ORIGINAL ARTICLE

Study on the Mechanism of Duodenal-jejunal Bypass for Improving Hepatic Glycolipid Metabolism in Zucker Diabetic Fatty Rats

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ABSTRACT

Background: Duodenal-jejunal bypass (DJB) is an experimental procedure to study the mechanism of metabolic surgery in type 2 diabetes mellitus treatment, but the exact molecular mechanism has not been elucidated. **Objective:** This study explored the effects of DJB surgery on hepatic insulin resistance and glucose, lipid metabolism in Zucker diabetic fatty (ZDF) rats. **Materials and Methods:** We established a DJB intervention model in ZDF rats, assess glucose tolerance and insulin secretion, detect total cholesterol (TC) and triglycerides (TGs) in serum, and detect the expression of key enzymes involved in glycolipid metabolism, including phosphoenolpyruvate carboxykinase (PEPCK), glucose-6-phosphatase (G-6-Pase), glycogen synthase kinase examined 3 beta (GSK-3β), and acetyl-coenzyme A carboxylase (ACC), and also studied factors related to the insulin signaling pathway, including insulin receptor (InsR), insulin receptor substrate 2 (IRS2), phosphoinositide 3-kinase (PI3K), protein kinase B (Akt), and P-Akt. **Results:** After DJB surgery, the glucose tolerance and insulin resistance of ZDF rats were significantly improved. The expressions of PEPCK, G-6-Pase, and GSK-3β in the liver were significantly decreased after DJB, and InsR, IRS2, PI3K, and P-Akt were significantly increased. After DJB intervention, the expression of serum TG, TC, and liver ACC was downregulated. **Conclusions:** Our findings indicated that DJB surgery improves liver glycolipid metabolism by regulating insulin-mediated PI3K/Akt signaling pathway, improves glucose homeostasis and insulin resistance, and effectively treats and prevents diabetes.

Key words: Blood glucose homeostasis, duodenal-jejunal bypass, glycolipid metabolism, insulin resistance, type 2 diabetes

INTRODUCTION

Gastric surgery has been changed to metabolic surgery for the wildly effect in metabolic dysfunction including obesity and type 2 diabetes mellitus (T2DM).[1,2] Both animal[3,4] and clinical researches[1,5] suggested that the gastric bypass surgery significantly alleviates blood glucose. The possible mechanisms involve the changes in gastrointestinal hormones, bile acid metabolism, intestinal flora, and neuronal perception, but the mechanisms underlying this phenomenon have largely remained elusive.[6] Understanding the mechanism of metabolic surgery in T2DM treatment may provide us clues regarding the pathophysiology of T2DM, which facilitates future improvement of surgical methods or device-based design of T2DM and its related diseases.[7,8]

Duodenal-jejunal bypass (DJB) is an experimental procedure used in the study of metabolic surgery treating diabetes, which was established by Rubino.[9] DJB improved the

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glucose homeostasis by changing the anatomical structure of the gut without food intake restricting or weight losing, presented a weight independent antidiabetes effect.[10] As the main organ in glucose homeostasis regulation, the liver plays an important role in diabetes pathogenesis.[11] In this study, the role and signal transduction involving glucose control of the liver after metabolic surgery were studied. ZDF rats, characterized by obesity, progressive insulin resistance, and impaired glucose tolerance, were used to study the mechanism of DJB on T2DM.[12-14] We propose that activation of the insulin signaling pathway and phosphoinositide 3-kinase (PI3K)/protein kinase B (P-Akt) in the liver is necessary for DJB surgery to lower glucose production in T2DM rats. First, DJB activated the insulin signaling and the downstream PI3K/Akt signaling pathway, and further regulated the glucose uptake, glycogen synthesis, gluconeogenesis and lipid metabolism.

MATERIALS AND METHODS

Chemicals

Insulin ELISA kits were purchased from Wuhan Yusheng Trading Co., Ltd. (Wuhan, China). Trizol was purchased from CW Bio (Beijing, China). Reverse Cycle Kit, qRT-PCR Master Mix were purchased from Toyobo (Osaka, Japan), BCA protein kits were purchased from Beijing Kangwei Century Biotechnology Co., Ltd. (Beijing, China). The sources of the antibodies and the dilution ratios are listed in Table 1.

