Correlation between Serum Albumin and Fasting Blood Glucose Level in Patients with Liver Cirrhosis

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ABSTRACT

Background: *Liver cirrhosis is a pathological condition describes the end-stage of liver fibrosis. On liver damage may occur impaired glucose metabolism such as insulin resistance and glucose intolerance. The correlation between chronic liver diseases with impaired glucose metabolism has been known as hepatogenous diabetes. Albumin levels were significantly affected by poorly controlled blood glucose seen from the high HbA1c. This study aims to determine correlation of serum albumin level and fasting blood glucose level in patients with liver cirrhosis.*

Method: *This cross-sectional study was conducted in 52 patients with liver cirrhosis in Gastroentero-hepatology Clinic and Inpatients, Hasan Sadikin Hospital. The study was conducted from February to June 2013. History taking, physical examination and laboratory tests including liver function tests and fasting blood glucose were performed. Data were analyzed using Spearman rank test for the correlation.*

Results: *There were 31 (59.6%) males and 21 (40.4%) females with mean age 53.4 ± 12.8 years. The mean serum albumin was 2.7 ± 0.5 g/dL and median fasting blood glucose was 100 (66-195) mg/dL. Etiology of liver cirrhosis was hepatitis B virus infection 28 (51.9%), hepatitis C virus infection 16 (30.8%) and non-viral hepatitis B and C infection 9 (17.3%). Severity of cirrhosis scored using child turcotte pugh (CTP) which was 43 (82.7%) of CTP B and 9 (17.3%) of CTP C. There was statistically significant correlation between albumin level and fasting blood glucose with* $\rho = -0.630$ *and* $p < 0.01$.

Conclusion: *In patients with liver cirrhosis have low serum albumin level correlates with high fasting blood glucose.*

Keywords*: cirrhosis, albumin, fasting blood glucose*

ABSTRAK

Latar belakang: *Sirosis hati adalah suatu kondisi patologis yang menggambarkan fase akhir fibrosis hati. Pada kerusakan hati mungkin terjadi gangguan metabolisme glukosa seperti resistensi insulin dan intoleransi glukosa. Korelasi antara penyakit hati kronis dengan metabolisme glukosa yang terganggu dikenal sebagai diabetes hepatogenous. Kadar albumin dipengaruhi secara signifikan oleh glukosa darah yang tidak terkendali yang dapat dilihat dari tingginya HbA1c. Penelitian ini bertujuan untuk mengetahui hubungan kadar serum albumin dan kadar glukosa darah puasa pada pasien dengan sirosis hati.*

Metode: *Penelitian cross-sectional ini dilakukan pada 52 pasien dengan sirosis hati di klinik Gastroentero-hepatologi dan pada pasien rawat inap, Rumah Sakit Hasan Sadikin. Penelitian dilakukan dari bulan Februari hingga Juni 2013. Rekam pemeriksaan fisik dan tes laboratorium termasuk tes fungsi hati dan glukosa darah puasa ditampilkan. Data dianalisis dengan menggunakan Spearman rank test untuk korelasi.*

Hasil: *Didapatkan 31 (59,6%) laki-laki dan 21 (40,4%) perempuan dengan rerata usia 53,4 ± 12,8 tahun. Rerata serum albumin adalah 2,7 ± 0,5 g / dL dan median glukosa darah puasa adalah 100 (66-195) mg / dL. Penyebab sirosis hati adalah infeksi virus hepatitis B 28 (51,9%), infeksi virus hepatitis C 16 (30,8%), dan non virus hepatitis B dan infeksi C 9 (17,3%). Keparahan sirosis dinilai menggunakan child turcotte pugh (CTP) yaitu sejumlah 43 (82,7%) dari CTP B dan 9 (17,3%) dari CTP C. Ada hubungan yang signifikan secara statistik antara kadar albumin dan glukosa darah puasa dengan* $\rho = -0,630$ *dan* $p < 0,01$.

Simpulan: *Pada pasien rawat inap dengan sirosis hati, kadar serum albumin yang rendah berkorelasi dengan glukosa darah puasa yang tinggi.*

Kata kunci: *sirosis, albumin, kadar glukosa darah puasa*

INTRODUCTION

Liver cirrhosis (LC) is a pathological condition that describes the end-stage of hepatic fibrosis characterized by progressive distortion of hepatic architecture and formation of regenerative nodules. There has been no official national data on LC in Indonesia. However, overall average prevalence of cirrhosis was 3.5% of all patients hospitalized in internal medicine wards or an average of 47.4% of all liver diseases.[1,2]

