Indian Journal of Public Health Research & Development
Volume 13 | Issue 4 | October-December 2022

A Study on the Spectrum of Thyroid Abnormalities in Liver Disease and Its Correlation with Liver Function

Manju Sharma[1], Anju Mittal[2], Sangeeta Jain Sharma[3], Atul Kumar[4], Akshay Sharma[5], Yatin Kumar[6]

[1]Assistant Professor, Dept of biochemistry, Muzaffarnagar medical college,
[2]Associate Professor, Dept of Biochemistry, Muzaffarnagar medical college,
[3]Assistant Professor, Dept of Community Medicine, Muzaffarnagar Medical College,
[4]Associate Professor, Dept of Microbiology, Muzaffarnagar Medical College,
[5]Assistant Professor, Dept of Medicine, Muzaffarnagar Medical College,
[6]Senior Resident, Dept of Medicine, Muzaffarnagar Medical College

How to cite this article: Manju Sharma, Anju Mittal, Sangeeta Jain Sharma, Atul Kumar, Akshay Sharma, Yatin Kumar[6]. A Study on the Spectrum of Thyroid Abnormalities in Liver Disease and Its Correlation with Liver Function. Volume 13 | Issue 4 | October-December 2022

Abstract

Introduction: liver diseases are associated with endocrine disturbances and secondary dysfunction of endocrine organ which apparent hormonal imbalance. This study aims to find out the correlation between the levels of FT3, FT4, TSH and severity of liver disease in Chronic Liver Disease patients.

Materials and Method: A total of 100 subjects with Chronic Liver disease satisfying inclusion and exclusion criteria visiting medicine OPD and admitted in IPD of Muzaffarnagar Medical College during the period of 18 months was taken for study which was a Cross Sectional Observational Study.Thyroid function tests which includes FreeT3, FreeT4, TSH was done for all patients and tests such as Anti-TPO antibodies, USG neck, Doppler thyroid, FNAC thyroid was done wherever indicated The liver function tests including total and direct bilirubin, total protein and albumin, AST and ALT, APTT, PT, INR was done for all patients and USG abdomen and Oesophago-gastro-duodenoscopy was done wherever indicated.

Results: The mean duration of liver disease in our study population was 5.92 ± 4.61 years (range 1-26 years). The mean FT3 levelwas 2.3059 ± 0.8883 p Mol/L. The mean FT4 level was1.1689 ± 1.0806 ng/dL . The mean TSH level was 3.3198 ± 1.0173 m IU/mL The mean total bilirubin was 8.445 ± 4.3438 mg/dL .

Conclusion: Thyroid dysfunction forms important part of spectrum of Chronic liver disease. Patients with liver disease should be evaluated for thyroid dysfunction periodically.

Keywords: Child-Pugh-Turcott score, FT3,FT4 ,TSH,Chronic liver disease

Introduction

Cirrhosis and chronic liver disease are the leading causes for mortality and morbidity in the whole world [1] . As a consequence of increasing prevalence of obesity, Non-Alcoholic Fatty Liver Disease (NAFLD) is the leading cause of chronic liver disease in the western world [2] . In India, the overall prevalence of Non-Alcoholic Fatty Liver disease is 5-30% [3] . The functions of liver include 1. Metabolism 2. Biosynthesis 3. Detoxification and excretion 4. Storage.

Corresponding Author:
Manju sharma
Assistant Professor
Muzaffarnagar Medical College, 207, Rambagh Road, Muzaffarnagar, UP - 251001
E-Mail: manju.kartik@gmail.com

