

# Impaired Glucose Metabolism in Liver Cirrhosis

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## ABSTRACT

**Introduction:** Approximately 30% of patients who suffer cirrhosis maybe diabetic, called hepatogenous diabetes (HD). Insulin resistance seems to be the pathophysiologic basis for HD. Aims of this study were to evaluate the glucose metabolism disorders in liver cirrhosis patients and to observe the insulin resistance in HD.

**Method:** This study was conducted from February-July 2013 in Koja Hospital Jakarta. In the first phase, with observational design, inclusion criteria were liver cirrhosis and exclusion was an acute complication. We recorded their oral glucose tolerance test (OGTT). Patients who met the HD criteria were continued to the second phase, using analytic design, and were compared with type 2 diabetes mellitus (T2DM) patients as control. Mean differences of 2-hours postprandial plasma glucose/fasting plasma glucose (2hPPG/FPG) ratio, as well as fasting insulin levels between both groups were assessed.

**Results:** Twenty four patients were included in our study. Normal glucose tolerance test were noted in 7 (29%) patients, impaired glucose tolerance (IGT) in 6 (25%) patients and HD in other 11 (46%) patients. In the second phase, we obtained the ratio of 2hPPG/FPG in HD was  $2 \pm 0.5$  and T2DM was  $1.5 \pm 0.4$  ( $p = 0.01$ ). Mean fasting insulin levels in HD was  $10.8 \pm 4.2$   $\mu$ IU/mL, while T2DM was  $9.3 \pm 5.3$   $\mu$ IU/mL ( $p = 0.5$ ). The ratio of 2hPPG/FPG was higher in HD compared to T2DM, assuming the role of insulin resistance in HD.

**Conclusion:** There were impaired glucose metabolism in liver cirrhosis patients, as well as hepatogenous diabetes. Insulin resistance and hyperinsulinemia appeared to play role in HD.

**Keywords:** hepatogenous diabetes, type 2 diabetes mellitus, 2hPP/FPG ratio, fasting insulin level

## ABSTRAK

**Latar belakang:** Sekitar 30% penderita sirosis hati juga menderita diabetes melitus, yang dikenal sebagai diabetes melitus (DM) tipe sirosis. Resistensi insulin diduga berperan dalam patofisiologinya. Tujuan penelitian ini adalah untuk mengevaluasi gangguan metabolisme glukosa pada pasien sirosis hati dan melihat adanya pengaruh resistensi insulin pada DM tipe sirosis.

**Metode:** Penelitian yang dilakukan dalam periode Februari - Juli 2013 di Rumah Sakit Koja Jakarta ini dibagi dalam 2 tahap. Tahap pertama menggunakan desain observasional, dimana kriteria inklusi adalah semua penderita sirosis hati namun dieksklusi bila mengalami komplikasi akut, untuk kemudian diperiksa toleransi glukosanya. Pasien yang memenuhi kriteria DM dilanjutkan ke tahap 2 dengan penderita DM tipe 2 (DMT2) sebagai kontrol. Selanjutnya dengan desain analitik dinilai perbedaan rerata rasio glukosa darah 2 jam post prandial (GD2PP)/glukosa darah puasa (GDP) dan kadar insulin puasa antara DM tipe sirosis dengan DMT2.

**Hasil:** Didapatkan 24 penderita sirosis hati dengan hasil tes toleransi glukosa menunjukkan 7 (29%) penderita normal, 6 (25%) toleransi glukosa terganggu (TGT), dan 11 (46%) DM tipe sirosis. Dari studi analitik tahap 2, didapatkan rerata rasio GDPP/GDP pada pasien DM tipe sirosis sebesar  $2 \pm 0,5$  dan pasien DMT2 sebesar  $1,5 \pm 0,4$  ( $p = 0,01$ ). Rerata kadar insulin puasa pada pasien DM tipe sirosis  $10,8 \pm 4,2$   $\mu\text{IU/mL}$  dan DMT2  $9,3 \pm 5,3$   $\mu\text{IU/mL}$  ( $p = 0,5$ ). Rasio GDPP/GDP lebih tinggi pada DM tipe sirosis dibandingkan DMT2 dan bermakna secara statistik.

**Simpulan:** Dalam penelitian ini didapatkan adanya gangguan metabolisme gula, bahkan DM tipe sirosis pada penderita sirosis hati. Pengaruh resistensi insulin dan hiperinsulinemia tampaknya berperan pada DM tipe sirosis.

