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# Effects of GLUT4 expression on insulin resistance in patients with advanced liver cirrhosis

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**Abstract:** Decreased glucose tolerance and diabetes are frequently observed in advanced liver cirrhosis patients and may be related to insulin resistance. Glucose transporter-4 (GLUT4), one of the most important glucose transporters, plays a key role in the development of type 2 diabetes. In order to study the mechanism of insulin resistance in liver cirrhosis patients, we measured the insulin sensitivity index and determined the GLUT4 protein and mRNA contents of skeletal muscle by Western blotting and reverse transcription-polymerase chain reaction (RT-PCR), respectively, in normal people and liver cirrhosis patients. The results showed that the levels of glucose, insulin, and C-peptide in two liver cirrhosis groups were higher and the insulin sensitivity index lower than those of the normal control group. The sensitivity of insulin may decrease with the decline of liver function. However, the contents of GLUT4 protein and mRNA in patients with advanced liver cirrhosis were similar to those of normal controls. In conclusion, insulin resistance is observed in patients with advanced liver cirrhosis but may not be correlated with the skeletal contents of GLUT4 protein and mRNA.

**Key words:** Glucose transporter-4 (GLUT4), Liver cirrhosis, Insulin resistance, Skeletal muscle
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## 1 Introduction

About 60% to 80% of patients with liver cirrhosis have impaired glucose tolerance, and 10% to 20% of those eventually develop diabetes mellitus (Singal and Ayoola, 2008; Hung *et al*., 2010). Diabetes mellitus following liver cirrhosis might relate to insulin resistance which is predominantly a peripheral tissue phenomenon (Anty *et al*., 2010; Malik and Ahmad, 2010). The mechanism of insulin resistance has yet not been clarified.

Glucose transporter-4 (GLUT4), the predominant insulin-responsive glucose transporter isoform, plays a key role in the process of transporting extracellular glucose into insulin-sensitive cells in vivo (Chang *et al*., 2004; Asano *et al*., 2007; Huang and Czech, 2007). It exists only in skeletal muscle and adipose tissues (Suárez *et al*., 2001), which are responsible for 50% to 80% of glucose transportation in the body. After being transported into insulin-sensitive cells, the glucose is decomposed or synthesized to glycogen to maintain normal glucose tolerance. It has been reported that the skeletal expression of GLUT4 in type 2 diabetes patients is significantly reduced, indicating that such patients have less capability to process glucose (Maier and Gould, 2000). However, the relationship between GLUT4 expression and insulin resistance in liver cirrhosis patients has not yet been clarified. The aims of our research were to determine the insulin sensitivity index and the skeletal expression of GLUT4 protein and mRNA, and to study the mechanism of insulin resistance in patients with advanced liver cirrhosis.

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## 2 Materials and methods

### 2.1 Patients and specimen collection

Forty-seven patients with chronic hepatitis B related advanced liver cirrhosis treated in our department were enrolled in this study from 1st May, 2007 to 31st December, 2009. Of those, 23 patients had liver failure (LF group) necessitating liver transplantation and 24 had a preserved liver function (PLF group) after undergoing splenectomy selectively for management of portal hypertension. Twenty-five healthy persons who were liver or renal transplant donors served as the control group (Table 1). Patients fulfilling the following criteria were excluded: (1) diagnosis of diabetes before suffering liver cirrhosis; (2) diagnosis of hepatocellular carcinoma; (3) heavy alcohol consumption (>80 g/d for males and >40 g/d for females, each for more than 10 years); (4) exposure to *Aspergillus flavus*, or diagnosis of drug- or poison-induced liver damage; (5) undergoing therapies involving insulin or other hypoglycemic agents; (6) using corticosteroids at the time of sampling of tissue; (7) undertaking >40 min of physical exercise four or more days per week or the initiation of a structured exercise program in the past three months; (8) obese persons (body mass index (BMI) >28 kg/m$^2$). Consent was obtained from all patients and controls participating in this study. The study was approved by the Research Ethics Committee of the First Affiliated Hospital, School of Medicine, Zhejiang University, China.

