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Original Article

Clinical study of abnormal glucose metabolism and insulin resistance in patients with liver cirrhosis

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Abstract: Background: To investigate the correlation between abnormal glucose metabolism and insulin resistance in patients with liver cirrhosis. Methods: A total of 254 participants were assigned into either the experimental group (EG) (n=123) or the normal group (NG) (n=131). We detected fasting blood glucose (FBG), postprandial blood glucose (PBG), fasting insulin (FINS), postprandial insulin, Hemoglobin A1c (HbA1c) and Insulin sensitivity index (ISI), at the same time, we compared various indexes in different Child-Pugh classification of the experimental group. Results: The 1-hour PBG and 2-hour PBG in the EG were significantly higher than the NG group (P<0.05), serum insulin level in each period was significantly higher (P<0.05). The insulin sensitivity index (ISI) in the experimental group was statistical significantly lower (-4.21±0.09) VS. (-4.03±0.32), (P=0.031<0.05). Furthermore, the 2-hour PBG and FIN of Child-Pugh grade B patients were significantly higher than that of Child-Pugh grade A patients. The fasting insulin level of patients with cirrhosis of Child-Pugh grade C patients was significantly higher than that of Child-Pugh grade B patients, while FBG, PBG and ISI had no significant difference compared with those of Child-Pugh grade B patients. The higher the level of fasting blood glucose and postprandial blood glucose, the higher the FIN with the aggravation of liver function damage. Conclusions: Patients with liver cirrhosis had different degrees of insulin resistance. Clinicians can take proactive measures to prevent the occurrence of hepatogenic diabetes mellitus.

Keywords: Abnormal glucose metabolism, insulin resistance, liver cirrhosis, relationship, clinical study

Introduction

The liver is an important organ of glucose metabolism, and it plays an important role in regulating blood glucose concentrations [1]. With liver injury, it can cause abnormal glucose metabolism, or even diabetes [2, 3]. In recent years, studies have found that hyperinsulinemia is an important clinical feature of liver cirrhosis [4, 5]. With the decrease of liver reserves and glycogen synthesis, insulin resistance gradually appears, and disorders of glucose metabolism are also aggravated. According to statistics, about 80% of patients with liver cirrhosis have glucose intolerance, and 20%-30% of patients develop diabetes directly [6]. When hepatocytes are damaged, especially in liver cirrhosis, the characteristic changes of enzymes related to glucose metabolism in the liver are: glucose-6-phosphate dehydrogenase, glyceraldehyde phosphate dehydrogenase, pyruvate phosphokinase, lactate dehydrogenase and so on; while the activities of aldolase, glycerophosphate dehydrogenase, isocitrate dehydrogenase, succinate dehydrogenase and malate dehydrogenase were also decreased [7-9].

It has been reported that hepatic glucose production in the patients with liver cirrhosis is both normal and decreased [10]; however, insulin-induced glucose uptake in the peripheral tissue is markedly decreased [11]. In contrast, hepatic insulin resistance is seen in cirrhotic patients with DM but not in patients with liver cirrhosis alone [11, 12]. Thus, the role of insulin resistance on hepatic glucose uptake in the patients with liver cirrhosis has remained unclear. There is no clear evidence that etiology, duration and disease degree in the patients with LC is related to glucose intolerance [13].

This study measured blood glucose, insulin, glycosylated hemoglobin, and insulin sensitivity index levels to investigate the characteristics of insulin function and glucose metabolism in patients with liver cirrhosis. We researched the

Table 1. Clinical characteristics of patients in experimental group and in normal group

	Experimental group (n=123)	Normal group (n=131)	t/χ^2	*P*
Age (years)	48.7±5.32	50.75±5.27	5.25	0.24
BMI (kg/m^2)	17.95±1.43	18.3±1.58	3.39	0 .48
Sex			7.28	0.43
Male (n%)	74 (60.2%)	80 (61.1%)		
Female (n%)	49 (39.8%)	51 (38.9%)		
Serum albumin (g/L)	30.4±5.35	35. 6±8.24	12.24	0.000
Total bilirubin (μmol/L)	23.7±6.34	19.5±8.32	9.68	0.000
Prothrombin time (s)	15.2±6.26	13.4±6.43	5.62	0.000
Hemoglobin A1c (HbA1c)	8.2±2.16	6.13±1.74	16.38	0.000
Child-Pugh classification				
Child A	62 (50.4%)			
Child B	37 (30.1%)			
Child C	24 (19.5%)			

Note: Significant difference as P<0.05.

pathogenesis of hepatogenic diabetes in order to guide clinical diagnosis and treatment.

