Partial Splenic Embolization Reverses Insulin Resistance in Patients with Liver Cirrhosis

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Abstract

Background It is well known that patients with liver cirrhosis often develop insulin resistance and diabetes mellitus. Recently, we encountered a liver cirrhosis patient in whom partial splenic embolization (PSE) improved insulin sensitivity. Therefore, we conducted further investigation about PSE and insulin resistance.

Methods Thirty-seven consecutive patients with liver cirrhosis underwent PSE. Hemodynamic changes, blood counts, and homeostasis model assessment of insulin resistance (HOMA-IR) were assessed before and 2 weeks after PSE.

Results PSE resulted in decreased splenic venous flow and increased intestinal venous flow to the liver. Platelet counts before and after PSE were $7.7 \pm 0.5 \times 10^4/\mu\text{L}$, $15.0 \pm 1.4 \times 10^4/\mu\text{L}$, respectively ($p < 0.01$). HOMA-IR before and after PSE were 6.5 ± 2.1 , 3.3 ± 0.6 , respectively ($p < 0.05$). HCV core antigen before and after PSE were $6,340 \pm 1,296$ fmol/L, $4,112 \pm 873$ fmol/L, respectively ($p < 0.05$).

Conclusion PSE significantly reverses insulin resistance in patients with liver cirrhosis. The increase in intestinal venous flow to the liver and reduced HCV viral load were thought to be mechanisms of improvement in insulin sensitivity after PSE.

Key words: partial splenic embolization, insulin resistance, liver cirrhosis, hepatic glucose uptake

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Introduction

Percutaneous transluminal partial splenic embolization (PSE) was developed to increase platelet counts in patients with liver cirrhosis-induced hypersplenism (1). For those who have chronic hepatitis C and are candidates for interferon therapy, lower platelet counts often preclude the therapy because interferon inevitably decreases platelet counts to a certain degree. PSE enables interferon therapy for patients who have lower platelet counts (2). Not only does PSE increase platelet counts, it also ameliorates portal hypertension and reduces esophageal varices by decreasing blood flow from the splenic vein (3). Recently, we encountered an intriguing case in which PSE reversed insulin resistance in a patient with liver cirrhosis. The patient had depended on subcutaneous insulin therapy to treat diabetes mellitus. Two weeks after PSE, the patient suffered from hypoglycemia.

After that time, subcutaneous insulin was no longer necessary to control blood glucose levels. This episode prompted us to investigate the relationship between PSE and the reversibility of insulin resistance. Several consecutive cases have shown that PSE significantly reverses insulin resistance in patients with liver cirrhosis. One of the mechanisms by which PSE reverses insulin resistance is the improvement of hepatic glucose uptake by decreasing splenic venous flow and increasing the relative rate of intestinal venous flow to the liver. In addition, significantly reduced HCV viral load after PSE might also play a part in improvement of glucose metabolism.

Patient

A 68-year-old man was admitted to our hospital by ambulance due to loss of consciousness. He had a history of chronic hepatitis C since he was 46 years old. When he was

56 years old, he underwent endoscopic sclerotherapy for esophageal varices. Subcutaneous insulin therapy was started to treat diabetes when he was 65 years old.

On admission, loss of consciousness and hyperammonemia were noted. He was diagnosed as hepatic coma and received branched-chain amino acids. After this treatment, his consciousness returned to the normal level. As for diabetes, fasting blood glucose was 265 mg/dL and HbA_{1c} was 8.9%. Intermediate-acting insulin (NPH) had been prescribed to treat diabetes at doses of 18 units before breakfast and 10 units before supper, respectively. The platelet count was $5.1 \times 10^4/\mu\text{L}$ and ecchymosis was noted. Esophageal varices with red color sign also were present. Endoscopic variceal ligation was conducted twice. At 1 month after admission, the patient underwent PSE in order to increase platelet counts and also to treat portal hypertension. Seventy four percent of splenic arterial perfusion area was successfully embolized. Splenic venous flow was decreased from 248 mL/min to 67 mL/min. As expected, platelet counts increased from $5.1 \times 10^4/\mu\text{L}$ to $9.1 \times 10^4/\mu\text{L}$ in 2 weeks. An unexpected finding was that hypoglycemia occurred 2 weeks after PSE. After the episode of hypoglycemia, neither insulin nor other oral medication for diabetes has been required for controlling blood glucose levels. HbA_{1c} declined from 8.9% to 6.2% in 2 months. Although we did not directly assess insulin resistance in this case because of previous use of insulin, it was assumed that PSE altered insulin sensitivity by uncertain mechanisms. This intriguing experience prompted us to investigate further the contribution of PSE to diabetes and insulin resistance.

