Comparison of Triiodothyronine (T3), Tetraiodothyronine (T4), Freethyoxine (FT4), Thyroid Stimulating Hormone (TSH) Levels in with Liver Cirrhosis Patients Based on Child-Pugh Score at H. Adam Malik Central General Hospital, Medan

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ABSTRACT

Background: *The liver is involved in thyroid hormone conjugation and excretion, as well as the synthesis of thyroid binding globulin. Tetraiodothyronine (T4) and Triiodothyronine (T3) regulate the basal metabolic rate of all cells.*

Method: *The sample of this research was collected crosssectionally on 40 patients with liver cirrhosis based Child-Pugh score. Ultrasonography and T3, T4, freethyoxine (FT4), thyroid stimulating hormone (TSH) levels examinations to know the difference between liver cirrhosis patients with Child-Pugh A, B, and C with enzyme-linked immunosorbent assay (ELISA) method.*

Results: *Statistical analysis showed there are not found significant differences in T3, T4, FT4, TSH levels in patients with of the liver cirrhosis based on the Child-Pugh score.*

Conclusion: *Not found significant differences in thyroid hormone levels among patients with liver cirrhosis Child-Pugh A, B, and C.*

Keywords: *liver cirrhosis, triiodothyronine (T3), tetraiodothyronine (T4), freethyxonine (FT4), thyroid stimulating hormone (TSH), Child-Pugh score*

ABSTRAK

Latar belakang: *Hati terlibat dalam konjugasi hormon tiroid dan ekskresi, serta sintesis tiroid binding globulin. Tetraiodothyronine (T4) dan triiodothyronine (T3) mengatur tingkat metabolisme basal dari semua sel. Perubahan T3 berkorelasi dengan tingkat keparahan penyakit dan sebagai prognosis sirosis hati.*

Metode: *Dilakukan dengan desain cross sectional terhadap 40 penderita sirosis hati berdasarkan ChildPugh score. Dilakukan ultrasonografi dan pemeriksaan kadar T3, T4, freethyoxine (FT4), thyroid stimulating hormone (TSH) untuk mengetahui perbedaan antara pasien sirosis hati dengan ChildPugh A, B dan C dengan metoda enzyme linked immune sorbent assay (ELISA).*

Hasil: *Secara statistik tidak dijumpai perbedaan yang signifikan kadar T3,T4,FT4,TSH pada penderita sirosis hati berdasarkan ChildPugh score.*

Simpulan: *Tidak dijumpai perbedaan yang signifikan pada kadar T3,T4,FT4,TSH pada penderita sirosis hati berdasarkan ChildPugh score.*

Kata kunci: *sirosis hati, triiodothyronine (T3), tetraiodothyronine (T4), freethyoxine (FT4), thyroid stimulating hormone (TSH), child pugh score*

INTRODUCTION

The liver an important at thyroid metabolisms such as conjugation, excretion, peripheral deiodination, and synthesis thyroid-binding globulin (TBG). Over 60% of tetraiodothyronine (T4) is converted to triiodothyronine (T3) at the liver. This change represents biochemical changes due to liver dysfunction and pathological changes associated with organ damage.[1]

The special purpose of this research is to finding the demographic and clinical characteristics of liver cirrhosis patients, to investigate the differences in T3, T4, Freethyoxine (FT4), thyroid stimulating hormone (TSH) levels in patients with liver cirrhosis based on Child-Pugh score A, B, and C in the period between October-November 2017 and to determine the effects of changes in thyroid hormone in patients with liver cirrhosis.

METHOD

This is a cross-sectional descriptive analytic study which was conducted at October-November 2017 in H Adam Malik General Hospital Medan on 40 hospitalized liver cirrhosis patients according to Child-Pugh score. All of them fulfills inclusion and exclusion criteria and blood samples were liver function tests (aspartate aminotransferase/AST, alanine aminotransferase/ALT, serum albumin, serum bilirubin, viral markers of hepatitis, thyroid function T3, T4, FT4, TSH using enzyme linked immune sorbent assay (ELISA) and ultrasonography (USG) of the abdomen.