Liver plays an important role in glucose metabolism and can store glycogen and glucose production through glycogenolysis and gluconeogenesis. Liver damage may occur glucose metabolism disorders. Patients with liver cirrhosis may have glucose intolerance and insulin resistance caused by impaired post- receptor, decreased ability of insulin binding to the target organ and the inability of pancreatic β cells to response the need of insulin. One of metabolic complications in LC known as hepatogenous diabetes (HD). More than 96% of patients had cirrhosis and 30% glucose intolerance is clinically diabetes. Diabetes will appear clinically as impaired liver function, so the HD can be used as an indicator of advanced liver disease. Furthermore, the etiology of liver disease is important in the incidence of diabetes: non-alcoholic fatty liver disease (NAFLD), alcohol, hepatitis C virus (HCV) and haemochromatosis are more frequently associated with diabetes.[3.4.5] Segade et al showed a negative correlation between HbA1c and serum albumin in patients with type 2 diabetes mellitus (T2DM). Albumin level were significantly affected by uncontrolled blood glucose seen from the high HbA1c, however, the opposite effect is still unknown.[6] Benedict et al reported increased protein destruction in diabetes mellitus (DM). Several studies have shown this metabolic disorder in type 1 DM (T1DM). Insulin deficiency is a protein catabolic state. However, protein metabolism in T2DM is still not consistent.[7,8] This study aims to determine correlation between serum albumin level and fasting blood glucose level in patients with liver cirrhosis.

METHOD

This is a cross-sectional study on liver cirrhosis patients in the Gastroentero-hepatology Clinic and Inpatients in Hasan Sadikin Hospital, Bandung. The study was conducted from February to June 2013. Inclusion criteria were patients with liver cirrhosis and willing to participate in this study. Exclusion criteria were patients with hepatocellular carcinoma, patients with type 1 diabetes, type 2 diabetes mellitus patients on insulin therapy, patients with acute infection or acute metabolic stress and patients with history of steroid for previous 6 months.

The selection of subjects based on arrival during the study period. Sample size was determined using the formula for the correlation analysis. Fifty two subjects were required in this study. Anamnesis, physical examination and laboratory tests (liver function tests including albumin and fasting blood glucose level) was performed on all subjects.

Serum albumin was independent variable and fasting blood glucose level was dependent variable. Analysis of correlation child turcotte pugh (CTP) components including albumin and fasting blood glucose (FBG) level used Spearman rank correlation test. The strength of correlation coefficient (r) based on Guilford criteria. Data were analyzed using SPSS version 17.0 for Windows with a significance value of $p < 0.05$.

RESULTS

Of the 52 subjects, 31 (59.6%) males and 21 (40.4%) females were included in this study. The mean age was 53.4 ± 12.8 years. No patient experienced hepatic encephalopathy. Patients with grade 1 ascites was 20 (38.5 %), grade 2 in 23 patients (44.2%) and grade 3 in 9 patients (17.3%). Etiology of liver cirrhosis was hepatitis B virus infection of 27 (51.9%) patients, hepatitis C virus infection of 16 (30.8%) and non-hepatitis B and C virus infections of 9 (17.3%)

patients. Median fasting blood glucose 100 (66-195) mg/dL. The mean serum albumin 2.7 ± 0.5 g/dL and the mean prothrombin time (PT) was 16.9 ± 2.7 seconds.

Table 1. Baseline Characteristic of the Subjects

Parameter	Mean ± SD Median (Min - Max) n (%)
Sex	
Male	31 (59.6)
Female	21 (40.4)
Age (years)	53.4 ± 12.8
Jaundice	13 (25.0)
Spleen enlargement	
Occupied of Traube space	47 (90.4)
Schuffner 1	1 (1.9)
Schuffner 2	4 (7.7)
Grade of ascites	
1	20 (38.5)
2	23 (44.2)
3	9 (17.3)
Hepatitis virus infection	-27 (51.9)
B	16 (30.8)
C	9 (17.3)
Non B Non C	2.7 ± 0.5
Albumin (g/dL)	16.9 ± 2.7
PT (second)	1.35 ± 0.25
INR	53 (14 - 339)
AST (U/L 37^{0}C)	33 (9 - 414)
ALT(U/L 37^{0}C)	1.74 (0.42 - 10.73)
Bilirubin (mg/dL)	100 (66 - 195)
Fasting Blood Glucose (mg/dL)	

PT: prothrombin time; INR: international normalized ratio; AST: aspartate transaminase; ALT: alanine transaminase

Correlation analysis of fasting blood glucose with CTP components used Spearman rank correlation test, significant if $p > 0.05$. The correlation between FBG and PT and grade of ascites has a correlation coefficient of -0116, and 0229, this indicates low correlation between these two variables. Negative value on the correlation coefficient indicates an inverse correlation, i.e the higher the level of FBG would be lower levels of PT, while direct correlation with the degree of ascites, although it was not statistically significant ($p > 0.05$). Fasting blood glucose and bilirubin ($\rho = -0240$, $p = 0.043$) has a low negative correlation. This means that the higher levels of FBG, the lower the bilirubin level. Correlation between FBG with albumin ($\rho = -0630$, $p < 0.01$) had a strong negative correlation meaning the higher levels of FBG, then the lower albumin levels. There was no correlation between FBG and CTP ($\rho = 0.063$, $p = 0329$).

