosis. However, there was no significant change seen in serum T4 and TSH levels.[19] Sanul et al. demonstrated a substantial drop in the average blood concentration of T3 and the T3/T4 ratio in cirrhotic patients ($p<0.01$). However, no significant alteration was seen in serum T4 and TSH levels [20]. In their investigation, Mansour-Ghanaei et al discovered a significant negative connection ($r=-0.453$, $p<0.001$) between child-Pugh scores and total serum T3 level.[21] Vincken et al. discovered a substantial decrease in fT3 and fT4 levels in patients with cirrhosis compared to healthy individuals ($p=0.001$ and 0.002, respectively). The TSH levels did not exhibit a statistically significant difference between the two groups.[22] In their study, Hong-Ling et al. discovered that the group of individuals with chronic hepatitis had significantly lower levels of FT3 (2.79±0.71 vs. 4.43±0.75 pmol/L, $p<0.001$) and TSH [0.618 (0.186-1.185) vs. 1.800 (1.570-2.590) mIU/L, $p<0.001$], and higher levels of FT4 (19.51±6.26 vs. 14.47±2.19 pmol/L, $p<0.001$) compared to the control group.[23] Liu et al. discovered that the levels of free triiodothyronine (FT3) and free thyroxine (FT4) were lower in the liver cirrhosis group compared to the control group ($p<0.001$). Additionally, the levels of thyroid-stimulating hormone (TSH) were greater in the liver cirrhosis group compared to the control group ($p<0.001$).[24]

In a study conducted by Chaudhary S et al,[25] a total of 110 patients with liver cirrhosis and 110 healthy controls were examined. The average age of the patients was 51.1±12.13 years, and the male to female ratio was 4:1. Out of the total number of patients, 62 (56.36%) were classified as Class C according to the Child Pugh score, whereas 35 (31.82%) were classified as Class B. Twenty-seven patients (24.6%) had a low level of FT3, whereas 11 patients (10%) had a low level of FT4. Additionally, 25 patients (22.7%) displayed a high TSH level. Abnormal thyroid function test (TFT) results were observed in a total of 43 individuals, accounting for 39.1% of the study population. Three patients (2.7%) had overt hyperthyroidism, 14 patients (12.7%) had subclinical hypothyroidism, and 11 patients (10%) had overt hypothyroidism. Fifteen individuals (13.06%) had a solitary decrease in FT3 levels. The correlation between AST, ALT, and ALP was shown to be statistically significant with both FT3 and FT4. A statistically significant correlation was seen between various CPS categories and the mean scores of FT3 ($p=0.0048$) and FT4 ($p=0.045$).

In a study conducted by G. Deepika et al,[26] a total of 310 patients with cirrhosis and 250 control persons were examined. They observed a substantial rise in

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TSH levels in cirrhotic patients compared to non-cirrhotic participants, as well as a small drop in T3 and T4 levels. The corresponding p-values were 0.039, 0.014, and 0.245, respectively. The average TSH levels in cirrhotic patients are greater than those in non-cirrhotic individuals, and this difference is statistically significant. Furthermore, there is a notable disparity in T4 levels between the two groups, although there seems to be no significant variation in T3 levels between the two groups.

Punekar P et al,[2] observed that the average levels of FT3 and FT4 were dramatically decreased, while the levels of TSH were significantly increased in individuals with liver cirrhosis. These hormone levels were also shown to be connected with the severity of the liver dise.

In their study, Jaswanth Kumar P et al,[27] examined 70 patients with alcoholic liver disease to evaluate and compare the concentrations of thyroid hormones - free T3, free T4, Thyroid Stimulating Hormone (TSH), and Gamma Glutamyl Transferase (GGT) before and after therapy. The administration of therapy resulted in a reduction in serum GGT levels, a rise in free T4 and T3 levels, and no significant alteration in TSH levels. Moreover, there was a notable association between free T3 and GGT both before and after therapy. Additionally, free T4 and TSH exhibited a substantial connection with GGT after treatment. It is necessary to assess the levels of thyroid hormones, namely free T3 and free T4, in patients with chronic alcoholic liver disease, as well as during the periods of withdrawal and abstinence. Decreased hormone levels in these individuals may exacerbate withdrawal symptoms and intensify the desire for alcohol.