Materials and methods

Study design

The study was based on observational research. This study was conducted at our Hospital from August 2018 and August 2020. Inclusion criteria: 1) Patients were in line with the clinical diagnostic criteria of liver cirrhosis approved by the National Academic Conference on infectious diseases and parasitic diseases [14]; 2) Patients had no history of diabetes before diagnosis of liver cirrhosis; 3) The subjects were willing to cooperate with the experiment. Exclusion criteria: 1) Patients had a history of mental illness; 2) History of blood system diseases; 3) History of chronic diseases such as diabetes, nephropathy, hypertension or coronary heart disease; 4) History of malignant tumors. The researchers systematically explained the role, purpose and process of the study to the patients and their families. The patients and their families voluntarily signed the informed consent form to participate in this study. This study was approved and recognized by the ethics committee of our hospital.

Participants and subgroups

A total of 278 participants were admitted to our hospital, including 254 participants meeting the inclusion and exclusion criteria. The 254 eligible participants included were allocated into two groups: the experimental group (suffered from liver cirrhosis) (n=123) or the normal group (healthy individuals) (n=131).

Interventions

All subjects underwent OGTT test, that is, 75 g glucose was dissolved in 300 ml of water and drunk within 5 min. Before taking the glucose, no restriction was imposed on diet before taking the sugar. Two ml blood was collected from elbow vein at 1 hour after taking glucose. The glucose value in the plasma was measured by the glucose oxidase method. Fasting (fasting for 8-12 h) 2 ml blood was drawn from elbow vein. The glucose value was measured by serum glucose oxidase method, the blood insulin and glycosylated hemoglobin were measured by radioimmunoassay.

Primary outcome measures

The blood samples were collected from the elbow vein in the morning of the next day after all subjects had fasted for 12-14 hours at night. FBG, and PBG were measured by glucose oxidase method; FINS was measured by radioimmunoassay. Insulin release index (=FINS/FBG), Hemoglobin A1c (HbA1c) and Insulin sensitivity index (ISI)(=(FBG ×FINS)/25) were also tested.

Statistical analysis

All data were analyzed by SPSS 22.0. The statistical results are expressed by mean ± standard deviation ($\bar{x}$ ± sd), the data comparison is conducted by t-test and the correlation analysis is conducted by person linear phase, P<0.05 was defined as statistical significance.

Results

Clinical characteristics

Table 1 shows the characteristics of the participants. The research included 123 subjects in the experimental group, with a mean age of (48.7±5.32) years old, while the 131 participants in the normal group had a mean age of

Table 2. Differences in OGTT between normal group and EG

OGTT	Experimental group (n=123)	Normal group (n=131)	t/χ^2	*P*
Blood glucose (mmol/L)				
Fast blood glucose	5.16±1.17	4.18±1.30	0.421	0.082
1 hour postprandial blood glucose	12.31±2.05	6.29±2.14	4.226	0.000
2 hour postprandial blood glucose	14.38±3.16	7.83±2.21	4.159	0.000
Insulin (IU/mL)				
Fasting insulin	10.63±6.21	10.14±5.44	0.315	0.773
1 hour postprandial insulin	45.68±11.63	26.31±7.11	5.331	0.000
2 hour postprandial Insulin	60.36±37.84	30.23±9.23	6.159	0.000
ISI	-4.21±0.09	-4.03±0.32	2.236	0.031

Note: Significant difference as P<0.05. ISI: Insulin sensitivity index.