Methods

Patient

From December 2005 to November 2007, 37 consecutive patients were enrolled in this study. The inclusion criteria were as follows: 1) Low platelet count $<10 \times 10^4/\mu\text{L}$ due to hypersplenism derived from liver cirrhosis. 2) Intractable portal hypertension (including ascites, hepatic encephalopathy, and varices), or 3) Interferon therapy was preferred but platelet count was not enough to tolerate interferon. The indication of PSE was determined for each patient according to the above factors. Written informed consent was obtained from all the patients.

PSE procedure (Takatsuka method)

Percutaneous catheter was inserted into the right femoral artery with local anesthesia of 1% lidocaine. The tip of the catheter was advanced into the hilum of the splenic artery. Branches of splenic arteries were embolized by microcoils and gelatin sponges. Upper branch of the splenic artery was left untreated so that the final embolization rate would be about 70%. The main characteristic of our PSE procedure is that microcoils are left straight in the branch of the splenic artery (4). Straight coils in the vessel shut down the run-off

Figure 1A. (Upper): Straight coils (arrow) were inserted into the branches of the splenic artery. Gelatin sponges were implanted proximally to the coils. **Figure 1B.** (Lower): Contrast-enhanced CT revealed the area of infarction.

of blood flow to the distal portion and prevent the development of collateral arteries. Gelatin sponges were implanted proximal to the microcoils (Fig. 1A). The area of infarction was confirmed by contrast material-enhanced computed tomography (Fig. 1B).

Doppler assessment of portal and splenic venous flow

Portal and splenic venous flow were assessed by Doppler ultrasound before and 2 weeks after PSE. The intestinal venous flow to the liver was calculated by subtracting the splenic venous flow from the portal venous flow.

Laboratory tests

Blood counts and chemistry were drawn before and after PSE. Homeostasis model assessment of insulin resistance (HOMA-IR) was also measured.

Patients who had fasting blood glucose >150 mg/dL were excluded from assessment of HOMA-IR, because HOMA-IR is not useful for severe hyperglycemia. Patients who depended on subcutaneous insulin therapy were also excluded.

Table 1. Characteristics of the 37 Patients at Baseline

Parameter	no. (%)
Sex	
Men	18 (49)
Women	19 (51)
Underlying disease	
HCV-induced liver cirrhosis	28 (76)
HBV-induced liver cirrhosis	2 (5)
Alcoholic liver cirrhosis	5 (14)
Idiopathic portal hypertension	1 (3)
Liver cirrhosis with unknown etiology	1 (3)
The objectives of PSE	
To increase platelet counts before interferon	14 (38)
For portal hypertension-induced symptoms	11 (30)
Treating pancytopenia	11 (30)
Prerequisite for chemoembolization	1 (3)
Medication for controlling blood glucose	
None	36 (97)
Sulfonylurea	1 (3)

Therefore, the patient presented in the case report was excluded from assessment of HOMA-IR.

The equation for calculating HOMA-IR is as follows:

$\text{HOMA-IR} = \text{immunoreactive insulin: IRI (mU/mL)} \times \text{fasting blood glucose (mg/dL)} / 405$

$\text{HOMA-IR} \geq 2.5$ is regarded as being insulin resistant. Fasting immunoreactive insulin (IRI: mU/mL) was also assessed as a surrogate for insulin resistance.

Statistical analysis

All data were expressed as mean $\pm$ SEM. Paired *t*-tests were used for statistical analyses. The Pearson correlation test was used to assess the correlation coefficients for scatter plots. A *p* value of <0.05 was considered statistically significant.

Results

Patients

Eighteen men (mean age: 59.2 years old), and 19 women (mean age: 66.9 years old) were enrolled in this study. Most patients had normal fasting blood glucose and required no medication for control of blood glucose. Only one patient depended on oral sulfonylurea. As mentioned, patients who were dependent on insulin therapy were not included. Twenty-eight patients had hepatitis C virus (HCV)-induced liver cirrhosis. Two patients had hepatitis B virus (HBV)-induced liver cirrhosis. One patient had liver cirrhosis with

Figure 2. Hemodynamic changes before and 2-weeks after PSE. “pre”(white bars): before PSE; “2W” (gray bars): 2 weeks after PSE; “PV”: portal venous flow; “SV”: splenic venous flow; “IV”: intestinal venous flow to the liver.

Figure 3. The relative rate of the intestinal venous flow in the portal venous flow increased significantly after PSE ($p < 0.01$).

unknown etiology (non B non C hepatitis). Five patients had alcoholic liver cirrhosis. One patient had idiopathic portal hypertension. The objectives of PSE for each patient were as follows; for increasing platelet counts before interferon therapy (14 patients), for ameliorating portal hypertension-induced symptoms such as ascites and hepatic encephalopathy (11 patients), for treating hypersplenism-induced pancytopenia (11 patients), and as a prerequisite for an intervention against hepatocellular carcinoma (1 patient) (Table 1).