**Kata kunci:** DM tipe sirosis, DM tipe 2, rasio G2PP/GDP, kadar insulin puasa

## INTRODUCTION

Around 17% to 30% of patients who suffer cirrhosis maybe clinically diabetic. Diabetes which develops as a complication of liver cirrhosis is known as "hepatogenous diabetes" (HD). Insulin resistance in the muscular, hepatic and adipose tissue as well as hyperinsulinemia, seem to be the pathophysiologic basis for HD. Impaired response of islet  $\beta$ -cells of the pancreas and hepatic insulin resistance are also known to be contributing factors.<sup>1,2</sup> In Indonesia there were limited published articles regarding HD. Formerly, a study by Boedisantoso found that in patients with liver cirrhosis 25% were impaired glucose tolerance (IGT) and 32% were diabetic.<sup>2</sup> Another follow-up study done in 1985<sup>3,4</sup> found that the prevalence of hepatogenous diabetes were increased to 34.7% and 48.6%, respectively. After decades there were no other published article regarding HD reported locally.

American Diabetes Association (ADA) 2005 classified diabetes into 4 groups which are: (1) Type 1: diabetes mellitus or insulin dependent diabetes mellitus (IDDM); (2) Type 2: diabetes mellitus or non-insulin dependent diabetes mellitus (NIDDM); (3) Other types of diabetes mellitus; (4) Gestational diabetes mellitus.<sup>5</sup> Other types of diabetes mellitus which intended in the classification of ADA 2005 refers to genetic defects in cell function, genetic defects of insulin's work, pancreatic exocrine gland disease, endocrinopathies, drugs or chemicals, infections, uncommon forms of immune-mediated diabetes and other genetic syndromes associated with diabetes. However, hepatogenous diabetes are not included in the classification. The fact raises some question, how is the existence of HD in the classification of diabetes mellitus today.

'Hepatogenous diabetes' is clinically different from type 2 diabetes mellitus (T2DM). A study by Compean found comparison of HD group to T2DM group with a higher 2-hours postprandial plasma glucose/fasting plasma glucose (2hPPG/FPG) ratio 2.27 vs. 8.38, fasting

insulin 23.2  $\mu\text{IU/mL}$  vs. 11.6  $\mu\text{IU/mL}$  and homeostatis model assessment insulin resistance (HOMA IR) index 8.38 vs. 3.52 respectively. This finding reflects the role of insulin resistance in the pathogenesis of HD.<sup>6</sup> Aims of this study were to evaluate the glucose metabolism disorders in liver cirrhosis patients and to observe the insulin resistance in HD.

## METHOD

The study was conducted in Koja Hospital, Jakarta, a tertiary government hospital from February 2013 - July 2013. Inclusion criteria for liver cirrhosis (LC) group were all liver cirrhosis patients admitted or visited the internal medicine outpatient (IM OPD) clinic. Patients were excluded if they experienced an acute complication, or if patients documented to have hepatoma. This study were divided into two phases; initially all patients with liver cirrhosis were collected for baseline characteristics: age, sex, glucose tolerance tests (GTT) and fasting insulin level. Patients were labeled as HD if the 2 hours post prandial plasma glucose was  $\geq 200$  mg/dL.

From all patients who met the HD criteria, we took 9 patients to continue into the second phase. The sample size was determined using the formula "mean difference between two independent groups". Those 9 patients then were matched with 9 patients with T2DM patients as control. Inclusion criteria for T2DM group were untreated diabetes, or more than two weeks discontinued hypoglycemic agent; sex and age were matched with LC group. Data collected from both group were fasting insulin, fasting plasma glucose, post-prandial plasma glucose, and the ratio of 2hPPG/FPG.

Univariate analysis of all qualitative variables were presented in n (%) and quantitative variables were presented in mean (SD). Independent T-test was used to determine mean differences of 2hPPG/FPG ratio and fasting insulin levels between HD group and T2DM group. All data analysis was done using SPSS version 20.

**RESULT**

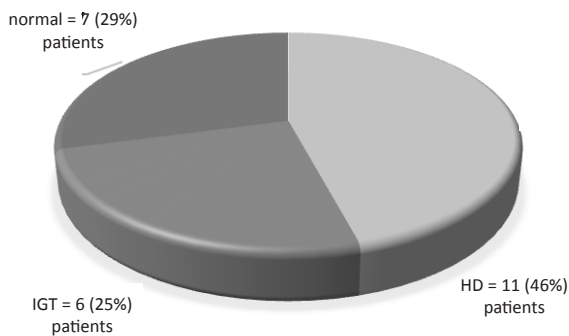
From February 2013-July 2013, 24 liver cirrhosis patients were included in this study. Baseline characteristics were described in Table 1.