**Table 1 Characteristics of subjects in each group**

| Group | $n_M/n_F$ | Age (year)[a] | BMI (kg/m$^2$)[a] | Child-Pugh class[b] |
|---|---|---|---|---|
| Control ($n$=25) | 19/6 | 32 (22–55) | 25.6 (24.3–27.9) | A: 25 |
| PLF ($n$=24) | 16/8 | 51 (35–64) | 23.8 (21.2–25.8) | A: 17, B: 7 |
| LF ($n$=23) | 19/4 | 51 (21–60) | 24.1 (21.3–26.0) | A: 3, B: 8, C: 12 |

$n_M/n_F$: male number/female number; BMI: body mass index; PLF: preserved liver function; LF: liver failure. [a] For each continuous variable, the upper line shows the median and the lower line presents the ratio between the control group and each other group with 95% confidence intervals. [b] The liver function was declined successively from capital A to C according to Child-Pugh class. Patients in the LF group had received perioperative treatment such as furosemide and albumin, so their liver function had improved

A total of 6 ml blood was collected from each of the subjects in our study at the beginning of the operation, under general anesthesia. The fasting blood glucose values were measured using rapid blood glucose meters. The blood samples were left to stand for 30 min and were then centrifuged at 3000 r/min for 10 min. After centrifugation, the serum was transferred to Eppendorf (EP) tubes, put in a −80 °C ultra-low temperature freezer, and measured for serum insulin and C peptide values. Pancreatic β cell function and insulin resistance status were determined and compared according to the insulin sensitivity index among the three groups. The index was calculated by $\ln[1/(c_{glucose}\times c_{insulin})]$, where $c$ is concentration.

A specimen of rectus abdomen was obtained at the beginning of the operation. Each specimen was dissected into several pieces of 50–100 mg, frozen in liquid nitrogen, and moved to a −80 °C ultra-low temperature freezer. These biopsy specimens were homogenated and the crude membrane and mRNA were separated and isolated. Standard protein or mRNA changes were titrated. The mRNA quality and purity were detected under 260 and 280 nm ultraviolet (UV) light.

### 2.2 Total GLUT4 protein content in skeletal muscles detected by Western blotting

Protein specimens were obtained through the decomposition of the protein lysate. The quantity of protein was examined using a 490-nm UV light. The target protein content was detected by Western blotting using anti-COOH-terminal peptide GLUT4 polyclonal antibody (Cell Signaling Technology Inc., Beverly, MA, USA). The labeled protein was visualized using enhanced chemiluminescence (ECL). Auto-radiograms were quantified by scanning densitometry. Muscle samples were run on every gel for comparison of samples from different immunoblots.

### 2.3 Reverse transcription-polymerase chain reaction (RT-PCR) for mRNA analysis

The primers used for GLUT4 mRNA were 5′-TGGTCTCGGTGTTGTTGGTG-3′ and 5′-GGCC ACAATGGAGACGTAGC-3′. The primers for control α-actin were 5′-GGTCGGAGTCAACGGATT TG-3′ and 5′-ATGAGCCCCAGCCTTCTCCAT-3′. mRNA samples were isolated by TRIzol extraction. The 5 μg of total mRNA, 1 μl of Oligo (dT), and 1 μl of 10 mmol/L deoxyribonucleotide triphosphate (dNTP), made up to 12 μl with diethylpyrocarbonate

(DEPC) water, were added to a thin wall EP tube in an ice bath. After gentle mixing, the samples were immediately dipped in a water bath at 65 °C for 5 min, and then bathed in an ice bath for at least 1 min. After brief centrifugation, the following components were added to the samples: 4 μl of 5× first strand reaction buffer, 2 μl of 0.1 mol/L dithiothreitol (DTT), 1 μl of RNaseOUT (40 U/μl), and 1 μl of SuperscriptII (200 U). Then the mixture was set in a 37 °C bath for 50 min. The PCR reaction was terminated by heating the sample at 70 °C for 15 min. The samples were preserved over ice for cryopreservation or for continued testing. The raw materials for the PCR were 2 μl of 25 mmol/L $MgCl_2$, 2.5 μl of 10× PCR buffer, 1 μl of 10 mmol/L dNTP, 1 μl of targeted primers, 2 μl of cDNA, 13.2 μl of $ddH_2O$, and 0.3 μl of Taq DNA polymerase for 40 cycles. The photos were processed using a Kodak digital system.