Liver diseases are associated with endocrine disturbances and secondary dysfunction of endocrine organ. This results in signs of apparent hormonal imbalance [4,5]. Thyroid hormone is necessary for normal growth, development, energy balance, and metabolism of the individual. It plays a role in determining the height of the individual by determining the skeletal growth [6]. It is also essential for neural tissue growth and development, lung maturation, maintenance of hepatocytes [7], renal tubular cells, cardiovascular function regulation and hemodynamics. The risk of cardiovascular mortality and atrial fibrillation is higher in individuals with subclinical hypo or hyperthyroidism [8]. Thyroid hormones influence hepatic lipid homeostasis through stimulation of free fatty acid delivery to liver and increase in beta oxidation of fatty acid. Through these mechanisms, thyroid hormones affect hepatic fat accumulation which leads to Non-Alcoholic Fatty Liver Disease [9]. Individuals with hypothyroidism are 1.5-2 times more likely to have Chronic Liver Disease [10] . Liver plays an important role in maintaining the level of thyroid hormone. Thyroid gland secretes Thyroxine (T4) and Tri-Iodo Thyronine (T3) with T4 at the rate of 90 microgram/day and T3 at the rate of 6.4 microgram/day. 100% of the total T4 and 20% of the total T3 is secreted by thyroid gland [11]. Liver contributes about 30-40% of peripheral conversion of T4 to T3 [12] . The thyroid hormone is inactivated by D3 deiodinase in liver [13] . 80% of T3 and 97.5% of rT3 is produced by deiodination in peripheral tissue. Liver plays an important role in thyroid hormone metabolism [14,15] This study aims to find out the correlation between the levels of FT3, FT4, TSH and severity of liver disease in Chronic Liver Disease patients.

Aims and Objectives

AIMS AND OBJECTIVES AIM To evaluate the Thyroid functions in patients with liver disease. OBJECTIVE To assess the severity of liver dysfunction in relation with interpretation of thyroid functions

MATERIALS AND METHODS : A total of 100 subjects with Chronic Liver disease satisfying inclusion and exclusion criteria visiting medicine OPD and IPD of MMCH, during the period of 18 months was taken for study.(2020-21) .After clearance from ethical committee ref no MMC/IEC/2020/70 dated 27/01/2020 the research work was started in Muzaffarnagar medical college. Cross Sectional Observational Study in Muzaffarnagar Medical College . Inclusion criteria: 1. Patients with clinical, biochemical and radiological evidence of Chronic Liver Disease. 2. Patients who himself or his/her relatives gave consent 3. Above 18 years.Exclusion criteria: 1. Patients with diabetes. 2. Pregnant subjects. 3. Patient with prior h/o thyroid disease. 4. Patient receiving drugs that may interfere with thyroid hormone metabolism and function. 5. Patients with any other chronic illness. 6. Below 18 years of age. Sample size calculation- Confidence Interval:95% (Z), Precision of study :15% of P(d) Prevalence(P) : 61% [15] · Formula :4×P(1-P)/d2 Sample size :100 . Informed consent was taken from the subjects who were included in the study. Socio- demographic details was recorded. Thyroid function tests which includes FreeT3, FreeT4, TSH was done for all patients and tests such as Anti-TPO antibodies, USG neck, Doppler thyroid, FNAC thyroid was done wherever indicated. The liver function tests was done for all patients and tests such as USG abdomen and Oesophago-gastro-duodenoscopy was done wherever indicated. The relationship between the levels of Free T3, FreeT4, and TSH with severity of liver disease in patients having chronic liver disease was analysed using appropriate statistical tests. Study tools Self-made questionnaire containing questions on socio-demographic details, age, gender, education, socio economic status, age of onset, duration of illness, smoking, alcoholism, exposure to risk factors, family history of thyroid disorders, drug history was sought. All relevant investigations were noted. Child-Pugh-Turkot score to classify the degree of cirrhosis. It ranges from 5 to 15.

Statistical analysis- After completing the data collection, data was entered and analysed using MSExcel and epi info. Quantitative variables were expressed in mean and standard deviation. Qualitative variables were expressed in fractions, percentage and proportion. The data of the quantitative variables was analysed by using chi-square test and qualitative variables by using appropriate 't' test.

Results

A hospital based cross-sectional study was done on chronic liver disease patients admitted in department of General Medicine in Muzaffarnagar medical college and hospital, Muzaffarnagar.