Animals and surgical interventions

Sixteen ZDF rats and eight paired lean non-diabetic ZDF rats (fa/+, genotype) (8 weeks old, 180–200 g) were purchased from Beijing Vital River Laboratory Animal Technology Co. Ltd. (Beijing, China).[15] The rats were housed under standardized conditions (22°C and a 12 h light-dark cycle). Sixteen diabetic rats were randomly separated into sham groups (sham) and DJB groups (DJB), eight in each group. Eight age-matched lean ZDF rats were assigned as control group (control). All rats were housed in a standardized condition at least 1 week before surgery. The rats were euthanized with 150 mg/kg sodium pentobarbital intravenously 6 weeks after the operation. All related procedures have been reviewed and approved by the Institutional Animal Care and Use Committee of Weifang Medical University.

Table 1: Serum TC measured by total cholesterol assay kit (mmol/L)

Dates	Control	Sham	DJB
Pre 1 week	2.78±0.08***	6.33±0.47###	6.28±0.45###
Post 2 week	2.65±0.19***	6.28±0.45###	4.30±0.25**
Post 4 week	3.10±0.33***	6.03±0.85###	4.22±0.54**

Data are the means±SD. TC: Total cholesterol. **P<0.01; ***P<0.001 versus sham; ###P<0.001 versus control

DJB and sham surgical procedures

After 12 h of fasting, rats of DJB and sham groups were anesthetized by intraperitoneal injection of ketamine 75 mg/kg. The surgical procedure is followed as described in our previous paper.[15,16] All the three group rats received the same post-operative care pattern, including a supply of parenteral nutrition within 48 hours, liquid diet from day 2 to day 5 post-operative and standard chow after day 5.

Detection of basic metabolic indicators

Fasting glucose was measured twice a week by glucose monitor (Sinocare Inc.). The fasting serum insulin before and 6 weeks, the operation was measured with insulin ELISA kit (Wuhan USCN Business Co. Ltd., China). Triglyceride (TG) and total cholesterol (TC) levels pre- and post-operative were measured by ELISA using automatic biochemical analyzer. Homeostatic model assessment-insulin resistance (HOMA-IR) and HOMA-insulin sensitivity index values were calculated according to the following formula: HOMA-IR = fasting insulin (mIU/L) × fasting glucose (mmol/L)/22.5. HOMA-ISI =1/fasting insulin (mIU/L) × fasting glucose (mmol/L).

For the OGTT and the ITT, rats were orally gavaged with 1 g/kg glucose or subcutaneously injected with insulin (0.5 U/kg) after 12 h of fasting. Blood glucose was measured at 0, 30, 60, 90, and 120 min after gavage. The area under the curve (AUC) of OGTT and ITT was calculated by GraphPad Prism 5 software (GraphPad Software Inc., USA).

Tissue processing and preparation

Six weeks after surgery, all rats were sacrificed by euthanasia. The liver tissue of each rat was collected, and one part was fixed in 4% paraformaldehyde for immunohistochemical (IHC) analysis, others were frozen in a −80°C refrigerator for Western blot and quantitative real-time-polymerase chain reaction analysis (qRT-PCR).

Western blotting analysis

The expression of insulin receptor (InsR), insulin receptor substrate 2 (IRS2), PI3K, Akt, P-Akt, phosphoenolpyruvate carboxykinase (PEPCK), acetyl-coenzyme A carboxylase (ACC), GSK-3β, and G-6-Pase in liver was detected by Western blot. Six weeks after surgery, liver tissues from the rats were weighed and homogenized in cold PBS (pH 7.2) at 4°C. Evaluation of protein concentration in supernatant after centrifugation using a BAC 100 protein determination kit (Sigma, USA). According to the different molecular weights of the proteins, equal amounts of protein were subjected using the SDS-PAGE gel and were then transferred to nitrocellulose membranes at 300 mA for 1.5 h at 4°C. The membrane was blocked in the blocking solution for 1.5 h and

bound to the primary antibody (4°C, 12 h). The membrane was then combined with goat anti-rabbit IgG or goat anti-mouse IgG (LI-COR Biosciences, Lincoln, NE) for 1 h in the dark. The Odyssey SA infrared imaging system (LI-COR Biosciences, USA) was used to visualize and analyze the expression of the protein. The intensity of specific bands was quantified with ImageJ software (National Institutes of Health, USA). The following primary antibodies were used in these experiments: TnsR (1:1000, Abcam), IRS2 (1:1000, Abcam), PI3K (1:1000, Abcam), Akt (1:300, Bioss), P-Akt (1:300, Bioss), PEPCK (1:500, Bioss), ACC (1:1000, Bioss), G-6-Pase (1:1000, Abcam), GSK-3β (1:300, Bioss), and β-actin (1:2000, Bioss).