### 2.4 Statistical analysis

Clinical and laboratory data were entered into an electronic spreadsheet. Statistical analysis was performed with the SPSS statistical package for Windows, Version 13.0 (SPSS Inc., Chicago, IL, USA). The data in the text and in the tables are presented either as mean±standard deviation (SD) or as prevalence (95% confidence intervals). Differences among the groups were checked for significance by means of analysis of variance (ANOVA). The $\chi^2$ test or Fischer's exact test was used, when necessary, to test for the significance of the prevalence of clinical and laboratory abnormalities. A *P* value of less than 0.05 was considered statistically significant.

## 3 Results

No differences were noted in gender or BMI among the three groups. The liver cirrhosis patients were about 20 years older than the normal controls. Liver function values declined successively in the control, PLF, and LF groups (Table 1). Preoperative fasting blood glucose, serum insulin and C peptide levels were significantly higher in the PLF and LF groups than in the control group ($P<0.05$), while the insulin sensitivity index was significantly lower in the PLF and LF groups than in the control group ($P<0.05$). The serum insulin and C peptide levels were higher in the LF group than in the PLF group ($P<0.05$). There was no statistically significant difference in insulin sensitivity index between the PLF and LF groups ($P>0.05$), although there were trends towards a lower insulin sensitivity index and a higher level of fasting blood glucose in the LF group (Table 2). There were no significant differences in GLUT4 protein and mRNA expression between the three groups ($P>0.05$) (Table 3).

**Table 2 Comparison of glucose, insulin and C-peptide levels, and insulin sensitivity index in the three groups**

| Group | Glucose (mmol/L) | Insulin (μU/ml) | C-peptide (ng/ml) | ISI |
|---|---|---|---|---|
| Con. | 5.45±0.48 | 6.71±3.55 | 1.63±0.75 | −3.44±0.61 |
| PLF | 6.86±1.67* | 12.61±6.51* | 2.79±1.10* | −4.23±0.61* |
| LF | 6.98±1.55* | 18.93±10.88*# | 4.73±1.91*# | −4.67±0.72* |
| *F* | 10.08 | 14.92 | 30.56 | 22.60 |

ISI: insulin sensitivity index. All blood samples were collected at the beginning of or before surgery. * $P<0.01$, compared with the control group; # $P<0.01$, compared with the PLF group

**Table 3 Protein and mRNA contents of GLUT4 in the three groups**

| Group | GLUT4 protein | GLUT4 mRNA |
|---|---|---|
| Control | 1.10±0.23 | 0.85±0.09 |
| PLF | 1.09±0.50 | 0.83±0.12 |
| LF | 1.64±0.16 | 0.81±0.16 |
| *F* | 1.437 | 1.832 |

All of the values above were compared to α-actin. All muscle samples were collected at the beginning of or before surgery

## 4 Discussion

The concept of hepatic diabetes was introduced as early as 1906 (Bragança and Álvares-da-Silva, 2010). It refers to diabetes brought about by chronic liver disease or liver cirrhosis which may be related to insulin resistance (Arai *et al*., 2010). Insulin resistance is defined as a condition in which a higher insulin concentration is needed to achieve normal glucose metabolism, or a normal insulin concentration fails to achieve normal glucose metabolism (Matsumoto *et al*., 2007; Kirwan *et al*., 2009). In this study, although the patients with liver cirrhosis had higher serum insulin levels, their fasting blood glucose levels were still significantly higher than those of

the normal control group, demonstrating the existence of peripheral insulin resistance in patients with liver cirrhosis.