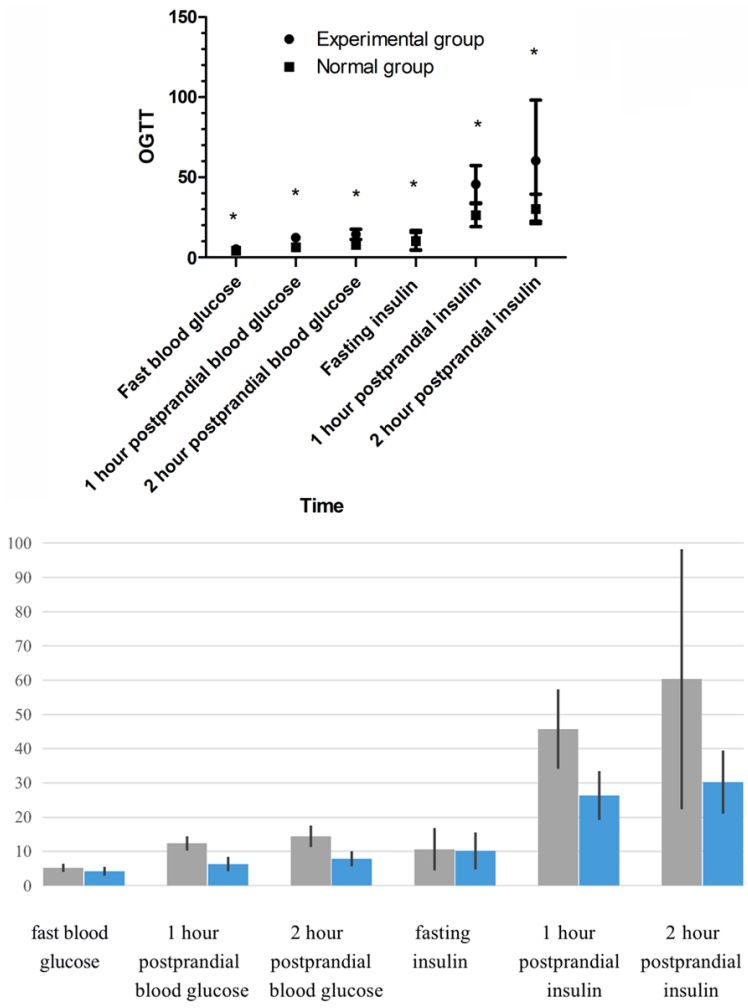

Figure 1. Differences in OGTT between normal group and EG. **P<0.05.*

(50.75±5.27) years old. The BMI before pregnancy in the EG was (17.95±1.43) kg/m^2, and in the normal group was (18.3±1.58) kg/m^2, there was no statistical significance between the two groups (P=0.48). Serum albumin in the EG was (35.6±8.24) g/L, while that in the normal group was (35.6±8.24) g/L; Total bilirubin level in the EG was (23.7±6.34) μmol/L, while that in the normal group was (19.5±8.32) μmol/L; and Prothrombin time in the EG was (15.2±6.26) s, while that in the normal group was (13.4±6.43) s. Moreover, the differences of serum albumin, total bilirubin and prothrombin time were statistically significant (P<0.05) between the two groups. Hemoglobin Alc (HbA1c) in the EG was higher (8.2±2.16) VS. (6.13±1.74), (P<0.05).

Differences in OGTT between the normal group and the EG

As shown in **Table 2** and **Figure 1**, there was no difference in FBG and FINS between two groups (P>0.05), and peak of glucose and insulin secretion was consistent. Furthermore, 1-hour PBG and 2-hour PBG in the EG were significantly higher than the other group (P<0.05), serum insulin level in each period was significantly higher (P<0.05). The insulin sensitivity index (ISI) in the experimental group was statistical significantly lower (-4.21±0.09) VS. (-4.03±0.32), (P=0.031).

