Original Article

DOI: 10.7860/JCDR/2022/55480.16603

Thyroid Dysfunction in Patients with Liver Cirrhosis and its Association with the Severity of Liver Disease: A Cross-sectional Study

Internal Medicine Section

RUKMA JAGANNATH KOLWALKAR[1], GAURI NILAJKAR[2], SAMIDHA NAIK[3], ROMA TELES[4]

ABSTRACT

Introduction: There exists a complex relation between the thyroid hormones and liver physiology in health and disease. The liver along with the thyroid gland play a significant role in the conversion of inactive Thyroxine (T_4) to active Triiodothyronine (T_3). The most common thyroid hormone profile in cirrhosis of liver is a low total T_3 and free T_3, secondary to reduced activity of deiodinase type 1 and increased conversion to reverse Triiodothyronine (rT3).

Aim: To assess the association between the thyroid hormone levels and severity of liver disease, expressed in terms of child pugh score in tertiary care hospital in Goa.

Materials and Methods: This cross-sectional observational study included hundred patients with liver cirrhosis, admitted at a tertiary care hospital in Goa, from October 2019 to September 2020. The thyroid hormone levels were estimated from an early morning fasting blood sample within 24 hours of admission, once the patient satisfied the inclusion criteria. The Child Turgott Pugh scoring system was used to classify patients as per their severity of liver disease. The data was entered and analysed in Statistical Package for Social Sciences (SPSS) software version 14.0.

Results: There were 95 males and 5 females. The study showed low mean levels of total T_4 and free T_3 in patients with cirrhosis of liver, which was significantly associated with Child Pugh classes of liver dysfunction. There was an association between levels of free T_3 and the classes of Child Pugh score. The difference in the mean levels of TSH, total T_3 and free T_4 across the Child Pugh classes were not statistically significant.

Conclusion: The study showed low free T_3 levels in patients with cirrhosis of liver as seen in similar studies done in various settings. Thus, Thyroid Function Tests (TFTs) especially free T_3 levels have a considerable potential to be used an independent predictor or a proxy to prognosis in patients with liver cirrhosis.

Keywords: Child pugh score, Free T_3, Liver dysfunction, Prognosis, Thyroid function test

INTRODUCTION

India belongs to the lower-middle income countries and liver cirrhosis was the 8th leading cause of death among these countries in the year 2019 [1]. India is currently passing through a cultural transition with an escalating adoption of western lifestyle especially sedentary habits and diet including alcohol consumption. This has contributed significantly to the increase in the incidence of liver diseases in India. Liver disease is a leading cause of death in India: it has moved from the 13th to 10th leading cause of death and the number of deaths has nearly doubled since 1990 [2]. In Goa, which is the center of the present study, chronic alcohol use is a major cause of morbidity as well as mortality with as much as 11% of deaths attributed to liver disease secondary to chronic alcohol consumption [3].

There exists a complex interrelation between the thyroid hormones and liver physiology in health and disease. The liver plays an important role in the activation, transport and inactivation of the thyroid hormones. The liver along with the thyroid gland and kidneys is involved in the conversion of inactive Thyroxine (T_4) to active Triiodothyronine (T_3) [4]. It is also the site for synthesis and secretion of the three major thyroid hormone-binding proteins i.e. Thyroxine-Binding Globulin (TBG), transthyretin and albumin which act as carriers of thyroid hormone.

Alteration in thyroid hormone functioning in liver disease is an established fact in medical literature [5]. The most common thyroid hormone profile in cirrhosis of liver is a low total T_3 and free T_3 secondary to reduced activity of deiodinase type 1 and increased conversion to rT_3 [6,7]. These biochemical parameters have been used to see response to medical therapy in patients with Alcoholic Liver Disease (ALD) and also has prognostic implications in these patients [8]. Conversely, low total T_3 and free T_3 levels are regarded as an adaptive hypothyroid state to reduce basal metabolic rate within the hepatocytes and preserve liver function and total body protein stores [9]. On the other hand, the free T_4 levels remain low or unchanged and the TSH levels remain normal or slightly raised in chronic liver diseases [10].

