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ORIGINAL ARTICLE

Yi-Qi-Zeng-Min-Tang, a Chinese medicine, ameliorates insulin resistance in type 2 diabetic rats

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Abstract

AIM: To investigate the effects of the Chinese herbal decoction, Yi-Qi-Zeng-Min-Tang (YQZMT), on insulin resistance in type 2 diabetic rats.

METHODS: Sprague-Dawley rats were divided into two dietary regiments by feeding either normal pellet diet (NPD) or high fat diet (HFD). Four weeks later, the HFD-fed rats were injected intraperitoneally with low-dose streptozotocin (STZ). Rats with non-fasting blood glucose level ⩾ 16.67 mmol/L were considered type 2 diabetic and further divided into five subgroups: the type 2 diabetes model group, low-dose, medium-dose and high-dose YQZMT groups, and rosiglitazone group. Age-matched NPD-fed rats served as controls. YQZMT or rosiglitazone were administered for 8 wk. Intraperitoneal glucose and insulin tolerance tests were performed before and after the treatment to measure the glucose tolerance and insulin sensitivity. Serum levels of biochemical parameters, adipocytokines, such as tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), as well as free fatty acids (FFAs), were also analyzed.

RESULTS: There was significant elevation of insulin resistance and serum levels of fasting glucose (12.82 ± 1.08 mmol/L *vs* 3.60 ± 0.31 mmol/L, $P < 0.01$), insulin (7197.36 ± 253.89 pg/mL *vs* 4820.49 ± 326.89 pg/mL, $P < 0.01$), total cholesterol (TC) (8.40 ± 0.49 mmol/L *vs* 2.14 ± 0.06 mmol/L, $P < 0.01$), triglyceride (2.24 ± 0.12 mmol/L *vs* 0.78 ± 0.05 mmol/L, $P < 0.01$), low-density lipoprotein cholesterol (LDL-c) (7.84 ± 0.51 mmol/L *vs* 0.72 ± 0.04 mmol/L, $P < 0.01$) and decrease in high-density lipoprotein cholesterol (HDL-c) (0.57 ± 0.03 mmol/L *vs* 1.27 ± 0.03 mmol/L, $P < 0.01$) in the low-dose STZ and high-fat diet induced type 2 diabetic group when compared with the control group. Administration of YQZMT induced dose- and time-dependent changes in insulin resistance, glucose and lipid profile, and reduced levels of FFA, TNF-α and IL-6 in the type 2 diabetic rats. After the treatment, compared with the diabetic group, the insulin resistance was ameliorated in the high-dose YQZMT (2.82 g/100 g per day) group, with a significant reduction in serum glucose (12.16 ± 1.00 mmol/L *vs* 17.65 ± 2.22 mmol/L, $P < 0.01$), homeostasis model assessment of basal insulin resistance (22.68 ± 2.37 *vs* 38.79 ± 9.02, $P < 0.05$), triglyceride (0.87 ± 0.15 mmol/L *vs* 1.99 ± 0.26 mmol/L, $P < 0.01$), TC (3.31 ± 0.52 mmol/L *vs* 6.50 ± 1.04 mmol/L, $P < 0.01$) and LDL-c (2.47 ± 0.50 mmol/L *vs* 6.00 ± 1.07 mmol/L, $P < 0.01$), and a significant increase in HDL-c (0.84 ± 0.08 mmol/L *vs* 0.50 ± 0.03 mmol/L, $P < 0.01$). But the body weight was not changed significantly.

CONCLUSION: YQZMT, which ameliorates insulin resistance and does not cause increase in body weight, may be a suitable therapeutic adjunct for the treatment of type 2 diabetes.

Key words: Yi-Qi-Zeng-Min-Tang; Insulin resistance; Type 2 diabetes; Lipids; Adipocytokines; Free fatty acids

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INTRODUCTION

The prevalence of type 2 diabetes is dramatically increasing throughout the world. Pathogenesis of this disease involves abnormalities in glucose and lipid metabolism, including inadequate insulin secretion from pancreatic β-cells and insulin resistance[1,2].