IHC analysis

The tissue handling was followed as described.[15] After dewaxed and rehydrated, the liver tissue sections (3 μm) was treated with 3% hydrogen peroxide and incubated with the corresponding primary antibody for 12 h at 4°C. The sources and dilution ratios of the experiment are listed in Table 1. The sections were washed 3 times by PBST and combined with the secondary antibody at 25°C for 1 h. After washed by PBST, sections were incubated with diaminobenzidine at room temperature for 5 min. The positive staining was observed and analyzed using microscope (IX71, Olympus, Japan).

qRT-PCR

Total RNA was extracted from liver tissue with Trizol (CWBio, Beijing, China) and 20 μL of DEPC water was added to dissolve it. cDNA was generated using a reverse transcription kit (TOYOBO, Osaka, Japan). Quantitative fluorescence analysis using Light Cycler 480 real-time PCR system (Roche, Germany). Primer sequences were as follows: TnsR (5′-GTCATCTCTGGCCTGAGACACTT-3′ and 5′-AG CACGCTGCACCTCTCT-3′); IRS (5′-CGG ACGCCAAGCACAAGTACC-3′ and 5′-TCCTGCTCC TGCTCGTTCTCC-3′); PI3K (5′-AGATCGCTC TGGCCTCATTG-3′ and 5′-AGCCAGTTCAGAAGGGC ATC-3′); Akt (5′-ATGGACTTCCGGTCAGGTTCA-3′ and 5′-GCCCTTGCCCAGTAGCTTCA-3′); PEPCK (5′-ATCCG AACGCCATTAAGACCATCC-3′ and 5′-CGCACGG TTCCTCATCCTGTG-3′); ACC (5′-TTGTGGATGG CTTGCGGGAATG-3′ and 5′-GTGCCGAGGATTGATGG TTGGG-3′); G-6-Pase (5′-CTCTGGGTGGCAGTGGTCGG A-3′ and 5′-CAGGACCCACCAATACGGGC-3′); GSK-3β (5′-ACGCCACAGCAGCCTCAGATACT-3′ and 5′-TGAC CAGTGTTGCTGAGTGGCA-3′); and β-actin (5′-GGATC AGCAAGCAGGAGTACGA-3′ and 5′-AACGCAGCTCAG TAACAGTCCG-3′).

Statistical analysis

Statistical data comparisons were performed using GraphPad Prism 5. Unpaired tests were used to assess differences before and after surgery. Data are expressed as the mean ± SD. One-way analysis of variance and analysis of variance of repeated measurement data were used for comparison between groups and then Tukey test. $P < 0.05$ indicates a statistically significant difference.

RESULTS

DJB improves the glucose homeostasis of the ZDF diabetic rats

As shown in Figure 1a, the fasting blood glucose significantly decreased on day 2 and remained at low levels for 6 weeks after DJB surgery. The body weight did not show significant difference between T2DM-DJB rats and T2DM-sham rats after surgery [Figure 1b]. OGTTs were performed 1 week before and 2, 4, and 6 weeks post the operation, and AUC for OGTT data showed that the oral glucose tolerance was significantly improved in DJB rats compared with sham rats at 2, 4, and 6 weeks post-operative [Figure 1c]. ITT was performed 1 week before and 2, 4, and 6 weeks post-operative, and the AUC of ITT showed that insulin resistance was significantly improved in post-operative DJB rats compared with sham rats at 2, 4, and 6 weeks post-operative [Figure 1d]. The HOMA-IR and HOMA-ISI calculated by the formula showed that the insulin resistance was significantly decreased while insulin sensitive index was significantly increased 6 weeks post-operative in DJB rats comparing to sham rats [Figure 1e and f]. The results suggested that DJB surgery improved the glucose regulation ability in ZDF T2DM rats.

DJB reversed the high expression of PEPCK, G-6-Pase, and GSK-3β in the liver of ZDF T2DM rats

To study the changes in liver glucose metabolism after DJB intervene, the expression of key enzymes involving glucose homeostasis including PEPCK, G-6-Pase, and GSK-3β was studied by Western blot, qRT-PCR, and IHC. As shown in Figure 2a, the expression of PEPCK and GSK-3β is significantly increased in sham rats comparing to the lean control rats, while DJB intervene significantly decreased the expression of PEPCK and GSK-3β expression comparing to the sham rats. Figure 2b shows the relative changing of protein expression analyzed by ImageJ software. Changes in PEPCK and GSK-3β mRNA expression in the liver of the three group rats, trends are similar to that of the protein expression [Figure 2c and d]. IHC results showed that G-6-Pase and PEPCK expression is significantly lower in DJB rats comparing to the sham rats [Figure 2e].