In India, similar to many developing countries, there are a few studies assessing the relation between liver disease and thyroid function and no such study has been reported in the state of Goa. Hence, this study was conducted to assess the association between the thyroid hormone levels and severity of liver disease expressed in terms of child pugh score in tertiary care hospital in Goa [11]. The current study also attempts to evaluate if thyroid hormone levels can be used as an independent predictor of prognosis in patients with liver cirrhosis.

MATERIALS AND METHODS

The cross-sectional observational study was conducted in Department of Internal Medicine at Goa Medical College, Bambolim, Goa, India (tertiary care hospital), from October 2019 to September 2020. Ethics approval was obtained from Institutional Ethics Committee (Letter no IEC-GMC/Oct-!9/E-5) of Goa Medical College and Hospital prior to commencement of the study. The study included 100 patients with liver cirrhosis admitted under the Department of Medicine. The sampling method used was universal sampling, and hence all the patients admitted during the study period who fulfilled the inclusion criteria were included in the study.

Inclusion criteria: Patient aged 12 to 80 years admitted in the Medicine ward with established liver cirrhosis who consented to participate in the study were included.

Exclusion criteria: Patients who had a pre-existing thyroid disease, those on drugs known for interfering with thyroid functions and those in sepsis, cardiac or renal failure were excluded from the study.

Procedure

The diagnosis of cirrhosis was established by radiological means using ultrasound findings showing shrunken coarse echotexture of liver supported by clinical and biochemical parameters. The thyroid hormone levels were estimated using electro-chemiluminescence assay after collecting an early morning fasting blood sample within 24 hours of admission once the patient satisfied the inclusion criteria.

Child Turgott Pugh scoring system

The Child Turgott Pugh scoring system is used to predict prognosis and mortality in patients with liver cirrhosis. Child Pugh score is calculated using serum bilirubin, serum albumin, prothrombin time, grade of hepatic encephalopathy and ascites [11]. Scores representing the increasing severity of liver dysfunction:

- Score 5-6: Class A
- Score 7-9: Class B
- Score 10-15: Class C

STATISTICAL ANALYSIS

The data was entered and analysed in Statistical Package for Social Sciences (SPSS) software version 14.0. The continuous variables were expressed in mean±SD while categorical variables were expressed in frequency and percentage. The Analysis of Variance (ANOVA) was used to test the significance of continuous variables within classes. In all tests a p-value <0.05 was considered statistically significant.

RESULTS

A total of 100 patients admitted with cirrhosis were included in the study, of which 95 were males and five were females. Based on the child turgott pugh score, class A included 15 patients, class B included 26, and class C included 59 patients. Thus a majority of 59 patients came at advanced stage of liver dysfunction. There was no significant difference in mean age across the three child pugh categories, with a p-value of 0.73 [Table/Fig-1].

Child pugh class	n	Mean age (years) (Mean±SD)	p-value
Class A	15	47.87±11.54	0.73
Class B	26	45.62±10.49	
Class C	59	47.27±9.62	
Total	100	46.93±10.08	

[Table/Fig-1]: Frequency distribution of class of child pugh score and its association with age.

[Table/Fig-2] shows the mean levels of total T_3, T_4, TSH and free T_3, free T_4 in the different child pugh categories and its association with thyroid hormone levels. The mean levels of total T_4 were highest i.e. 6.92 µgm/dL in child pugh category A. Whereas, the mean total T_4 levels were lowest i.e. 5.56 µgm/dL in child pugh category C. Also, there was a statistically significant difference in mean total T_4 levels across the child pugh classes, with an F-statistic of 3.59 and a p-value of 0.031. This implies that patients with severe liver disease had a lower level of total T_4.

Similarly, there was a statistically significant difference in mean levels of free T_3 across the three child pugh classes, with the highest mean level of free T_3 i.e. 2.2 pg/mL being reported in the child pugh class B. In contrast, there was no significant difference in mean total T_3, Free T_4 and TSH levels across the child pugh categories of liver cirrhosis.

Based on the statistically significant association between total T_4 and free T_3, these were subjected to posthoc analysis to assess if there was a statistically significant association within the class. As depicted in [Table/Fig-3], the intraclass comparison was not statistically significant for mean total T_4 levels. In contrast, there was a statistically significant difference in the mean free T_3 levels across the child pugh class B and class C with a with a p-value of 0.02. This could indicate an association of free T_3 levels with a higher child pugh score.