Insulin resistance is a hallmark of type 2 diabetes, characterized by a decreased response of the peripheral tissues to insulin action[3,4], and it most often precedes the onset of hyperglycemia and predicts development of type 2 diabetes[5]. Insulin resistance produces elevations in glucose and lipid levels[6]. It has become increasingly evident that obesity and the concomitant development of inflammation are major components of insulin resistance. Studies have revealed a clear association between pro-inflammatory signaling pathways and decreased insulin sensitivity[7]. Pro-inflammatory adipokines including tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), as well as free fatty acids (FFAs), have been implicated to play important roles in inflammation, insulin resistance, and type 2 diabetes[8-11]. These inflammatory markers have been proposed to be risk factors for cardiovascular disease (CVD) in type 2 diabetes mellitus patients[12].

Since insulin resistance both precedes and predicts type 2 diabetes, it is important to develop drugs to reverse insulin resistance[13]. At present, thiazolidinediones (TZD), the agonists of the peroxisome proliferators-activated receptor (PPAR)γ, are the main agents to improve insulin sensitivity in the liver, adipose tissue, and skeletal muscle, thus improving glycaemic control in patients with type 2 diabetes[14]. Despite the efficacy, some deleterious side effects of TZDs, including rosiglitazone and pioglitazone, have been noted, such as increasing body weight and aggravating heart failure through fluid retention[15,16]. Therefore, development of new agents may help treat type 2 diabetic patients with insulin resistance.

Traditional Chinese Medicine (TCM) has a long history in the treatment of type 2 diabetes[17]. Because of the supposedly less side effects when compared with modern medicine[18], the use of traditional Chinese medicine and botanicals has been increasing rapidly[19]. Yi-Qi-Zeng-Min-Tang (YQZMT), a traditional Chinese compound recipe of 10 medicinal herbs, is considered a useful medicine for the amelioration of insulin sensitivity of type 2 diabetic patients. *Radix Astragali* (Huangqi), the chief herb of YQZMT, has been shown to alleviate glucose intolerance and insulin resistance[20]. It seems that this traditional Chinese herbal compound recipe is valued in the glucose homeostasis, and may be utilized as adjuvant therapy for the control of diabetes and its complications.

The high-fat diet and low-dose streptozotocin (STZ) induced type 2 diabetic rat model mimicking the natural history of the disease events (from insulin resistance to β cell dysfunction) as well as metabolic features of human type 2 diabetes, where the high-fat diet initiated a state of insulin resistance and followed by the addition of low-dose STZ, has been known to induce a mild impairment of insulin secretion characteristic of the later stage of type 2 diabetes mellitus[21]. For this study, we aimed at investigating the effect of the Chinese herbal decoction YQZMT on insulin resistance in rats with type 2 diabetes.

MATERIALS AND METHODS

Composition and preparation of YQZMT

YQZMT was composed of 10 medicinal herbs, as shown in Table 1. The mixture was decocted for three times by refluxing with water (1:8, w/v) for 2 h, 1 h and 1 h, respectively. The solution obtained was concentrated to give an extract. The yield of YQZMT extract was 36.76% (w/w) compared with the original herbs. The process was manipulated by the National Engineering and Research Center for Traditional Chinese Medicine under internationally certified good manufacturing practice guidelines. Thin-layer chromatography and high-performance liquid chromatography identification was used to authenticate the plants. The YQZMT extract was stored at 4℃, and was diluted to the desired concentrations in distilled water before use.

Animal experiments

Sixty-five Sprague-Dawley rats (male, weight 180-220 g) were obtained from Shanghai Slaccas Laboratory Animal Company Limited, Shanghai, China. Animals were housed in standard polypropylene cages (three rats/cage) in a temperature- and humidity-controlled room with a 12 h light-dark cycle. All the rats were provided with rat normal pellet diet (NPD) (Shanghai Slaccas Laboratory Animal Company Limited, Shanghai, China) and water ad libitum, prior to the dietary manipulation.