SPSS version 22 (SPSS Inc.,Chicago) was used for the analysis. The data were analysed using unpaired numerical comparative analytic with 95% confidence interval. Data in an analysis using Kruskal Wallis test with the power of study is 90%. To assess the correlation between T3, T4, FT4, and TSH with the liver function using Spearmen correlation test with a significance levels set at $p < 0.05$.

RESULTS

In this study, the subjects are liver cirrhosis 40 patients. The results of this research are explained by the following tables. Table 1 shown as many as 22 men (55%) and women 18 (45%) with an average age of subjects was 47.43 years. Serology results showed 22 people (55%) positive subjects of hepatitis B, only 1 person (2.5%) subjects with hepatitis C, the rest did not found the virus. Some subjects (50%) had a history of consuming alcohol and 27 (67.5%) subjects with Child-Pugh C.

Table 1. Study subjects characteristics (n = 40)

Characteristics of the subject	n (%)
Gender, n (%)	
Man	22 (55)
Women	18 (45)
Age, average (SD), year	47.43 (13.72)[a]
Body mass index, the mean (SD), kg/m^2	21.78 (4.12)[b]
Tribe, n (%)	
Acehnese	1 (2.5) [a]
Bataknese	20 (50)
Javanese	5 (12.5)
Karonese	3 (7.5)
Melayunese	10 (25)
Padangnese	1 (2.5)
Roughing, n (%)	
Housewife	11 (27.5) [a]
Civil servants	3 (7.5)
Employee	7 (17.5)
Farmer	19 (47.5)
Etiology, n (%)	
Hepatitis B	22 (55) [a]
Hepatitis C	1 (2.5)
Non-B Non-C	17 (42.5)
Child-Pugh, n (%)	
A	6 (15) [a]
B	7 (17.5)
C	27 (67,5)

[a] Categorical Data : n (%); [b] Mean (SD)

Table 2. Laboratory test results

Laboratorium	n = 40
Aspartate aminotansferase/AST (mg/dL)	40,50 (8 - 311)[b]
Alanine aminotransferase/ALT (mg/dL)	33,50 (8 - 577)[b]
Alkaline phospatase/ALP (mg/dL)	85 (20 - 467)[b]
Billirubin direk (mg/dL)	1,60 (0,10 - 19)[b]
Billirubin total (mg/dL)	3,50 (0,20 - 29,80)[b]
Albumin (mg/dL)	2,20 (1,40 – 3,90)[b]
Thyroid stimulating hormone/TSH (µIU/mL)	1.57 (0,01- 7,57)[b]
Triiodothyronine (T3) (ng/mL)	0,51 (0,24)[a]
Tetraiodothyronine (T4) (µg/dL)	4.84 (1,19-18,02)[b]
Freethyoxine (T4) (ng/dL)	0,90 (0,40-10,99)[b]

[a] Numerical data, normal distribution: mean (standard deviation)
[b] Numerical dat a, abnormal distribution: median (minimum-maximum)

Table 2 shows show median value (min-max), laboratory result of liver and thyroid function. Median (min-max) AST is 40.50 (8-311). Median (min-max) ALT is 33.50 (8 - 577), Median (min-max) ALP is 85 (20-467). Median (min-max) Billirubin direct is 1.60 (0.10-19). Median (min-max) The total billirubin

is 3.50 (0.20-29.80). Median (min-max) albumin is 2.20 (1.40-3.90). Median (min-max) globulin is 3.40 (0.85-5.30). Median (min-max) PT is 1.40 (0.83 -4.12). Median (min-max) TSH is 1.57 (0.01-7.57). The median (min-max) T3 is 0.46 (0.25-1.22). Median (min-max) T4 is 4.84 (1.19-18.02). The median (min-max) FT4 is 0.90 (0.40-10.99).

Table 3 shows the six markers of liver function only albumin and PT had a significant correlation with one of the thyroid hormone T4 ($p < 0.05$). Albumin has a moderately significant correlation ($p = 0.008$) and is positive ($r = 0.415$) with T4, meaning an increase in albumin levels will be followed by an increase in T4 levels.