Thyroid Function Tests (TFTs)		Mean difference (Mean±SD)	Standard error	95% CI for mean		F Statistic	p-value
				Lower bound	Upper bound		
Total T_3 (ng/mL)	Class A	0.81±0.35	0.09	0.61	1.00	0.43	0.65
	Class B	0.91±0.42	0.08	0.74	1.08		
	Class C	0.84±0.39	0.05	0.73	0.94		
	Total T3	0.85±0.39	0.04	0.77	0.93		
Total T_4 (µgm/dL)	Class A	6.92±1.86	0.48	5.89	7.95	3.59	0.031
	Class B	6.50±2.09	0.41	5.66	7.35		
	Class C	5.56±2.12	0.28	5.01	6.11		
	Total T3	6.01±2.13	0.21	5.59	6.43		
TSH (µIU/mL)	Class A	2.47±1.28	0.33	1.76	3.17	2.56	0.08
	Class B	2.08±1.09	0.21	1.64	2.52		
	Class C	1.69±1.32	0.17	1.35	2.04		
	Total T3	1.91±1.28	0.13	1.66	2.16		
Free T_3 (pg/mL)	Class A	1.88±0.49	0.13	1.61	2.15	4.01	0.02
	Class B	2.21±0.76	0.15	1.90	2.51		
	Class C	1.72±0.75	0.10	1.53	1.92		
	Total T3	1.87±0.74	0.07	1.73	2.02		
Free T_4 (µgm/dL)	Class A	1.06±0.17	0.04	0.97	1.15	0.61	0.54
	Class B	0.99±0.19	0.04	0.91	1.06		
	Class C	0.99±0.23	0.03	0.94	1.06		
	Total T3	1.00±0.21	0.02	0.96	1.05		

[Table/Fig-2]: Comparison of mean levels of TFTs across classes of child pugh score {Class A (n=15), Class B (n=26), Class C (n=59) and Total T3 (n=100)}. p-value <0.05 was considered significant

TFTs vs Child pugh class			Mean difference	Standard error	p-value	95% CI	
						Lower bound	Upper bound
Total T_4 (µgm/dL)	Class A	B	0.42	0.67	0.81	-1.19	2.02
		C	1.36	0.60	0.06	-0.06	2.79
	Class B	A	-0.41	0.67	0.81	-2.02	1.19
		C	0.95	0.49	0.13	-0.21	2.11
	Class C	A	-1.36	0.60	0.06	-2.79	0.06
		B	-0.95	0.49	0.13	-2.11	0.21
Free T_3 (pg/mL)	Class A	B	-.033	0.23	0.34	-0.89	0.23
		C	0.15	0.21	0.74	-0.34	0.65
	Class B	A	0.33	0.23	0.34	-0.23	0.89
		C	0.48	0.17	0.02	0.08	0.89

[Table/Fig-3]: Posthoc analysis (Tukey HSD) showing pairwise comparison of mean total T_4 and Free T_3 levels across class of child pugh score. p-value <0.05 was considered significant

DISCUSSION

The present study was designed to assess the association between the thyroid hormone levels and severity of liver disease expressed in terms of child pugh score. A majority of the patients enrolled in the study were males. This could be due to the fact that chronic alcohol use is a major contributor toward liver disease related mortality in Goa and the prevalence of male pattern of alcohol consumption reported among the Goa population [3,12]. A majority of the patients enrolled in the study belonged to the child pugh class C, thus had a severe liver dysfunction, based on the child pugh classification.

The levels of mean total T_4 and free T_3 were found to be lower in patients with higher child pugh score. On assessment of difference in mean thyroid hormone levels, it was observed that there was a significant difference in mean T_4 and free T_3 across the three child pugh classes of severity of liver disease. This finding suggests an association between mean T_4 and free T_3 across the classes of child pugh classes. In contrast, there was no such statistical association between T_3, free T_4, and TSH levels across the child pugh classes. This findings are similar to a study done in Lucknow, India by Verma

SK et al., where it is reported that a lower free levels are found in patients with increasing severity of liver disease [13]. Similar findings were reported by Patira NK et al., in Rajasthan, India, Taş A et al., in Turkey and Kayacetin E et al., in Turkey [14-16].