After 1 wk of acclimatization, the rats were randomly divided into two dietary regiments consisting of 10 and 55 rats by feeding either NPD or high fat diet (HFD) (18% lard, 8% yolk powder, 2% cholesterol, 0.2% sodium cholate and 71.8% powdered NPD, as a percentage of

Table 1 Composition of Yi-Qi-Zeng-Min-Tang

Component	Part used	Amount used (%)
Radix Astragali	Root	16.0
Mung bean coating	Seed bark	16.0
Folium Perillae	Leaf	10.6
Phellodendron amurense Rupr.	Bark	10.6
Pollen Typhae	Pollen	10.6
Serissa foetida	Whole strain	10.6
Ramulus Cinnamomi	Twig	6.4
Radix Aconiti Lateralis Preparata	Prepared root	6.4
Coptis Chinensis Franch	Root	6.4
Rhizoma Alismatis	Tuberous stem	6.4

total kcal, manufactured by Shanghai Slaccas Laboratory Animal Company Limited, Shanghai, China) ad libitum, respectively, for the initial period of 4 wk.

After the 4 wk of dietary manipulation, the 55 HFD-fed rats were injected intraperitoneally (ip) with low-dose STZ (35 mg/kg, Sigma), while the 10 NPD-fed rats were injected ip with vehicle citrate buffer (pH 4.4) in a dose volume 1 mL/kg 3 d after the STZ or vehicle injection, non-fasting blood glucose (NFBG) was measured in whole blood collected from the tail vein by a portable Glucometer (Accu-Check Active, Roche Diagnostics Limited, Germany). Rats with NFBG level ≥ 16.67 mmol/L were considered diabetic and selected for further studies. Fasting blood was collected from retro-orbital plexus of the rats under light ether anesthesia using capillary tubes at day 7 after the STZ or vehicle injection to measure biochemical parameters [fasting glucose level, triglycerides (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-c), low-density lipoprotein cholesterol (LDL-c), and insulin]. The rats were fed on their respective diets until the end of the study.

Fifty diabetic rats (the diabetic success rate was 90.9%) were further divided into five subgroups: type 2 diabetes model group (MOD, n = 10), low-dose YQZMT group (LDY, n = 10), medium-dose YQZMT group (MDY, n = 10), high-dose YQZMT group (HDY, n = 10), and rosiglitazone group (ROS, n = 10). The age matched NPD-fed rats served as control group (CON, n = 10). Administration of YQZMT or rosiglitazone lasted 8 wk. LDY, MDY and HDY rats were dosed orally with YQZMT 0.47, 1.41, 2.82 g/100 g per day, respectively. ROS rats were given by oral gavage (4 mg/kg per day), this dose was selected since it was found to rapidly induce PPARγ-dependent genes[22]. CON and MOD group rats were given with an equal volume of distilled water once a day for 8 wk. Fasting blood was collected from retro-orbital plexus of the rats under light ether anesthesia using capillary tubes at 4 wk and 8 wk after treatment. The experiments were approved by the ethics committee of our institution. All procedures were in accordance to the rules and guidelines of the Experimental Animal Center of Fudan University.

Intraperitoneal glucose and insulin tolerance tests

The intraperitoneal glucose tolerance test (IPGTT) and insulin tolerance test (ITT) were performed at day 7 after the STZ or vehicle injection in diabetic (n = 5) and control (n = 5) rats, also at the end of the experiment in various groups (n = 5 for each group). After an overnight fast (12-16 h), fasting blood was collected from retro-orbital plexus (time 0), and then 50% glucose solution (2 g/kg body weight) or neutral insulin (Novo Nordisk, Denmark) was injected intraperitoneally. Blood samples were collected from retro-orbital plexus at 30, 60, and 120 min for measurement of glucose. The areas under the glucose curves (AUC) were calculated for each parameter by the trapezoidal rule in IPGTT. In ITT, the value was presented as a percentage of initial glucose level.

Blood sampling and analysis

Blood sample of rats were collected from retro-orbital plexus under light ether anesthesia using capillary tubes. Samples were centrifuged at 2500 × g for 10 min at 4℃, blood serum was removed and aliquot for the respective analytical determinations, stored at -80℃ until analysis. The serum was analyzed for glucose, TG, TC, HDL-c, LDL-c, and insulin. Serum glucose concentration was measured by glucose oxidase method (Applygen Technologies Inc, Beijing, China). Insulin was analyzed by rat insulin enzyme-linked immunosorbent assay (ELISA) kit (Mercodia, Sweden). Levels of TG, TC, HDL-c and LDL-c were assayed with enzymatic assay kits (Shanghai Kexin Biotechnology Research Institute, Shanghai, China). Serum levels of FFA, TNF-α and IL-6 were measured by commercially available rat ELISA kits. The homeostasis model assessment of basal insulin resistance (HOMA-IR) = fasting glucose (mmol/L) × fasting insulin (IU/L)/22.5. Lower HOMA-IR values indicated a greater insulin sensitivity, whereas higher HOMA-IR values indicated a lower insulin sensitivity (insulin resistance).