Table 2. Correlation between CTP Criteria and Fasting Blood Glucose

Variable	Fasting Blood Glucose	
	ρ (correlation coefficient)	P value
PT	-0.116	0.207[a]
INR	-0.138	0.164[a]
Bilirubin	-0.240	0.043[a]*
Albumin	-0.630	<0.01[a]*
Grade Ascites	0.229	0.051[b]
CTP criteria	-0.002	0.987[b]

PT: prothrombin time; INR: international normalized ratio

DISCUSSION

In this study, the mean age of patients with cirrhosis was 53.4 ± 12.71 years, where the ratio of male and female was 1.4 : 0.7. Etiology of liver cirrhosis was hepatitis B virus infection of 28 (52.8%), while hepatitis C virus infection of 16 (30.2%) patients. In Indonesia hepatitis B virus causes cirrhosis of 40-50% and hepatitis C virus of 30-40 %.[1] Cirrhosis frequently impairs glucose tolerance. Twenty to fourty percent of patients with cirrhosis develop diabetes mellitus, another 40% are glucose intolerant, whereas about 30% have normal glucose tolerance curve.[9] When liver cirrhosis is diagnosed, hyperglycemia will develop 20% of cases in 5 years.[10] Nishida et al, conducted a study on the oral glucose tolerance test in predicting the prognosis of patients with liver cirrhosis. They found the 5 year survival in patients with liver cirrhosis DM was lower than liver cirrhosis patients with normal blood glucose levels (56.6 % vs. 94.7 %) .[11] Holstein et al, found that the Child - Pugh A has a higher blood glucose levels lower than the Child - Pugh B and Child - Pugh C, although statistically there was no difference.[12] Mangia et al, showed that severity of cirrhosis did not affect the onset of DM. They found the prevalence of DM was 37.4% in Child-Pugh (CP) class A, 34% in the CP class B and 15% in the CP class C.[13]

Liver is an important organ in the metabolism of carbohydrate, protein, fat and various hormones. It plays a pivotal role in glucose homeostasis since it stores glycogen in the fed state and produces glucose through glycogenolysis and gluconeogenesis in the post-absorptive period.[3] Relative hyperglycemia and hyperinsulinemia often occurs in patients with cirrhosis. Insulin is an important regulator of protein synthesis and proteolysis in skeletal muscle. Insulin resistance or insulin deficiency produces disturbances in muscle protein turnover and muscle wasting (loss of muscle mass).[14] It has been demonstrated experimentally that in diabetes not only impaired glucose metabolism but also protein metabolism. In 1912, it was reported increased protein destruction in patients with diabetes.[7] Insulin deficiency is a protein catabolic state. In type 1 insulin deficiency increases protein breakdown and amino acid oxidation but it improved with insulin therapy. But in type 2 diabetes impaired protein metabolism has not been consistent. Gougeon et al found that in patients with T2DM with moderate hyperglycemia, insulin therapy can improve protein metabolism. It is characterized by a greater nitrogen retention and decreased turnover protein.[7,15] This study found the correlation between low albumin

level with high FBG. Holstein et al mentioned a difference between mean albumin liver cirrhosis patients with diabetes and glucose intolerance ($p < 0.0001$).[12] Yagmur et al, found a negative correlation ($r = -0477$) between albumin level with severity of liver cirrhosis.[16] This is consistent with study conducted by Segade et al reported a negative correlation between albumin levels and HbA1c levels in poorly controlled T2DM.[6] Diabetes mellitus is a systemic disorder known to alter the expression of numerous genes in a variety of tissues. Hypoalbuminemia is a common problem in diabetic animals and is generally attributed to the presence of diabetic nephropathy. Previous studies have shown that hepatic levels of albumin and its mRNA are decreased within 3 days following the onset of DM. Study conducted by Wanke and Wong, found decreased albumin promoter activity in hepatonuclear extracts 3-4 times lower in diabetic rats compared with controls. It means there is inhibition of albumin promoter activity in diabetic rats.[17]

Branched-chain amino acids improve glucose metabolism in rats with liver cirrhosis. Nishitani et al found that administration of leucine and isoleucine, but not valine, decreased blood glucose levels by enhancing glucose uptake in a rat model of cirrhosis. It is therefore possible in cirrhosis that leucine and isoleucine may partially substitute for insulin in the regulation of glucose transport and also improve glucose metabolism by promoting glycogen synthesis and glucose uptake. Recently, several preliminary clinical studies in Japan indicated that BCAA supplementation given as LIVACT granules has beneficial effects on abnormal glucose metabolism in cirrhotic patients.[18]

CONCLUSION

Patients with liver cirrhosis may have glucose intolerance and insulin resistance. In diabetes not only impaired glucose metabolism but also protein metabolism. We find in liver cirrhosis patients, low serum albumin correlates with high fasting blood glucose.

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