DJB lowered the blood lipids level and decreased the ACC expression in liver of T2DM rats

Diabetes often accompanied with abnormal lipid metabolism, which are mainly manifested by elevated TC and TG levels. ELISA kit checking the lipid level of the three group rats showed that DJB reversed the significantly increased serum TC and TG in sham rats. The TC and TG of pre-operative

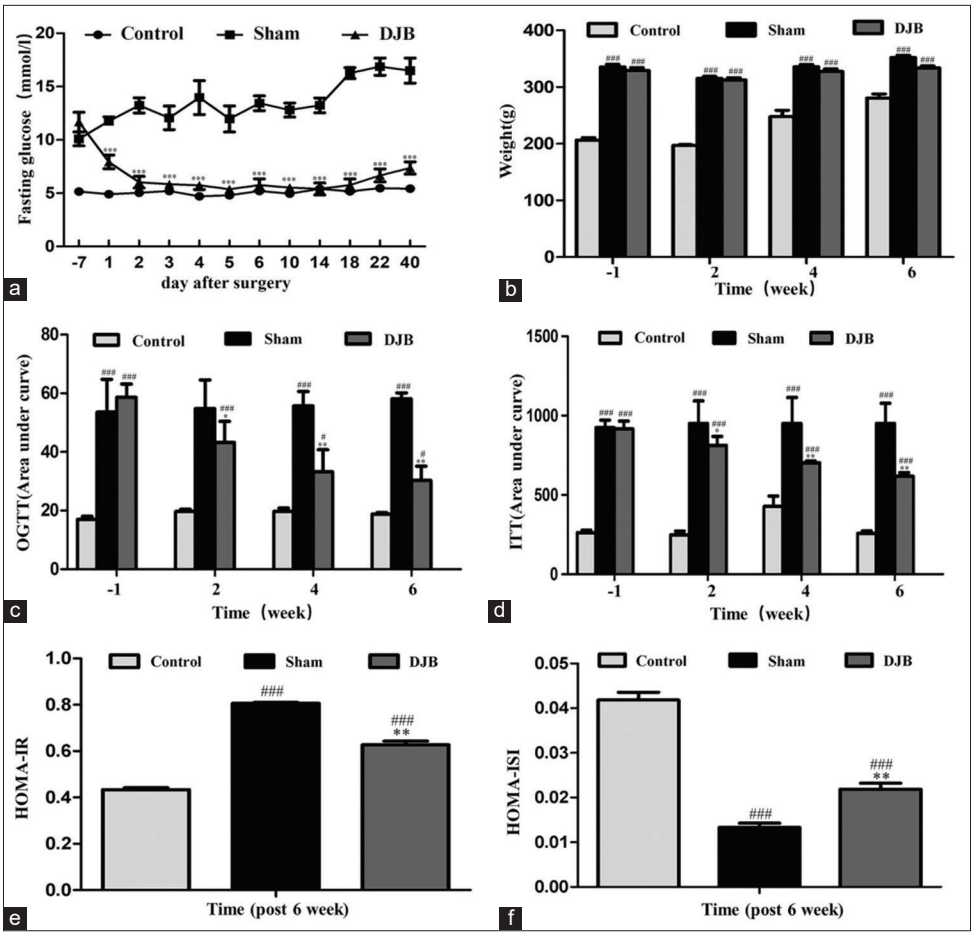

Figure 1: Duodenal-jejunal bypass improves blood glucose and insulin resistance in type 2 diabetic rats. (a) Fasting blood glucose (FBG) pre- and post-operative. (b) Weight change pre- and post-operative. (c) The area under the curve (AUC) for OGTT results. (d) The area under the curve (AUC) for ITT results. (e) Homeostatic model assessment (HOMA)-insulin resistance 6 weeks after surgery. (f) HOMA-ISI 6 weeks after surgery. $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$ versus sham; $^{\#}P < 0.05$; $^{\#\#\#}P < 0.001$ versus control. Bars represent the mean ± SD of eight rats

Table 2: Serum TG measured by triglyceride assay kit (mmol/L)