In their study, W et al,[28] did a meta-analysis and found compelling epidemiological data supporting the association between hypothyroidism and non-alcoholic fatty liver disease (NAFLD). Both persons with subclinical and overt hypothyroidism have a greater susceptibility to non-alcoholic fatty liver disease (NAFLD) compared to those with normal thyroid function. It is crucial for clinicians to be aware of the connection between hypothyroidism and abnormal liver function indicators. This knowledge helps them in assessing thyroid function when investigating patients with abnormal liver function tests.

CONCLUSION

Patients with liver cirrhosis had abnormalities in thyroid function tests, namely in the levels of circulating thyroid hormones, as compared to healthy individuals. Furthermore, it was shown that more severe abnormalities were linked to an advanced Child Pugh score.

REFERENCES

1. Sudip R, Sumesh PM, Dutta S, Majumder N, Mahapatra U, Swaika BC. A study on thyroid profile in chronic liver disease patients admitted in a rural tertiary care hospital of West Bengal, India. International Journal of Health and Clinical Research. 2022;5(2):257-60.
2. Punekar P, Sharma AK, Jain A. A study of thyroid dysfunction in cirrhosis of liver and correlation with severity of liver disease. Indian J Endocrinol Metab. 2018 Sep-Oct;22(5):645-50. doi: 10.4103/ijem.IJEM_25_18, PMID 30294575, PMCID PMC6166553.
3. Sharma A, Nagalli S. Chronic liver disease. StatPearls. 2022.
4. Peng Y, Qi X, Guo X. Child-Pugh Versus MELD Score for the Assessment of Prognosis in Liver Cirrhosis: A Systematic Review and Meta-Analysis of Observational Studies. Med (Baltim). 2016;95(8): e2877. doi: 10.1097/MD.0000000000002877, PMID 26937922.
5. Giri R, Singh VP, Gulati Y, Kumar V. A study of thyroid function profile in patients of chronic liver disease and its correlation with child Pugh score. Int J Adv Med. 2023;10(6):441-5. doi: 10.18203/2349-3933.ijam20231437.
6. Raj A, Pillai G, Divakar A, Shivam V, Nair A. Association of thyroid function and severity of illness in liver cirrhosis as measured by Child-Pugh score. Cureus. 2023 Mar 24;15(3): e36618. doi: 10.7759/cureus.36618, PMID 37155441, PMCID PMC10122753.
7. Kharb S, Garg MK, Puri P, Brar KS, Pandit A, Srivastava S. Assessment of thyroid and gonadal function in liver diseases. Indian J Endocrinol Metab. 2015;19(1):89-94. doi: 10.4103/2230-8210.131761, PMID 25593833.
8. Cheemerla S, Balakrishnan M. Global epidemiology of chronic liver disease. Clin Liver Dis (Hoboken). 2021;17(5):365-70. (PMC Free article). doi: 10.1002/cld.1061, PMID 34136143, Google Scholar.
9. Raja M. Role of mean corpuscular volume in alcohol use disorders. The J Med Sci. 2022; 01:23-33. Google Scholar.
10. Kalmani VM, H.s M, S.n. R, S.r T, M K. A Cross-Sectional Study of Thyroid Dysfunction in Patients Suffering from Liver Cirrhosis in a Tertiary Care Hospital in Bengaluru, India. J Evid Based Med Healthc. 2021;09(23):1904-8. doi: 10.18410/jebmh/2021/358.
11. Kharb S, Garg MK, Puri P, Brar KS, Pandit A, Srivastava S. Assessment of thyroid and gonadal function in liver diseases. Indian J Endocrinol Metab. 2015;19(1):89-94. doi: 10.4103/2230-8210.131761, PMID 25593833.
12. J L J, K M, R K, T RS, A A, K CS et al. Thyroid dysfunction in patients with liver cirrhosis. IOSR JDMS. 2017;16(4):18-22. doi: 10.9790/0853-1604081822, Google Scholar.
13. Patira NK, Salgiya N, Agrawal D. Correlation of Thyroid Function Test with Severity of Liver Dysfunction in Cirrhosis of Liver. J Assoc Physicians India. 2019;67(3):51-4. doi: 10.18535/jmscr/v5i5.109. PMID 31304707.
14. Mansour-Ghanaei F, Mehrdad M, Mortazavi S, Joukar F, Khak M, Atrkar-Roushan Z. Decreased serum total T3 level in hepatitis B and C related cirrhosis by severity of liver damage. Ann Hepatol. 2012;11(5):667-71. doi: 10.1016/S1665-2681(19)31440-1, PMID 22947527.
15. Mukherjee PS, Vishnubhatla S, Amarapurkar DN, Das K, Sood A, Chawla YK, et al. Etiology and mode of presentation of chronic liver diseases in India: A multi centric study. PLOS ONE. 2017;12(10): e0187033. doi: 10.1371/journal.pone.0187033, PMID 29073197.
16. Rinella ME. Nonalcoholic fatty liver disease: a systematic review. JAMA. 2015;313(22):2263-73. doi: 10.1001/jama.2015.5370, PMID 26057287.
17. Buzzetti E, Pinzani M, Tsochatzis EA. The multiple-hit pathogenesis of non-alcoholic fatty liver disease (NAFLD). Metabolism. 2016;65(8):1038-48. doi: 10.1016/j.metabol.2015.12.012, PMID 26823198.
18. Kumar A, Ahuja V, kaur I, Pandov V, Singh A, Sibia R. PREVALENCE OF THYROID DYSFUNCTION IN PATIENTS OF CIRRHOSIS OF LIVER AND ITS CORRELATION WITH SEVERITY OF CIRRHOSIS. Int J Adv Res;08(4):91-5. doi: 10.21474/IJAR01/10749.
19. Agha F, Qureshi H, Khan RA. Serum thyroid hormone levels in liver cirrhosis. J Pak Med Assoc. 1989;39(7):179-83. PMID 2504964.
20. Sanul AR, Özütemiz AÖ, Gürsoy K. Serum thyroid Hormone Levels in Liver Cirrhosis. Tepecik Dergisi. 1992;2(2):140-4. doi: 10.5222/terh.1992.31391.