**Table 1. Baseline characteristics of liver cirrhosis patients**

Characteristic	n (%), mean ± SD
Sex	
Male	15 (62.5)
Female	9 (37.5)
Age (years)	
< 40	5 (20.8)
40-60	11 (45.8)
> 60	8 (33.4)
Fasting insulin	7.2 ± 5.7
Fasting plasma glucose	107.8 ± 42.4
Post-prandial plasma glucose	205.5 ± 86.4
2hPPG/FPG	1.9 ± 0.4

2hPPG/FPG: ratio of 2 hours postprandial plasma glucose/fasting plasma glucose

From 24 patients, we found that 17 (71%) patients with liver cirrhosis have impaired glucose metabolism, and 7 (29%) patients have normal glucose tolerance. From patients with liver cirrhosis, 6 (25%) patients met the criteria for IGT and 11 (46%) people were HD. Figure 1 showed the proportion of HD to all patients with liver cirrhosis.



**Figure 1. Distribution of patients with liver cirrhosis according to the oral glucose tolerance test (n = 24)**

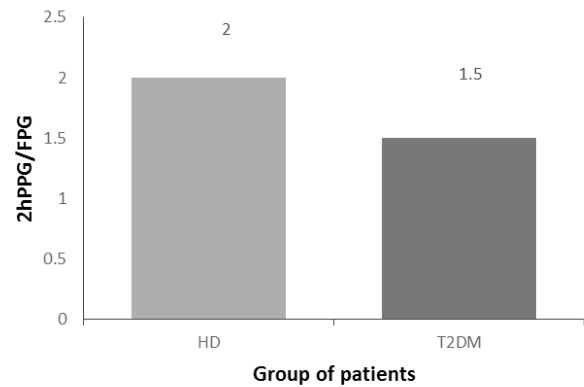
From 11 patients with HD, 9 patients rendered to the second phase. Nine T2DM patients were taken as controls. Characteristics of LC group and T2DM group were described in Table 2.

This study included 9 patients who met criteria for HD and compared them with control group. In both groups, we collect the fasting plasma glucose (FPG), 2-hours postprandial plasma glucose (2hPPG), and fasting insulin. The insulin resistances were assessed by measuring the ratio of 2hPPG/FPG (Figure 2) and fasting insulin levels (Figure 3).

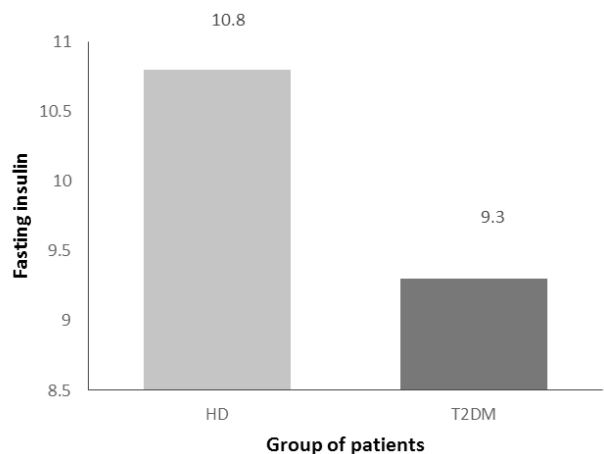
**Table 2. Characteristics of liver cirrhosis group vs. T2DM group**

Characteristic	Group of patients	
	LC	T2DM
Sex		
Male	6 (66.7)	6 (66.7)
Female	3 (33.3)	3 (33.3)
Age (years)		
< 40	1 (11.1)	0 (0)
40-60	5 (55.6)	6 (66.7)
> 60	3 (33.3)	3 (33.3)
Fasting insulin	10.8 ± 4.2	9.3 ± 5.3
Fasting plasma glucose	133.7 ± 51.5	210.7 ± 77.6
Post-prandial plasma glucose	263.8 ± 73.3	304.6 ± 59.9
2hPPG/FPG	2 ± 0.5	1.5 ± 0.4

2hPPG/FPG: ratio of 2 hours postprandial plasma glucose/fasting plasma glucose; LC: liver cirrhosis; T2DM: type 2 diabetes mellitus



**Figure 2. Mean 2-hours post-prandial glucose/fasting plasma glucose (2hPPG/FPG) in hepatogenous diabetes (HD) and type 2 diabetes mellitus groups (T2DM) (p = 0.01)**



**Figure 3. Mean fasting insulin level in hepatogenous diabetes (HD) and type 2 diabetes mellitus (T2DM) groups (p = 0.5)**

The 2-hours postprandial plasma glucose/fasting plasma ratio in HD group was 2 ± 0.5 and T2DM was 1.5 ± 0.4 (p = 0.01). Meanwhile, mean fasting insulin levels in patients with HD was 10.8 ± 4.2 μIU/mL and T2DM was 9.3 ± 5.3 μIU/mL (p = 0.5).