Dates	Control	Sham	DJB
Pre 1 week	1.44±0.47***	7.31±0.99###	7.35±0.91
Post 2 week	1.46±0.38***	7.13±1.21###	3.99±0.74***
Post 4 week	0.80±0.15***	5.57±1.65###	2.72±0.79**

Data are the means±SD. TG: Triglyceride. **P<0.01; ***P<0.001 versus sham; ###P<0.001 versus control

in sham and DJB groups were higher than control group. Compared with the sham group rats, the serum TC and TG of the DJB group rats were significantly decreased after DJB surgery [Figure 3a-b and Table 1-2]. To investigate the mechanism of lipid decline, we examined the expression of ACC, key enzyme in fatty acid synthesis. Figure 3c shows the expression of ACC detected by Western blot in the three group rats. Gray scale scanning by ImageJ showed that ACC expression was significantly increased in T2DM sham rats and DJB significantly decreased ACC expression in the liver tissue comparing to sham rats [Figure 3d-f]shows ACC mRNA levels checking by qRT-PCR and protein levels checking by IHC, respectively. The results confirmed that DJB surgery could significantly lower the level of TG and TC, and decrease the expression of lipid synthesis key enzyme ACC.

DJB enhanced the liver PI3K/Akt signaling pathway in ZDF rats

The insulin signaling pathway plays an important role in regulating tissue insulin sensitivity glucose and lipid metabolism. The Western blot results showed that the expression of InsR, IRS2, PI3K, and P-Akt significantly decreased in the liver of T2DM sham rats comparing to control, DJB significantly increased the expression of InsR, IRS2, PI3K, and P-Akt in the liver comparing to sham rats [Figure 4a and b]. Figure 4c-f shows the qRT-PCR results of the mRNA levels of InsR, IRS2, PI3K, and Akt, respectively. These results showed that DJB surgery promoted the liver's PI3K/Akt signal in ZDF rats by upregulate the expression of InsR, IRS2, PI3K, and P-Akt, thereby lowering blood glucose and improving liver glycolipid