Mean duration of liver disease The mean duration of liver disease in our study population is 5.92 ± 4.61 years (range 1-26 years). Free T3 The mean FT3

level in patients included in our study is 2.3059 ± 0.8883 p Mol/L (range 0.14-5.7 p Mol/L). Free T4 The mean FT4 level in our patients included in the study is 1.1689 ± 1.0806 ng/dL (range 0.45-12.2 ng/dL). TSH The mean TSH level in the patients included in our study is 3.3198 ± 1.0173 m IU/mL (range 0.4-5.11 m IU/mL). Total bilirubin The mean total bilirubin in the chronic liver disease patients in our study is 8.445 ± 4.3438 mg/dL (range 1.4-20.8) Of the various etiologies studied, alcohol and other hepatotoxic drugs accounts for 81% of liver disease. 19% of liver disease is caused by viral etiology Of the 100 patients, 97 (97%) had signs of liver cell failure. 29% and 19% of the patients had upper GI bleed and hepatic encephalopathy respectively. 59% had hepatosplenomegaly, 53% of our patients had CPT Class C (advanced, decompensated liver disease) and 43% of the patients had CPT Class B (moderate liver disease) and 4% had CPT Class A (well compensated liver disease)

TSH & CPT Class

Among the study population, 22 patients (22%) had increased TSH and 78 had normal TSH (78%). Among the CPT-A patients, 3 had increased TSH (75%) and 1 had normal TSH (25%). Those patients with CPT class B, 35 patients (81.39%) had normal TSH and 8 (18.61%) had increased TSH. In CPT class C patients, 42 patients (79.24%) had normal TSH and 11 (20.76%) had increased TSH. In our patients, none had reduced TSH to suggest hyperthyroidism. CPT class C patients had more prevalent hypothyroidism than CPT-B. P value is found to be 0.0332 and is statistically significant.

FREE T3 AND CPT Class

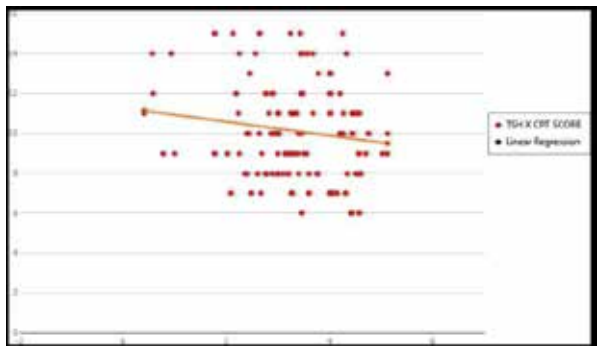
Among the study population, 84 patients (84%) had reduced FT3 and 16 had normal FT3 (16%). Among the CPT-A patients, 1 had reduced FT3 and 3 had normal FT3 (25% and 75% respectively). Those patients with CPT class B, 34 patients (79.06%) had reduced FT3 and 09 (20.94%) had normal FT3. In CPT class C patients, 49 patients (92.45%) had reduced FT3 and 4 (7.55%) had normal FT3. In our patients, none had increased FT3 to suggest hyperthyroidism. More number of CPT class C patients had reduced FT3 than CPT-B patients. P value found to be 0.0008 and is statistically significant

FREE T4 AND CPT Class

Among the study population, 27 patients (27%) had reduced FT4, 69 patients had normal FT4(69%) and 4 had increased FT4 (4%). Among the CPT-A patients, 1 patient (25%) had reduced FT4, 3 (75%) had normal FT4. Those patients with CPT class B, 09 (20.93%) patients had reduced FT4, 31 patients (72.09%) had normal FT4 and 3 (6.98%) had increased FT4. In CPT class C patients, 17 (32.07%) patients had reduced FT4, 35 patients (66.03%) had normal FT4 and 1 (1.9%) had increased FT4. P value is found to be 0.5217 and is statistically insignificant.