## DISCUSSION

Hepatogenous diabetes is generally subclinical, and commonly has a normal fasting glucose level; that is why the oral glucose tolerance test (OGTT) is obligatory to establish the diagnosis.<sup>6</sup> From the OGTT results, 11 (46%) patients were diabetic, 6 (25%) patients have impaired glucose tolerance and only 7 (29%) patients have normal glucose metabolism. A study by Compean, in patients with liver cirrhosis noted 96% of patients have impaired glucose metabolism and 30% of them were HD.<sup>6</sup> In our data, we documented 71% of patients have impaired glucose metabolism and 65% of them were HD. Compared to the previous study, less patients have impaired glucose metabolism (71% vs. 96%), but more patients met the criteria for hepatogenous diabetes (46% of the total patients, 65% of total impaired glucose metabolism). Liver plays an important role in the metabolism of carbohydrates, particularly through the process of glycogenogenesis and glycogenolysis.<sup>7,8</sup> In the presence of chronic liver disease, glucose metabolism is weakened, meanwhile insulin resistance, glucose intolerance and hepatogenous diabetes developed. Insulin resistance and hyperinsulinemia are postulated as a pathophysiology basis for cirrhosis type diabetes mellitus.<sup>9</sup> Management of HD is slightly different from type 2 DM because in HD, we rarely record microangiopathy and physician must be more vigilant to anticipate the hepatotoxic effects of oral hypoglycemic agents. However, in the classification of diabetes according to the ADA 2005 the term "hepatogenous diabetes" was not explicitly stated as one of other types of DM.<sup>5,6</sup>

To determine hyperinsulinemia, fasting insulin levels was examined in all 24 patients. We obtained 17 (70.8%) patients had normal fasting insulin (2.6-24.9  $\mu$ IU/mL), 4 (16.7%) had low fasting insulin (<2.6  $\mu$ IU/mL) and 3 (12.5%) had high fasting insulin (> 24.9  $\mu$ IU/mL). Kawaguchi recorded approximately 57% of patients with liver cirrhosis showed an increase insulin resistance.<sup>10</sup> Insulin level in patients with HD was higher than T2DM. Hyperinsulinemia in liver cirrhosis could be due to damage to the liver parenchymal cells, causing impaired insulin degradation. In this study, 12.5% patients were hyperinsulinemia.

Mean fasting insulin levels in HD group were compared to the T2DM group. Insulin levels in HD patients were  $10.8 \pm 4.2$   $\mu$ IU/mL and in T2DM patients were  $9.3 \pm 5.3$   $\mu$ IU/mL ( $p = 0.5$ ). These data indicated a relative hyperinsulinemia in HD group compared to

the T2DM ( $10.8 \pm 4.2$   $\mu$ IU/mL vs.  $9.3 \pm 5.3$   $\mu$ IU/mL), but apparently this difference was not statistically significant. This was likely due to the small sample size, less accurate technique of blood sampling, or laboratory error.

Furthermore, the 2hPPG/FPG ratio was assessed in both groups. The higher ratio 2hPPG/FPG indicated the failure of insulin to enter glucose into the cells, therefore the higher the ratio, the higher the insulin resistance. In HD group, we found that 2hPPG/FPG ratio was  $2 \pm 0.5$  and  $1.5 \pm 0.4$  in T2DM ( $p = 0.01$ ). The 2hPPG/FPG ratio was higher in HD group, and was statistically significant. These data supported the existence of a higher insulin resistance in HD compared with T2DM.

## CONCLUSION

There were impaired glucose metabolism in liver cirrhosis patients, as well as hepatogenous diabetes. Insulin resistance and hyperinsulinemia appear to play a role in HD. Correspondent with the high prevalence of hepatogenous diabetes in this study as well as others, we propose to include hepatogenous diabetes in the classification of diabetes mellitus as a subtype of other specific types.

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