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

21. Mansour-Ghanaei F, Mehrdad M, Mortazavi S, Joukar F, Khak M, Atrkar-Roushan Z. Decreased serum total T3 level in hepatitis B and C related cirrhosis by severity of liver damage. Ann Hepatol. 2012;11(5):667-71. doi: 10.1016/S1665-2681(19)31440-1, PMID 22947527.
22. Vincken S, Reynaert H, Schiettecatte J, Kaufman L, Velkeniers B. Liver cirrhosis and thyroid function: friend or foe? Acta Clin Belg. 2017;72(2):85-90. doi: 10.1080/17843286.2016.1215641, PMID 27553585.
23. Feng HL, Li Q, Cao WK, Yang JM. Changes in thyroid function in patients with liver failure and their clinical significance: A clinical study of non-thyroidal illness syndrome in patients with liver failure. Hepatobiliary Pancreat Dis Int. 2020;19(6):561-6. doi: 10.1016/j.hbpd.2020.05.001, PMID 32535064.
24. Liu C, Li L, Zeng L. The Clinical Value of thyroid Hormone Levels and Correlation with Severity of Liver Cirrhosis. Comput Intell Neurosci. 2022; 2022:5365172. doi: 10.1155/2022/5365172, PMID 35707192.
25. Chaudary S, Shahi A, Jaiswal NK, Dhakal PR, Khatri P, Pandey S et al. Thyroid function test abnormalities in patients with liver cirrhosis. Jour of Diab and Endo Assoc of Nepal. 2019;3(2) :(25-31). doi: 10.3126/jdean. v3i2.27521.
26. Deepika G, Veeraiah N, Rao PN, Nageshwar Reddy D. Prevalence of hypothyroidism in Liver Cirrhosis among Indian patients. Int J Pharm Med Res. Jun 2015;3(3).
27. Papineni JK, Pinnelli VBK, Davanum R. Thyroid hormone levels in chronic alcoholic liver disease patients before and after treatment. J Clin Diagn Res. 2017 Jul;11(7): BC13-6. doi: 10.7860/JCDR/2017/24552.10276, PMID 28892881.
28. He W, An X, Li L, Shao X, Li Q, Yao Q et al. Relationship between Hypothyroidism and Non-Alcoholic Fatty Liver Disease: A Systematic Review and meta-analysis. Front Endocrinol. 2017; 8:335. doi: 10.3389/fendo.2017.00335, PMID 29238323.