Hemodynamic changes after PSE

Mean volume of the spleen was 524 ± 300 cm³. As intended, the mean infarction rate was 71%. Splenic venous flow before and 2 weeks after PSE were 341 ± 53 mL/min, 209 ± 31 mL/min, respectively ($p < 0.001$). Portal venous flow

Figure 4. PSE significantly reduced HOMA-IR ($p < 0.05$).

before and two weeks after PSE were 975 ± 95 mL/min, 930 ± 94 mL/min, respectively ($p = 0.38$). Intestinal venous flow to the liver before and after PSE were 634 ± 74 mL/min, 721 ± 80 mL/min, respectively ($p = 0.06$) (Fig. 2). The relative rate of the intestinal venous flow in the portal venous flow before and after PSE were $62.9 \pm 6.1\%$, $75.8 \pm 3.7\%$, respectively ($p < 0.01$) (Fig. 3).

PSE significantly increased platelet counts

Platelet counts before PSE was $7.7 \pm 0.5 \times 10^4/\mu\text{L}$. Two weeks after PSE, platelet counts rose to $15.0 \pm 1.4 \times 10^4/\mu\text{L}$ ($p < 0.01$).

PSE significantly reversed insulin resistance

HOMA-IR before PSE was 6.5 ± 2.1 . Two weeks after PSE, HOMA-IR reduced to 3.3 ± 0.6 ($p < 0.05$) (Fig. 4). IRI before PSE was 17.7 ± 4.4 mU/mL. Two weeks after PSE, IRI reduced to 10.2 ± 1.0 mU/mL ($p < 0.05$).

PSE significantly reduced HCV viral load

HCV core antigen before PSE was $6,340 \pm 1,296$ fmol/L. Two weeks after PSE, HCV core antigen reduced to $4,112 \pm 873$ ($p < 0.05$) (Fig. 5).

The HCV log drop correlated with decline of the HOMA-IR with a correlation coefficient of 0.57 ($p < 0.01$) (Fig. 6).

Discussion

Patients with liver cirrhosis often develop insulin resistance and diabetes mellitus (5). The prevalence of impaired glucose tolerance and overt diabetes in cirrhotic patients are about 60% and 20%, respectively (6). Petrides et al. reported a case of idiopathic portal hypertension (IPH) with marked hyperinsulinemia (7). Hyperinsulinemia in IPH is caused by decreased hepatic first pass of insulin and increased porto-systemic shunting (5). Basal hyperinsulinemia *per se* leads to insulin resistance by various mechanisms, irrespective of the underlying etiology (8). As in the case of

Figure 5. PSE significantly reduced HCV core antigen ($p < 0.05$).

Figure 6. The log-drop of HCV core antigen correlated with decrease of the HOMA-IR. Note that negative values indicate the decline of the values after PSE.

liver cirrhosis, hyperinsulinemia is regarded as the main cause of impaired glucose tolerance (9). A dramatic improvement of insulin sensitivity in our study suggests the importance of hemodynamic factors in glycemic control in liver cirrhosis with portal hypertension.

Previously, PSE by microcoils seemed to be less effective than surgical splenectomy because of the collateral arteries formation. The rationale for our straight-coil method is that this procedure prevents collateral arteries formation by blocking run-off flow. Indeed, the effects of PSE in this study persisted throughout the observation period. In addition, percutaneous transluminal PSE is a less invasive technique than a surgical splenectomy. Therefore, our PSE

method is a promising therapeutic alternative to a surgical splenectomy.

The mechanism by which PSE reverses insulin resistance is mainly due to hemodynamic improvement of intestinal venous flow into the liver. In cases of portal hypertension, intestinal venous flow to the liver is disturbed due to the overflow of splenic venous return. Decrease of splenic venous flow by PSE might contribute to relative increase of the intestinal portal flow among the total amount of portal flow.

We observed a reduction of HCV viral load after PSE. HCV is known to cause insulin resistance (10). Shintani et al. proved the direct involvement of HCV on insulin resistance via hyperexpression of tumor necrosis factor- α (TNF- α) in the liver (11). The reason why HCV viral load reduces after PSE is as yet unknown; however, Cao et al. reported that splenectomy converts T-helper type-1 (Th1)/Th2 cytokine balance to a Th1-dominant pattern (12). An enhanced Th1 response is essential for the eradication of HCV (13).

Reportedly, interleukin-2 and interferon- γ levels increase while interleukin-10 levels decrease after splenectomy (12). Whether such conversions also occur after PSE is unknown, because we did not measure the levels of Th1/Th2 cytokines.

One of the limitations of this study is that we only assessed the short-term effects of PSE. Therefore, further research is needed to determine the long-term effects of PSE.

In conclusion, PSE reverses insulin resistance by ameliorating hemodynamic derangement in liver cirrhosis and possibly by reducing HCV viral load. The notion of hepatic glucose uptake is increasingly recognized as an important mechanism for regulating blood glucose levels. To date, hepatic glucose uptake has been exclusively discussed in the context of transcription factors in hepatocytes (14). Our findings shed light on the role of extrahepatic hemodynamic factors in hepatic glucose uptake, and also the anti-HCV effect of PSE.

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