Table 3. Child-Pugh classification

	Fraction IIIV		
	One	Two	Three
Hepatic encephalopathy	None	I-II	III-IVIII-IV
Ascites	None	easy to fade	hard to fade
Albumin (g/L)	>35	28-35	<28
Prothrombin time (s)	≤14	15-17	≥18
Bilirubin (mol/L)	<34	34-51	>51

Note: Grade A: 5-8 points; grade B: 9-11 points; grade C: 12-15 points.

Comparison of various indexes in different Child-Pugh classifications of the experimental group

The Child-Pugh classification was shown in the **Table 3**. The 2-hour PBG and FIN of Child-Pugh grade B patients were significantly higher than that of Child-Pugh grade A patients, but the differences of FBG and ISI had no statistical significance (P>0.05). The fasting insulin level of patients with cirrhosis of Child-Pugh grade C patients was significantly higher than that of Child-Pugh grade B patients, while FBG, PBG and ISI had no significant difference compared with those of Child-Pugh grade B patients. There was no significant difference in FBG between Child-Pugh grade C patients and Child-Pugh grade A patients, but the 2-hour PBG and FIN were significantly higher than those in Child-Pugh grade A, and the ISI was significantly lower than that in Child-Pugh grade A patients (**Table 4** and **Figure 2**).

Insulin sensitivity index (ISI) in different Child-Pugh classifications of the experimental group

Insulin Sensitivity Index in the Child-Pugh A group was (-4.6±0.33), and that in the Child-Pugh B group was (-4.8±0.57), and those in the Child-Pugh B group was (-5.19±0.37). The higher the level of fasting blood glucose and postprandial blood glucose, the higher the FIN with an aggravation of liver function damage (**Table 4**).

Discussion

In our research, we indicated that the levels of blood glucose and insulin in patients with liver cirrhosis were significantly increased, and insulin sensitivity was decreased, which confirmed that patients with liver cirrhosis had hyperinsulinemia and insulin resistance. Moreover, Child-Pugh classification was positively correlated with fasting blood glucose level. With the aggravation of liver injury, fasting blood glucose gradually increased, which indicated that the degree of liver injury is closely related to the occurrence of abnormal glucose metabolism. Child-Pugh classification was positively correlated with insulin level and negatively correlated with insulin sensitivity index. We demonstrated that the degree of liver function damage is related to insulin resistance.

The liver is the main organ that maintains the dynamic balance of blood glucose. It is also the target organ for degradation and transformation of hormones such as insulin and glucagon. Therefore, liver injury can interfere with glucose production or glucose utilization mechanism and cause abnormal glucose metabolism [15, 16]. According to the results of our study, although FBG in decompensated liver cirrhosis was slightly increased, there was no significant difference (P>0.05). Interesting, glucose metabolism disorder was characterized by impaired glucose tolerance and increased insulin level after eating, and the changes of blood glucose and insulin levels were significantly higher than those in the compensatory period group and the normal group (P<0.05). The causes of this phenomenon maybe [17-20]: 1) glycogen synthesis is impaired and hyperglycemia stimulates the secretion of islet beta cells; 2) the sensitivity of β-cells to insulin feedback inhibition is decreased; 3) insulin inactivation slows down in liver injury; 4) due to portosystemic shunting, insulin enters systemic circulation directly without liver inactivation. Sibley et al. [21] produced hyperinsulinemic euglycemic clamp test in 24 patients with liver cirrhosis and found that all patients had severe insulin resistance and increased hepatic glucose output, which was consent with our study.

Insulin resistance may be the most important factor of abnormal glucose metabolism in patients with liver cirrhosis. Due to serious damage of hepatocytes, the number of insulin receptors on the membrane of hepatocytes is reduced, and the affinity between the receptors and insulin is reduced, so that the utilization of insulin is reduced [22]. When the concentration of insulin in the blood is too high, the insulin receptors on the target cell membrane are occupied for a long time, resulting in the degradation of the insulin receptor, thus the number

Table 4. Comparison of various indexes in different child-Pugh classification in the experimental group