Correlation: TSH AND CPT

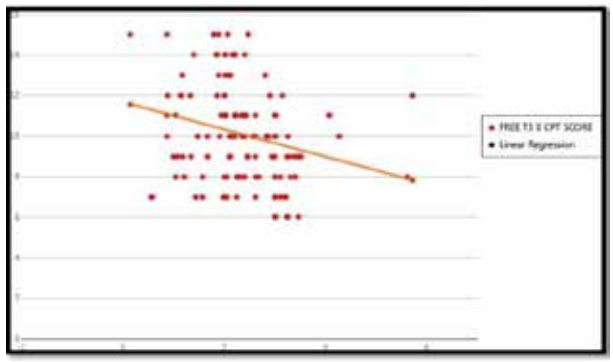
FIG 1



TSH level is found to be negatively correlated with Child-Pugh-Turcott score with correlation co-efficient of -0.062 but it is found to be statistically insignificant with P value 0.119086.

Correlation: FREE T3 AND CPT

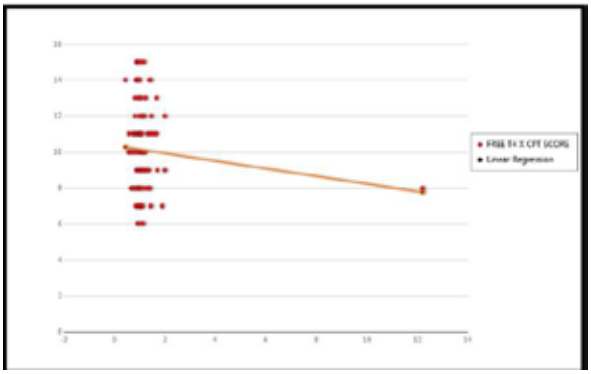
FIG 2



FT3 level is found to be negatively correlated with Child-Pugh-Turcott score with correlation co-efficient of -0.674 and it is found to be statistically significant with P value 0.007797.

Correlation: FREET4 AND CPT

FIG 3



FT4 level is found to be negatively correlated with Child-Pugh-Turcott score with correlation co-efficient of -0.212 but it is found to be statistically insignificant with P value 0.315042.

Discussion

In our study 100 patients with chronic liver disease were enrolled after getting informed consent from the subjects. Thyroid function tests which include FreeT3, FreeT4, TSH were done for all patients. The liver function tests were done for all. Liver cirrhosis-was diagnosed based on standard clinical features. After diagnosis, was classified according to standard Child-Pugh score.