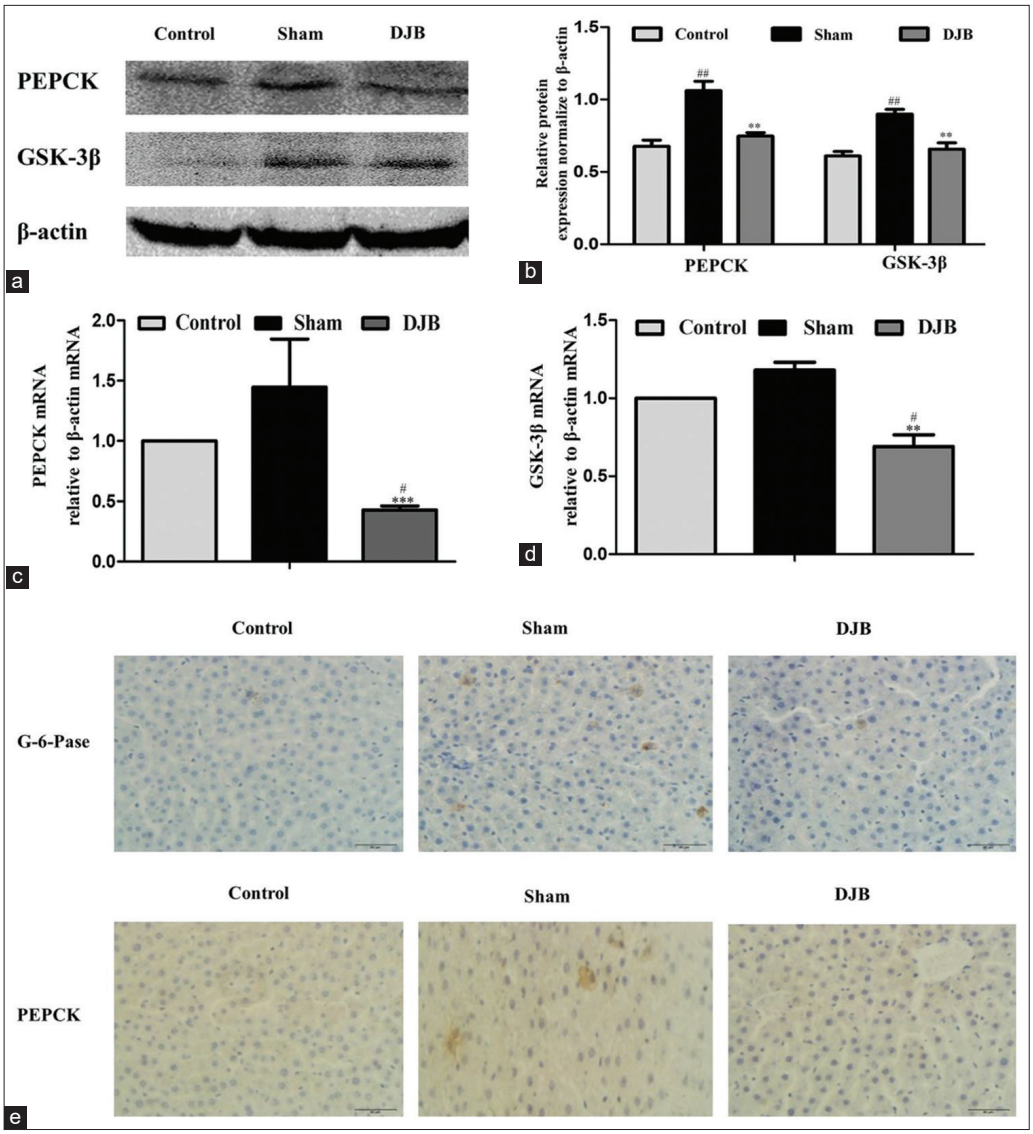

Figure 2: Duodenal-jejunal bypass reduces the expression of phosphoenolpyruvate carboxykinase (PEPCK), G-6-Pase, and GSK-3β in the liver of Zucker diabetic fatty rats. (a and b) Western blotting detected the expression of PEPCK and GSK-3β in the liver of different group rats. (c and d) qRT-PCR detected mRNA expression of PEPCK and GSK-3β in the livers of the three groups rats. (e) IHC staining for G-6-Pase and PEPCK in the livers of the three groups rats (×200). Scale bar, 100 μm. $^{**}P< 0.01$; $^{***}P< 0.001$ versus sham; $^{\#}P< 0.05$; $^{\#\#}P< 0.01$ versus control. Bars represent the mean ± SD of eight rats

metabolism. It is speculated that DJB surgery improved liver glucose, lipid metabolism, and insulin resistance in ZDF rats by activating insulin-PI3K/AKT pathway.

DISCUSSION

T2DM is a chronic metabolic disease characterized by hyperglycemia and insulin resistance. The number of T2DM patients worldwide is predicted increasing to 642 million by 2040.[17,18] The liver is the main organ for the regulation of blood glucose homeostasis. The liver provides glucose through gluconeogenesis and glycogen decomposition to increase blood glucose level. Inhibition of glucose production in the liver is the main reason for decreasing blood glucose by insulin. Moreover, insulin resistance prevents the liver from suppressing endogenous glucose production might be the main reason of diabetes. Gluconeogenesis key enzymes, such as PEPCK and G6Pase, have been shown to increase insulin resistance and disturbances of glucose metabolism *in vivo*.[19-21] PEPCK and G-6-Pase are rate-limiting enzymes in gluconeogenesis[22,23] and GSK-3β is a key enzyme in inhibiting hepatic glycogen synthesis.[24] Hepatic insulin resistance plays a leading role in type 2 diabetes pathogenesis.[25-27] Moreover, the PI3K/Akt signaling pathway is the main downstream pathway of insulin signal in liver.[28,29]

Over the past 20 years, bariatric surgery was originally designed for weight loss, has proven successful in treating not