OGTT	Child-Pugh A (n=62)	Child-Pugh B (n=37)	Child-Pugh C (n=24)	t/χ^2	*P*
Blood glucose (mmol/L)					
Fast blood glucose	6.52±0.33	6.69±0.35	6.91±0.48	0.32	0.697
2 hour postprandial blood glucose	8.78±0.62	10.46±1.19	11.24±2.15	5.36	0.012
Insulin (IU/mL)					
Fasting insulin	15.32±1.32	18.15±1.59	21.54±3.78	12.71	0.000
2 hour postprandial Insulin	50.12±21.54	53.32±26.23	58.16±19.92	15.93	0.000
ISI	-4.6±0.33	-4.8±0.57	-5.19±0.37	4.19	0.021

Note: Significant difference as P<0.05. ISI: Insulin Sensitivity Index.

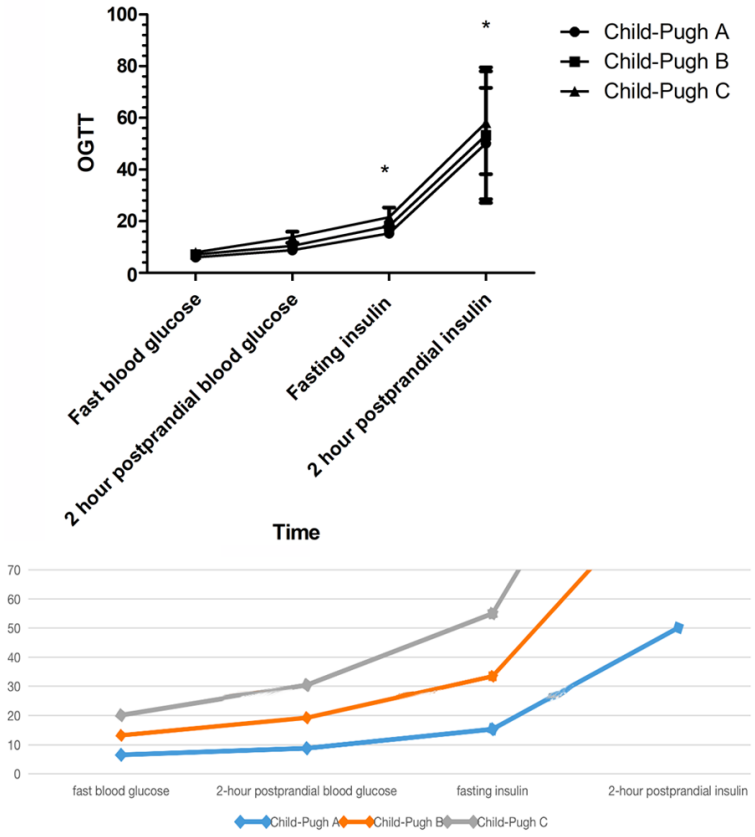

Figure 2. Comparison of various indexes in different child-Pugh classification in the experimental group. **P<0.05.*

of receptors further decreases, and the affinity decreases, which is called "down regulation" [23]. Furthermore, the levels of plasma glucagon, growth hormone and free fatty acids were increased due to the decrease of liver inactivation, resulting in insulin resistance in peripheral tissues [24]. The ability of islet β-cells to respond to decreased glucose may fail. When liver function is obviously abnormal, the activities of glucokinase and glycogen synthetase are decreased, thus affecting the phosphorylation and glycogen synthesis of glucose. The activities of glucose oxidation rate limiting enzymes, hexokinase and phosphofructokinase are also low, which affects the utilization and transformation of glucose and leads to the increase of glucose concentration [25-27].

Certainly, our research has weakness. Firstly, our current study is a small in samples and a single center study. Particularly, the difficulties in enrolling patients was a limit with the number of liver cirrhosis patients in our hospital. Secondly, although our results are promising, the explanation is inadequate by lack of a mechanism in our research.

In summary, this study provides preliminary evidence that patients with liver cirrhosis often have abnormal glucose tolerance and insulin resistance. If this cannot be prevented and treated in time, the disease may develop into hepatogenic diabetes. Therefore, treatment and protection of liver function is the key to reduce the incidence of hepatogenic diabetes.

Disclosure of conflict of interest

None.

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