Table 3. Correlation of Triiodothyronine (T3), Tetraiodothyronine (T4), Freethyoxine (FT4), thyroid stimulating hormone (TSH) and liver functions

		p	r
Aspartate aminotransferase (AST)	T3	0,400	0,137
	T4	0,982	0,004
	FT4	0,421	0,131
	TSH	0,265	0,180
Alanine aminotransferase (ALT)	T3	0,319	0,162
	T4	0,202	0,206
	FT4	0,263	0,181
	TSH	0,690	0,065
Alkaline phospatase (ALP)	T3	0,837	0,034
	T4	0,834	-0,034
	FT4	0,819	-0,037
	TSH	0,423	0,130
Direct billirubin	T3	0,723	0,058
	T4	0,242	-0,189
	FT4	0,913	-0,018
	TSH	0,729	-0,057
Total billirubin	T3	0,920	0,016
	T4	0,113	-0,254
	FT4	0,388	-0,140
	TSH	0,879	-0,025
Albumin	T3	0,509	0,108
	T4	0,008*	0,415
	FT4	0,218	0,199
	TSH	0,516	0,106

*p < 0,05

Table 4 shows Correlation of Differences Levels T3, T4, FT4, TSH Based on Child-Pugh Score.

Tabel 4. Correlation of differences levels Triiodothyronine (T3), Tetraiodothyronine (T4), Freethyoxine (FT4), thyroid stimulating hormone (TSH) based on Child-Pugh score

	CP A (n=6)	CP B (n=7)	CP C (n=27)	p
Triiodothyronine (T3)	0,47 (0,46)	0,54 (0,19)	0,51 (0,18)	0,861
Tetraiodothyronine (T4)	8,71 (2,95)	4,80 (3,08)	5,85 (3,76)	0,063
Freethyoxine (FT4)	0,97 (0,57)	2,21 (3,89)	1,14 (0,97)	0,827
thyroid stimulating hormone (TSH)	1,49 (1,78)	2,26 (1,67)	1,65 (1,41)	0,315

DISCUSSION

From the results of greater than that of 22 patients (55%) and 18 (45%). The ratio between men and women is 1.2: 1. This result is in accordance with previous studies. the number of men suffering from cirrhosis was greater than that of 22 patients (55%) and 18 (45%). The ratio between men and women was 1.2: 1. In a study conducted by Patira et al in USA in 2017 reported that more men had liver cirrhosis (78%) in the United States.[8] While the study of Joeimon J L et al in 2017 in Indian reported the majority of patients with liver cirrhosis were male (72%).[3] El-Feki et al reported that 66.7% of liver cirrhosis in Egypt were male.[4] While the study by Rey I (2012) in Medan reported 72.5% of subjects with liver cirrhosis were male.[5]

The average liver cirrhosis patients in this study aged 47.42 years, which is classified as productive age. The mean age in this study also did not differ from previous studies. Studies by Mobin et al in 2016 in Pakistan reported an average age of 50.57 years of liver cirrhosis patients.[6] While Wang et al in 2016 in China reported an average age of 46 + 12 years of liver cirrhosis patients.[7] Rey I et al in 2012 in Medan reported the mean age of patients with age-bearing liver cirrhosis was 50, 95 years.[5]

In this study, the most etiological causes of cirrhosis of the liver are hepatitis B 22 (55%), hepatitis C 1 (2.5%) and Non B Non C 17 (42.5). In contrast to the results of a study by Joeimon J L et al in 2017 in India in 111 patients it was reported that the etiology of most causes of cirrhosis were 64 patients with ethanol, hepatitis B 21 patients, hepatitis C 5 patients and autoimmune 5 patients.[3] The results study of Patira et al in 2017 in India reported that the most aetiological causes of cirrhosis were alcohol (70%) patients, hepatitis B 13 (26%) patients and hepatitis C 2 (4%) patients.[8] The results of Khean et al in 2011 in Malaysia reported that the most aetiological causes of cirrhosis were hepatitis B 212 (46.1%) patients, hepatitis C 8 5 (18.5%) patients, 58 patients (12.6%), Kryptogenic 71 (15.4%) patients, 58 alcohol (12.6%) patients and autoimmune 9 (2%) patients.[9]