Statistical analysis

Data were presented as mean ± SE. The unpaired Student's t test was used for analyzing the data between two groups. Statistical differences among more than two groups were determined using one-way analysis of variance. P value < 0.05 was considered statistically significant. The statistical SPSS Version 16.0 software was used for statistical calculations.

RESULTS

General characteristics of NPD-fed rats and HFD-fed/STZ induced diabetic rats

Type 2 diabetic rats induced by STZ (35 mg/kg, ip) after 4 wk of HFD feeding exhibited significant hyperglycemia, dyslipidemia and hyperinsulinemia compared with NPD-fed control rats injected with vehicle citrate buffer (1 mL/kg, ip) (Table 2). In addition, the feeding of HFD for 4 wk resulted in significant increase (data not shown) in body weight as compared with NPD-fed rats, and STZ produced reduction in the body weight of the HFD-fed rats, which was still considerably higher than NPD-fed control rats injected with vehicle citrate buffer (Table 2). The HOMA-IR score in the diabetic rats was 6.2-folds higher than in the control rats (Table 2).

Table 2 General characteristics of normal pellet diet-fed rats and high fat diet-fed/streptozotocin induced diabetic rats (mean ± SE)

	NPD (n = 10)	HFD+STZ (n = 50)
Body weight (g)	411.30 ± 2.74	457.90 ± 2.43[b]
Glu (mmol/L)	3.60 ± 0.31	12.82 ± 1.08[b]
FINS (pg/mL)	4820.49 ± 326.89	7197.36 ± 253.89[b]
HOMA-IR	18.74 ± 1.56	97.26 ± 4.98[b]
TG (mmol/L)	0.78 ± 0.05	2.24 ± 0.12[b]
TC (mmol/L)	2.14 ± 0.06	8.40 ± 0.49[b]
HDL-c (mmol/L)	1.27 ± 0.03	0.57 ± 0.03[b]
LDL-c (mmol/L)	0.72 ± 0.04	7.84 ± 0.51[b]

Glu: Fasting serum glucose; FINS: Fasting serum insulin; HOMA-IR: Homeostasis model assessment of basal insulin resistance; TG: Triglyceride; TC: Total cholesterol; HDL-c: High-density lipoprotein cholesterol; LDL-c: Low-density lipoprotein cholesterol; NPD: Normal pellet diet; HFD: High fat diet; STZ: Streptozotocin. [b]P < 0.01 *vs* NPD group.