The mean duration of illness in our study population is 5.92 ± 4.61 years (range 1-26 years). The mean FT3 level in patients included in our study is 2.3059 ± 0.8883 p Mol/L (range 0.14-5.7 p Mol/L). The mean FT4 level in our patients included in the study is 1.1689 ± 1.0806 ng/dL (range 0.45-12.2 ng/dL). The mean TSH level in the patients included in our study is 3.3198 ± 1.0173 m IU/mL (range 0.4-5.11 m IU/mL). These results are in consistency with study by Punekar et al [16] . The mean total bilirubin in the chronic liver disease patients in our study is 8.445 ± 4.3438 mg/dL (range 1.4-20.8 mg/dL). This is in consistent with the study of Bianchi et al [17] . In our study population, patients had exposure to various hepatotoxic factors such as hepatotoxic drugs, alcohol, indigenous medications, viral causes. Of these, the majority includes hepatotoxic drugs, and alcohol. Of the 100 patients, 97 patients (97%) had signs of liver cell failure. 29%). In this study, 22% patients (25 patients) with CLD have hypothyroidism. . Among thyroid hormone abnormalities, hypothyroidism was more frequently seen, and hyperthyroidism has also been reported. This is proposed to be due to varied etiology and severity. This is in consistent with the study by Sandeep Kharb et al [18], K.V.S. Hari Kumar et al [19] , G Deepika et al [1]. This is in consistent with Punekar et al [20] , and Joeimon JL et al [21] , El-Feki MA et al , Antonelli A et al [22] . In the study by Punekar et al [20] , 20% patients had increased TSH and in the study by Joeimon et al [21], 21.6% patients had increased TSH. But this finding does not correlate with the studies by Patira NK et al [23] and Mobin A et al [24] in which 62%, 2.63% patients had increased TSH. Among the study population, 84 patients (84%) had reduced FT3 and 16 had normal FT3 (16%). This is in correlation with the studies by Punekar et al [20] , and Mobin A et al [24] where 71% and 76.3% of the patients showed reduced FT3 levels respectively. This finding also goes in consistency with D Costa L et al [25], Saleem WM et al [26] , Kayacetin E et al [27] , El Sawy AA et al [28] . Among the study population, 27 patients (27%) had reduced FT4, 69 patients had normal FT4(69%) and 4 had increased FT4 (4%). This result goes in correlation with Punekar et al [20] and Kayacetin E et al [27]. This study shows that significant decrease in FT3, insignificant change in FT4 and mild increase in TSH levels. This is in agreement with Hussein Awad Mousa et al [29], who found that a significant decrease level of T3 and an insignificant change in TSH and T4 levels. Takahashi et al [30] concluded that serum Free T3 (FT3) levels reduced in CLD. These findings do not go with the study conducted by G Deepika et al [1] showed that there was a significantly increased TSH and slightly decreased T3 and T4 levels. These findings are not in agreement with Mohamed Abdel-Fattah ElFeki et al [31]. Several lines of evidence suggest a reduced dopaminergic tone as a consequence of the accumulation of false neurotransmitters, which might be responsible for raised basal TSH concentrations, as dopamine has been shown to exert an inhibitory effect in the regulation of TSH secretion [22]. Antonelli, A., et al [22] result is consistent with our study who found that the level of TSH was significantly higher in patients with chronic hepatitis C. In our study, Increase in T4 has been observed in patients with acute and chronic liver disease is due to increase in Thyroxine Binding Globulin levels, which is synthesized as acute phase reactant. It can be stated that in the initial state of acute liver diseases the T4 production increases and subsequently as liver function is worsen it will be reduced due the higher and low concentration of TBG. In our patients, none had reduced TSH to suggest hyperthyroidism. TSH level is found to be

negatively correlated with Child-Pugh-Turcott score with correlation co-efficient of -0.062 but it is found to be statistically insignificant with P value 0.119086. This is not in agreement with Oren R et al [32] who found a significant negative correlation was found between thyroid-stimulating hormone blood levels and both functional and synthetic liver function tests. In our patients, none had increased FT3 to suggest hyperthyroidism. P value is found to be 0.0008 and is statistically significant. FT3 level is found to be negatively correlated with Child-Pugh-Turcott score with correlation co-efficient and it is found to be statistically significant with P value 0.007797. This is in agreement with Fariborz Mansour-Ghanaei et al , Patira NK et al reported that there is a negative correlation was found between Child-Pugh scores and serum T3 level. Also concluded that serum T3 concentration is a good index of hepatic function, decreasing by the severity of liver damage. This goes in agreement with Hussein Awad Mousa et al [29], M Borzio et al who evaluated thyroid function in 33 patients with liver disease and found that T3, FT3 and T3/thyroxine binding globulin and thyrotropin after thyrotropin releasing hormone were significantly reduced. Takahashi H et al conducted a study on thyroid hormones in different categories of liver disease and concluded that Serum Free T3 level is reduced in CLD. This is in agreement with Sandeep Kharb et al who studied thyroid function in 75 patients with liver disease concluded that there was significantly lower T3 level. This result goes with Sanu A et al who found that serum T3 and FT3 showed an inverse correlation with serum bilirubin and positive correlation with serum albumin.