One reason for the insulin resistance is that liver cirrhosis patients lack insulin secretion. Although the level of serum insulin is increased, it is still not enough for them to maintain a normal glucose tolerance. At the early stage of liver cirrhosis, patients do not lack insulin secretion or synthesis. The pancreatic β cells can secrete enough insulin to compensate for the insulin resistance and maintain a generally normal glucose tolerance. With the development of advanced liver cirrhosis, eventually the pancreatic β cells cannot continue to increase the secretion of insulin to compensate for the insulin resistance. Thus, relatively insufficient insulin secretion and impaired glucose tolerance appear (Bragança and Álvares-da-Silva, 2010). The liver cirrhosis patients in our study were precisely at this stage. Another reason for insulin resistance in liver cirrhosis patients is that the diseased liver cannot inactivate the contra-insulin hormones (glucagon, growth hormone, insulin-like growth factor, free fatty acids, and cytokines) effectively (Petrides *et al*., 1991; 1998). Insulin resistance is aggravated by the deterioration of liver function (Kimura *et al.*, 2011). Inhibition downstream of the receptor in the insulin signaling cascade may also be one of the reasons for insulin resistance (Aytug *et al*., 2003). In our study, the insulin sensitivity index declined successively in the control, PLF, and LF groups, showing that the insulin resistance had a negative correlation with liver function.

Combined with the insulin receptor, insulin can activate the insulin transduction signal pathway and regulate the process of glucose uptake to stabilize the level of glucose. Any malfunction in the insulin transduction signal system can result in insulin resistance. GLUT4 is one of the most important downstream sites of the insulin receptor because it sits at the rate-limiting step in the insulin transduction signal pathway. It has been reported that GLUT4 protein and mRNA are reduced in type 2 diabetes (Chen *et al*., 2003). However, our study showed that GLUT4 protein and mRNA contents in the skeletal muscle did not reduce in liver cirrhosis patients in comparison with normal people. The mechanism of insulin resistance in liver cirrhosis may differ from that of type 2 diabetes mellitus.

Although the skeletal contents of GLUT4 protein and mRNA in our liver cirrhosis patients did not reduce, the ability of glucose transportation was decreased. The inhibition of GLUT4 translocation is one of the most important reasons for poor glucose transportation in the body. Translocation is the process by which vesicles in the cytoplasm containing GLUT4 move to the plasma membrane and fuse with it under the stimulation of insulin. Malfunction of the process can lead to insulin resistance (Peck *et al*., 2009). Adipose GLUT4 translocation impairment is found in type 2 diabetes patients (Ramm *et al*., 2006; MacLaren *et al*., 2008; Ng *et al*., 2008; Yip *et al*., 2008). The translocation of GLUT4 is impaired in skeletal muscle in models of acute biliary cirrhosis in animals (Jessen *et al*., 2006). However, it is not known whether the translocation of skeletal GLUT4 is also impaired in liver cirrhosis.

In this study, the content of GLUT4 mRNA in liver cirrhosis was normal at the fasting state in liver cirrhosis patients, which differs from previous findings (Holland-Fischer *et al*., 2007). The discrepancy may be due to different experimental designs. In the study by Holland-Fischer *et al*. (2007), the skeletal muscle samples were taken mainly from patients with alcoholic cirrhosis 2 h after an oral glucose tolerance test (OGTT) to study the expression of GLUT4 and to investigate their bodies' ability to deal with the rapid rise of blood glucose. In our study, the expression of GLUT4 was determined in patients with liver cirrhosis after overnight fasting and reflected the baseline of GLUT4. However, its further investigation is needed to determine whether the skeletal expression of GLUT4 mRNA in liver cirrhosis patients could increase reactively after OGTT, to transport glucose into the cells to stabilize the glucose level in the body.

The shortcoming of this study was that only the total content of GLUT4 was determined, including GLUT4 on the cell membrane and in the cytoplasm. We cannot distinguish the quantity of GLUT4 on the cell membrane from that in the cytoplasm. So our study cannot determine if patients with liver cirrhosis have translocation impairment.

In summary, our study demonstrates that there is insulin resistance in liver cirrhosis patients. This insulin resistance may have no correlation with the skeletal expression of GLUT4 protein or mRNA. The exact mechanism needs further investigation.

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