The majority of the subjects included Child-Pugh C 27 (67.5%) patients. This is consistent with a study by Verma et al reported in 2017 in India that 102 patients with Child-Pugh C 56.8% (n = 58), Child-Pugh B 39.8% (n = 40) and Child-Pugh A 3.9% (n = 4). This suggests that most subjects have advanced stages with decompensated liver cirrhosis.[11]

In this study, the mean T3 shows no significant correlation between with Child-Pugh Child-Pugh score

(p = 0.861). The highest T3 levels were found in Child-Pugh B with a mean of 0.54 and the lowest in Child-Pugh A with a mean of 0.47. This is in accordance with research Eshraghian et al in 2014 in Iran reported that patients with liver cirrhosis had low T3.[12] This is due to a decrease in D1 activity and the impaired hepatic T4 conversion when the conversion becomes T3. This is also in accordance with the study of Mansour et al in 2012 in Egypt who reported that in liver cirrhosis occurs binding protein disorders, adaptive hypothyroidism occurs to reduce BMR in hepatocytes and disruption of total body protein availability due to malnutrition and liver defense mechanisms.[13]

In this study, the mean T4 shows no significant correlation between with Child-Pugh score (p = 0.063). The highest T4 levels were found in Child-Pugh A with the mean of 8.71 and lowest on Child-Pugh B with the mean of 4.80. According to research by Antonelli et al in 2004 that low T4 levels in patients with advanced liver cirrhosis are due to decreased metabolism of T4 and increased T3. This probably depends on the extent of hepatocellular damage and repair in liver function so that T4 can be a prognostic index.[11] Malik R et al in 2002 in explains that the liver plays a major role in the conversion of T4 in the periphery.[14]

In this study, the mean TF4 shows no significant correlation between with Child-Pugh score (p = 0.827). The highest FT4 levels were found in Child-Pugh B with the mean of 2.21 and lowest in Child-Pugh A with the mean of 0.97. Based on the research Malik R et al in 2002 that the normal FT4 levels in patients chronic liver disease.[14] However, this is in contrast to Antonelli et al in 2004 reporting a significant increase in FT4 in cirrhosis groups. This is due to the different geographic distribution, population genetic background, and environmental factors, such as iodine intake or infectious agents.[11] Elkabbany et al in 2012 reported that there was no significant difference in F T4 levels in patients with liver cirrhosis.[16]

In this study, the mean TSH shows no significant correlation between with Child-Pugh score (p = 0.315). The highest TSH levels were found in Child-Pugh B with the mean of 2.26 and the lowest in Child-Pugh A with an average of 1.49. Based on the results of TSH found that experienced 80% euthyroid and 20% hypothyroid. This is consistent with the research of Antonelli et al in 2009 that abnormalities in TSH secretion are caused by presence hypothalamic-pituitary dysfunction in advanced liver disease and body adjustment of liver cirrhosis and basal metabolic rate savings, decreased dopaminergic as a consequence of the accumulation of false neurotransmitters that may be responsible for increasing basal TSH concentrations, as dopamine has been shown to have an inhibitory effect on regulation TSH secretion.[11] This is also consistent with the study of Moustafa et al in 2009 who reported that elevated serum TSH levels in decompensated cirrhosis patients were compared with compensated cirrhosis patients.[15] This is in accordance with Ghanaei et al in 2014 that TSH levels are higher in patients with cirrhosis with Child-Pugh score C. There is a positive correlation between TSH levels and Child-Pugh score scores in patients with liver cirrhosis.[17]

The limitations of this study are it is this study is not to consider the geographical area of research subjects such as living in mountainous areas affecting iodine intake. Not found significant differences in T3, T4, FT4, TSH levels in patients with cirrhosis of the liver based on Child-Pugh score. Level of T3, FT4, and TSH can not correlation with the severity of liver disease.

CONCLUSION

In conclusion, that thyroid hormone levels did not different significantly among patients with liver cirrhosis Child-Pugh A, B and C.

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