There are several hypothesis postulated for the low levels of free T_3 observed in severe liver disease. The most common hypothesis for the low free T_3 levels in liver disease is the reduced levels of Type I deiodinase and hence reduced peripheral conversion of T_4 to T_3 [15,17-20]. Alcohol intake is also associated with impaired deiodinase activity [21]. Since chronic alcohol use contributes to the majority of liver disease in Goa, it may be a contributing factor in reduced levels of total T_4 and free T_3 observed it the study findings [3]. Also, release of inflammatory cytokines has been postulated as a factor responsible for low thyroid hormone levels in liver disease which acts by reducing deiodinase activity [22].

In the current study, there was no significant association between free T_4 and TSH levels across the child pugh classes of liver dysfunction. This finding was similar to that reported by Mansour-Ghanaei F et al., in Iran [23]. The studies done by Hepner GW and Chopra IJ, in United States, Penteado KR et al., in Brazil and Malik R and Hodgson H in London reported that there was no association between TSH levels and severity of liver dysfunction [24-26].

The posthoc analysis suggests a significant difference only for mean free T_3 levels between class B and class C. The difference between mean total T_4 levels across each class of child pugh classes was not significant on posthoc analysis. However, due to these confounding level of significance on posthoc analysis, a larger study with a bigger sample size is needed to reaffirm these findings.

Limitation(s)

One of the limitation of present study is its cross-sectional observational design. The findings do not establish a causal relationship between liver cirrhosis and low free T_3 levels which can be addressed by having a prospective design with a larger sample size.

CONCLUSION(S)

Although, the posthoc analysis only showed a statistically significant difference between child pugh class B and class C, low free T_3 levels are found in patients with cirrhosis of liver as seen in similar studies done in various settings. Also, the levels associate inversely with severity of liver disease determined by child pugh score. Thus, TFTs especially free T_3 levels have a considerable potential to be used an independent predictor or a proxy to prognosis in patients with liver cirrhosis. Since, the current study was an observational cross-sectional study, no causal relationship could be established. Also a larger sample size and control arm can help in more detailed analysis and extrapolation of the findings to general population.