Limitations of the Study Our study data derived from a small group of patients do not give enough evidence to suggest that the observed endocrinopathies are merely coincidental or due to the underlying cirrhosis. Further large- scale studies with a greater number of patients are required to confirmthe findings observed in our study.

Funding : self

Conflict of interest: there was no conflict of interest

Conclusion

The present study revealed that cirrhotic patients had more prevalent thyroid dysfunction specially hypothyroidism. The liver has important role in thyroid hormone metabolism because it is the manufacturer of protein that bind thyroid hormone, such as thyroid-binding globulin (TBG), Transthyretin, and albumin. It is also the major site of thyroid hormone peripheral metabolism such as conjugation, biliary excretion, oxidative deamination and the, extra thyroidal deiodination of thyroxin (T4) to tri-iodo-thyronine (T3) and to reverse T3. The thyroid hormone is also important to normal hepatic function and bilirubin metabolism

As liver abnormalities worsen the T3 production from T4 is also reduced. It is believed this reduction of T3 which mainly correspond to even lower basic metabolism rate, can be useful due to preventing energy consumption. Free T3 concentration corresponding with the state of liver disease and it seems the serum T3 concentration directly related to liver abnormalities progress. In conclusion, thyroid dysfunction forms important part of spectrum of Chronic liver disease. Patients with liver disease should be evaluated for thyroid dysfunction periodically

Bibliography

1. Deepika G, Veeraiah N, PN Rao, Nageshwar Reddy. Prevalence of hypothyroidism in liver cirrhosis among Indian patients. International journalof pharmaceutical and medical research.2015;3:4.
2. Loomba R, Sanyal AJ. The global NAFLD epidemic. Nat RevGastroenterology Hepatic.2013;10:686-90.
3. Pagadala MR, Zein CO, Dasarathy S, Yerian L, Lopez R, McCollougg AJ. Prevalence of hypothyroidism in non-alcoholic fatty liver disease. Dig Did sci.2012;57:528-34.
4. Maheshwari A, Thuluvath P. Endocrine Diseases and the Liver. Clinics inLiver Disease.2011;15(1):55-67.
5. Zietz B, Lock G, Plach B, Drobnik W, Grossmann J, Schölmerich J et al. Dysfunction of the hypothalamo-pituitary-glandular axis and relation to ChildPugh classification in male patients with alcoholic and virus-related cirrhosis. European Journal of Gastroenterology & Hepatology.2003;15(5):495-501.
6. Riukees SA, Bode HH, Crawford JD. Long term growth in juvenile acquired hypothyroidism: The failure to achieve normal adult stature. N English J Med.1988; 318:599-60
7. Malik R, Mellor N, Selden C, Todgson H. Tri-iodo thyronine enhances the regenerative capacity of the liver following partial hepatectomy. Hepatology.2003 ;37:79-8.
8. Hernando VV, Eliana MS. Role of thyroid hormones in different aspects of cardiovascular system. Endocrinol Metabolism Syndrome.2015;4:166.

9. Van Horngiven, Wind L, Dullaart RPF. Low normal thyroid function as a determinant of increased large VLDL particles. Clin Biochemical.2015;58:489- 94

10. Chung GE, Kim D, Kim W, Yim JY, Park MJ, Kim YJ, et al. Non-alcoholic fatty liver disease across the spectrum of hypothyroidism. J Hepatic.2012;57:150-6.

11. Jameson, Fauci, Kasper, Hauser, Longo, Loscalzo. Harrison's principles of internal medicine.20thed. New York: McGraw-Hill Education;2018. p.2695.

12. Shlomo M, Richard J, Allison B. Ronald J, Clifford J. Williams textbook of endocrinology. 14thed. Philadelphia: Elsevier Inc;2020. p.343.

13. Greg Kelly. Peripheral metabolism of thyroid hormones: A review. AlternMed Rev.2000;5(4):306-333.

14. Malik R. The relationship between the thyroid gland and the liver. QJM. 2002;95(9):559-569.

15. Bandyopadhyay SK, Moulick A, Saha M, Dutta A, Bandyopadhyay R, Basu AK. A study on endocrine dysfunction in adult males with liver cirrhosis. J Indian Med Assoc.2009;107:866–9.