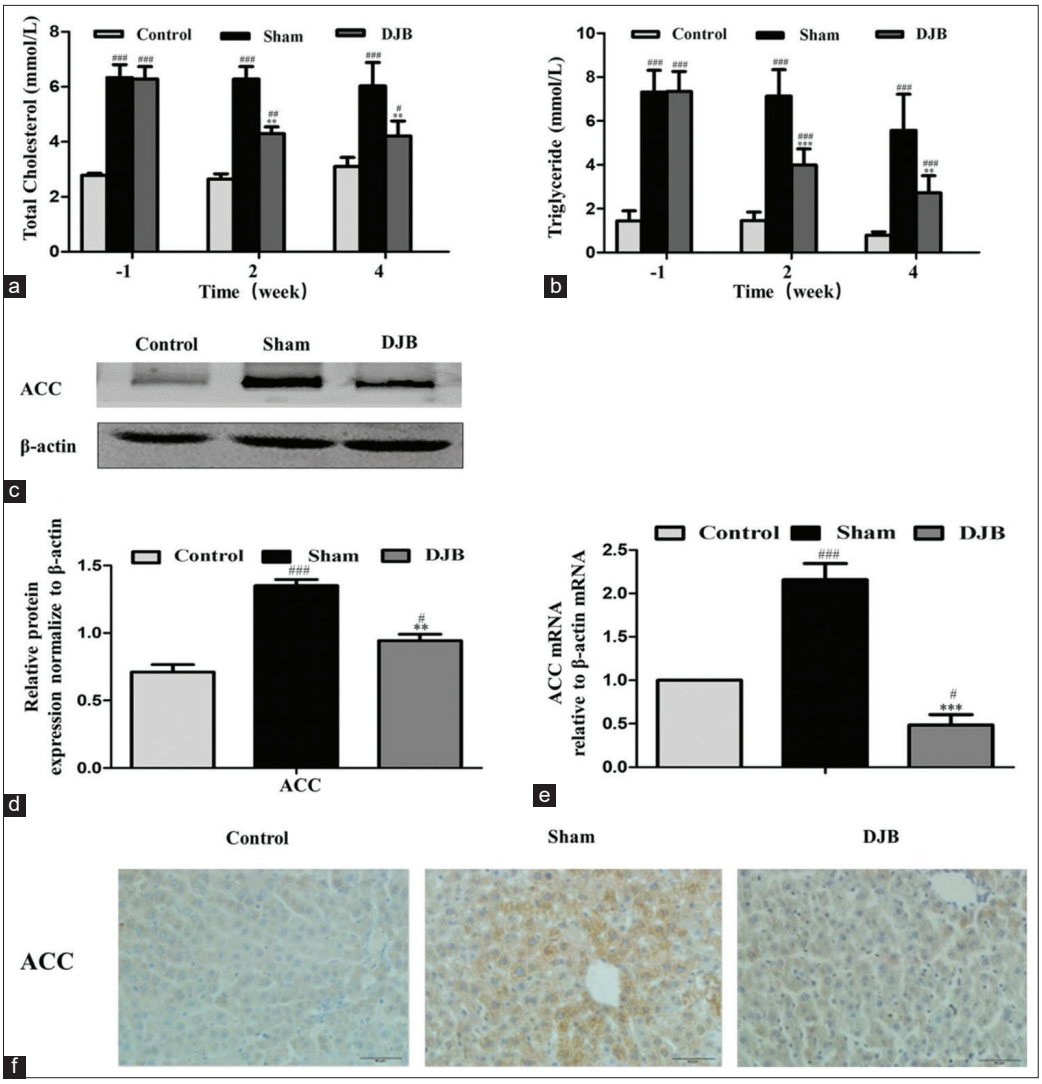

Figure 3: Duodenal-jejunal bypass reduces the level of total cholesterol, triglyceride (TG) in blood, and the expression of acetyl-coenzyme A carboxylase (ACC) in the liver in Zucker diabetic fatty rats. (a) Serum total cholesterol pre- and post-operative. (b) TG pre- and post-operative. (c and d) Western blotting results of the expression levels of ACC in the liver of rats. (e) qRT-PCR results of the mRNA expression of ACC in the liver of rats. (f) IHC staining for ACC in the liver of rats (×200). Scale bar, 100 μm. $^{**}P< 0.01$; $^{***}P< 0.001$ versus sham; $^{\#}P< 0.05$; $^{\#\#}P< 0.01$; $^{\#\#\#}P< 0.001$ versus control. Bars represent the mean ± SD of eight rats

only obesity but also type 2 diabetes.[30,31] The gastric surgery was renamed as "metabolic surgery" in 2013, for the weight loss independent effects.[32] Rubino and Marescaux first setup a new procedure to study the role of duodenal-jejunal exclusion caused a direct antidiabetic in non-obesity T2DM rats model.[33] Other studies also showed that DJB improves glucose and adipokine metabolism with no weight loss in a diabetic rat model.[34,35] In 2013, the study by Hu *et al*. showed DJB surgery upregulates key regulatory enzymes of gluconeogenesis in liver and intestine of diabetic Goto-Kakizaki rats.[22,36] That study confirmed the important role of liver in DJB surgery, but the signal transduction pathway remains unclear.

In summary, we established a DJB intervention model in ZDF rats and explored the effects of DJB surgery on hepatic insulin resistance and glucose, lipid metabolism in T2DM rats. The results showed that DJB improved glucose homeostasis, significantly reduced blood glucose, blood lipids, and insulin resistance in ZDF rats. These effects may be caused by increased expression of genes and proteins of InsR, IRS2, PI3K, and P-Akt in the insulin signaling pathway and decreased expression of PEPCK, G-6-Pase, GSK-3β, and ACC.