REFERENCES

[1] World Health Organization. The top 10 causes of death. Geneva, Switzerland: WHO; 2020. Available from: https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death.
[2] Ritchie HA, Roser M. Causes of Death. Our World in Data. [Internet] 2018. Available from: http://ourworldindata.org/causes-of- death.
[3] Borkar S. Emerging disease death profile of Goa: What changed with time? Int J Health Sci (Qassim). 2016;18(1):31-48.
[4] Jameson JL, Mandel SJ, Weetman AP. Thyroid Gland Physiology and Testing. In: Jameson J, Fauci AS, Kasper DL, Hauser SL et al. (ed.). Harrison's Principles of Internal Medicine. 20th ed. McGraw Hill; 2018. p. 2692-98.
[5] Piantanida E, Ippolito S, Gallo D, Masiello E, Premoli P, Cusini C, et al. The interplay between thyroid and liver: Implications for clinical practice. Journal of endocrinological investigation. 2020;43(7):885-99.
[6] L'age M, Meinhold H, Wenzel KW, Schleusener H. Relations between serum levels of TSH, TBG, T4, T3, rT3 and various histologically classified chronic liver diseases. Journal of Endocrinological Investigation. 1980;3(4):379-83.
[7] Faber J, Thomsen HF, Lumholtz IB, Kirkegaard C, Siersbaek-Nielsen K, Friis T. Kinetic studies of thyroxine, 3,5,3'-triiodothyronine, 3,3,5'-triiodothyronine, 3',5'-diiodothyronine, 3,3'-diiodothyronine, and 3'-monoiodothyronine in patients with liver cirrhosis. J Clin Endocrinol Metab. 1981;53(5):978-84.
[8] Van Thiel DH, Udani M, Schade RR, Sanghvi A, Starzl TE. Prognostic value of thyroid hormone levels in patients evaluated for liver transplantation. Hepatology. 1985;5(5):862-66.
[9] Deepika G, Veeraiah N, Rao PN, Reddy DN. Prevalence of hypothyroidism in liver cirrhosis among Indian patients. Int J Pharm Med Res. 2015;3(3):04-07.
[10] Green JR, Snitcher EJ, Mowat NA, Ekins RP, Rees LH, Dawson AM. Thyroid function and thyroid regulation in euthyroid men with chronic liver disease: Evidence of multiple abnormalities. Clinical Endocrinology. 1977;7(6):453-61.
[11] Tsoris A, Marlar CA. Use of the Child Pugh score in liver disease. StatPearls Publishing; 2022 Jan.
[12] D'Costa GL, Nazareth I, Naik D, Vaidya R, Levy G, Patel V, et al. Harmful alcohol use in Goa, India, and its associations with violence: a study in primary care. J Family Med Prim Care. 2007;42(2):131-37.
[13] Verma SK, Kumar V, Tiwari P, Joge NK, Misra R. Thyroid profile in patients of cirrhosis of liver: A cross-sectional study. J Clin Diagn Res. 2017;11(12):OC06-09.
[14] 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):51-54.
[15] Taş A, Köklü S, Beyazit Y, Kurt M, Sayilir A, Yeşil Y, et al. Thyroid hormone levels predict mortality in intensive care patients with cirrhosis. Am J Med Sci. 2012;344(3):175-79.
[16] 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(13-14):210-13.
[17] Dehghani SM, Haghighat M, Eghbali F, Karamifar H, Malekpour A, Imanieh MH, et al. Thyroid hormone levels in children with liver cirrhosis awaiting a liver transplant. Exp Clin Transplant. 2013;11(2):150-53.
[18] Al-Jarhi UM, Awad A, Mohsen M. Low serum free triiodothyronine is associated with increased risk of decompensation and hepatocellular carcinoma development in patients with liver cirrhosis. Open Journal of Gastroenterology. 2016;6(6):166-74.
[19] Kamath PS, Kim WR. The model for end-stage liver disease (MELD). Hepatology. 2007;45(3):797-05.
[20] El-Kabbany ZA, Hamza RT, Abd El Hakim AS, Tawfik LM. Thyroid and hepatic haemodynamic alterations among Egyptian children with liver cirrhosis. International Scholarly Research Notices. 2012;2012:595734.
[21] Rachdaoui N, Sarkar DK. Effects of alcohol on the endocrine system. Endocrinol Metab Clin North Am. 2013;42(3):593-615.
[22] Gionfra F, De Vito P, Pallottini V, Lin HY, Davis PJ, Pedersen JZ, et al. The role of thyroid hormones in hepatocyte proliferation and liver cancer. Front Endocrinol (Lausanne). 2019;10:532.
[23] 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.
[24] Hepner GW, Chopra IJ. Serum thyroid hormone levels in patients with liver disease. Arch Intern Med. 1979;139(10):1117-20.
[25] Penteado KR, Coelho JC, Parolin MB, Matias JE, Teixeira de Freitas AC. The influence of end-stage liver disease and liver transplantation on thyroid hormones. Arq Gastroenterol. 2015;52(2):124-28.
[26] Malik R, Hodgson H. The relationship between the thyroid gland and the liver. QJM. 2002;95(9):559-69.

PARTICULARS OF CONTRIBUTORS:
1. Assistant Professor, Department of Internal Medicine, Goa Medical College, Bambolim, Goa, India.
2. Assistant Professor, Department of Internal Medicine, Goa Medical College, Bambolim, Goa, India.
3. Senior Resident, Department of Internal Medicine, Goa Medical College, Bambolim, Goa, India.
4. Junior Resident, Department of Internal Medicine, Goa Medical College, Bambolim, Goa, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Rukma Jagannath Kolwalkar,
Kesar, H. No. 138/7, Angod, Mapusa, Goa, India.
E-mail: rukmadk@gmail.com

PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Feb 17, 2022
- Manual Googling: Apr 20, 2022
- iThenticate Software: Jun 04, 2022 (11%)

ETYMOLOGY: Author Origin

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Feb 13, 2022**
Date of Peer Review: **Apr 06, 2022**
Date of Acceptance: **Apr 21, 2022**
Date of Publishing: **Jul 01, 2022**