16. Punekar P, Ashvanee Kumar Sharma, Jain A. A study of thyroid dysfunction in cirrhosis of liver and correlation with severity of liver disease. Indian J Endocrinol Metab.2018;22(5):645-650.

17. Bianchi GP, Zoli M, Marchesinia, Volta U, Vecchi F, Lervese T, Bonazzi C, Pisi E. Thyroid gland size and function in patients with cirrhosis of liver. Liver.1991;11:71-78.

18. Garg M, Puri P, Brar K, Pandit A, Srivastava S, Kharb S. Assessmentof thyroid and gonadal function in liver diseases. Indian Journal of Endocrinology and Metabolism.2015;19(1):89.

19. Kumar KH, Pawah AK, Manrai M. Occult endocrine dysfunction in patients with cirrhosis of liver. J Family Med Prim Care.2016;5:576-80.

20. Punekar P, Ashvanee Kumar Sharma, Jain A. A study of thyroid dysfunction in cirrhosis of liver and correlation with severity of liver disease. Indian J Endocrinol Metab.2018;22(5):645-650.

21. Joeimon JL, Mohanraj K, Karthikeyan R, Solomon RT, Aravind A,Selvi CK, et al. Thyroid dysfunction in patients with liver cirrhosis. IOSR J Dent Med Sci.2017;16:18-22.

22. Antonelli A, Ferri C, Fallabi P, Giuggioli D, Nesti C, Longombardo G, et al. Thyroid involvement in patients with overt hepatitis C virus related mixed cryoglobulinemia. QJM Int J Med.2004;97:499-506.

23. Patira NK, Salgiya N, Agrawal D. Correlation of thyroid function tests with severity of liver dysfunction in cirrhosis of liver. J Med Sci Clin Res.2017;5:21921-7.

24. Mobin A, Haroon H, Shailch H, Qureshi S, Ali M. Decompensated cirrhosis; Thyroid hormone levels in patients. Prof Med J.2016;23:34-8.

25. D'Costa L, Dhume CY. Assessment of thyroid parameters inAlcoholic Liver Disease. Int J Pharm Bio Sci.2016;7:771-6

26. Saleem WM, Wadea FM. Evaluation of thyroid dysfunction in Egyptian chronic hepatitis C virus cirrhotic patients complicated with portalhypertension. Int J Sci Res.2016;5:595-600

27. Kayacetin E, Kisakol G, Kaya A. Low serum Total thyroxine and Free T3 in patient with hepatic encephalopathy due to non-alcoholic cirrhosis. Swiss Med Weekly.2003;133:210-3.

28. El-sawy AA, Tawfik M. low serum free and total T3 hormones as possible prognostic factors in liver cirrhosis patients because of chronic hepatitis C. Tanta Med J.2015;43:46-51

29. Hussein Awad M, Husham O, NassrEldin M, Amna O. Serum Thyroid Hormone Levels in Sudanese Patients with Liver Cirrhosis. IOSR Journal of Pharmacy and Biological Sciences (IOSR-JPBS).2016;11:14-18.

30. Takahashi H, Yamada S. Studies on changes of thyroid hormones in various liver diseases. Usefulness of free thyroid hormones as liver function test. Japanese Journal of Medicine.1989;28(3):297-302.

31. El-Feki M, Abdalla N, Atta M, Ibrahim A. Serum Level of Thyroid Hormones in Patients with Chronic Hepatitis C Virus Infection. Open Journalof Endocrine and Metabolic Diseases.2016;06(03):126-134

32. Oren R, Brill S, Dotan I, Halpern Z. Liver Function in Cirrhotic Patients in the Euthyroid Versus the Hypothyroid State. Journal of Clinical Gastroenterology.1998; 27(4):339-341.