CONCLUSIONS

DJB surgery can inhibit liver gluconeogenesis and fatty acid production, increase liver glycogen synthesis, improve insulin resistance, and effectively treat and prevent diabetes by regulating the PI3K/Akt signaling pathway mediated by insulin.

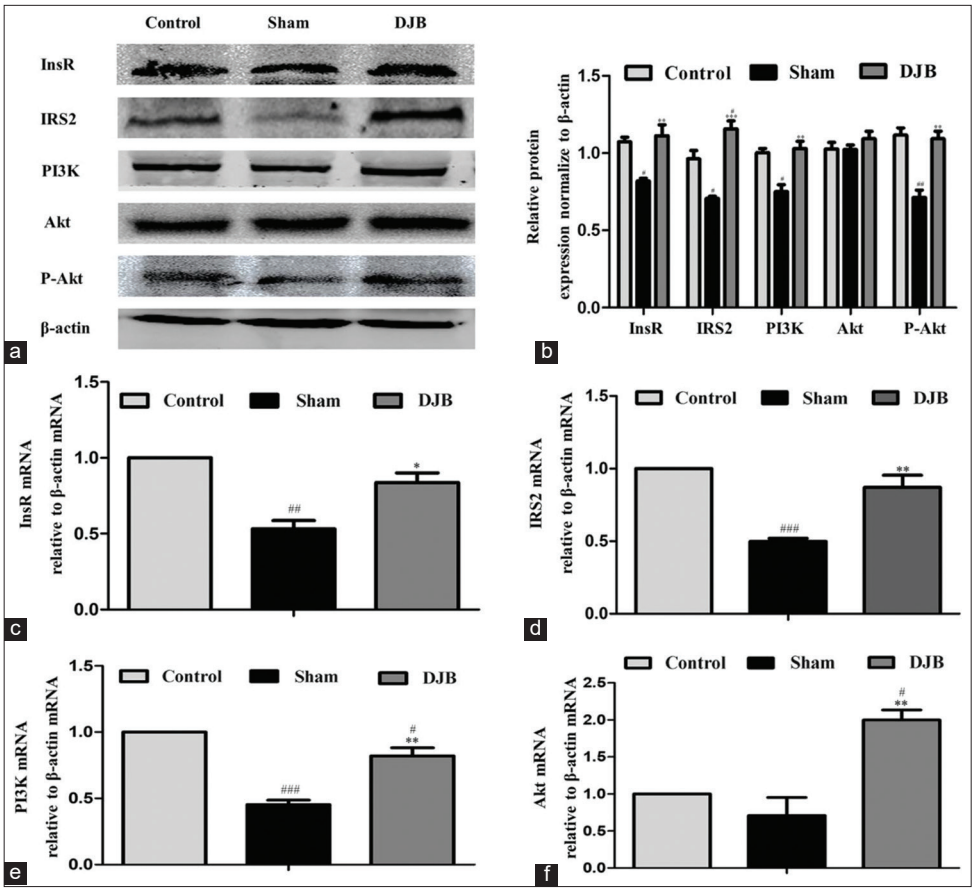

Figure 4: Activation of the phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt) pathway in the liver after duodenal-jejunal bypass. (a and b) Western blotting results of the expression levels of insulin receptor (InsR), insulin receptor substrate 2 (IRS2), PI3K, Akt, and p-Akt in the livers of rats. (c-f) qRT-PCR results of the mRNA expression levels of InsR, IRS2, PI3K, and Akt in the livers of rats. **P*< 0.05; ***P*< 0.01; ****P*< 0.001 versus sham; #*P*< 0.05; ##*P*< 0.01; ###*P*< 0.001 versus control. Bars represent the mean ± SD of eight rats

A statement of animal rights

This study was carried out in accordance with the recommendations of Weifang Medical University, China. The experimental protocol was approved by the Research Ethics Committee of Weifang Medical University, China.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

FUNDING

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AUTHORS' CONTRIBUTIONS

M.Q., Z.G., R.P., and Q.Y. designed, led the study, and wrote the manuscript. H.W., B.J., W.W., H.S., N.L., S.M., and M.Z performed the experiments and statistical analysis. All coauthors commented on the manuscript and agreed with the manuscript results and conclusions.

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