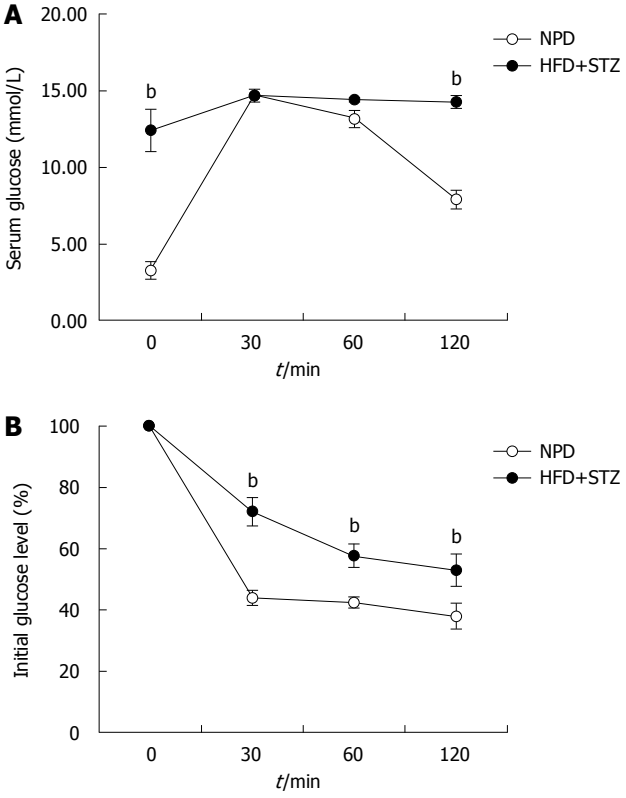

Figure 1 Intraperitoneal glucose tolerance test and insulin tolerance test in normal pellet diet-fed control rats and high fat diet-fed/streptozotocin induced type 2 diabetic rats. A: Serum glucose during intraperitoneal glucose tolerance test in normal pellet diet (NPD)-fed rats and high fat diet (HFD)-fed/streptozotocin (STZ) induced diabetic rats (n = 5/group); B: Percentage of initial glucose level during insulin tolerance test in NPD-fed rats and HFD-fed/STZ induced diabetic rats (n = 5/group). [b]P < 0.01 *vs* NPD group.

IPGTT and ITT in NPD-fed rats and HFD-fed/STZ induced diabetic rats

IPGTT and ITT were carried out in NPD-fed control rats and HFD-fed/STZ induced type 2 diabetic rats to measure glucose tolerance and insulin sensitivity. Figure 1A shows that HFD+STZ, as expected, led to glucose intolerance, since serum glucose concentrations increased from fasting levels of 12.41 ± 1.38 mmol/L to nearly 14.75 ± 0.2 mmol/L by 30 min and were still greatly increased over basal levels 2h after the glucose challenge. The NPD-fed control rats showed a significant elevation in serum glucose concentrations at 30 min but returned nearly to the basal levels within 2h after the glucose administration. Accordingly, the AUC was significantly greater in the HFD+STZ group than in the NPD group (1704 ± 40.05 mmol/L per minute *vs* 1315.2 ± 60.45 mmol/L per minute, P < 0.01). To investigate the differences in insulin sensitivity, we performed an ITT at different time points (Figure 1B). Insulin was given intraperitoneally and blood was collected for the measurement of glucose. After insulin administration, the percentage of initial glucose level in HFD+STZ was shown to be significantly higher than in the NPD group during 120 min. These results indicated that HFD with STZ 35 mg/kg injection developed a diabetic model which was an analogue to type 2 diabetes mellitus with insulin resistance.

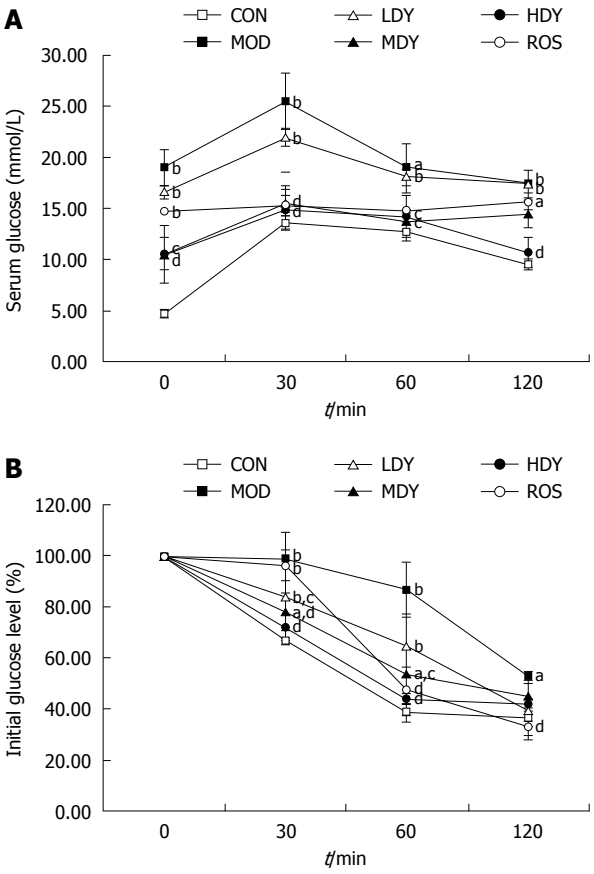

Figure 2 Intraperitoneal glucose tolerance test and insulin tolerance test in diabetic rats after 8 wk of treatment. A: Serum glucose during intraperitoneal glucose tolerance test (IPGTT) in diabetic rats (n = 5/group); B: Percentage of initial glucose level during insulin tolerance test (ITT) in diabetic rats (n = 5/group). YQZMT: Yi-Qi-Zeng-Min-Tang; CON: Control group; MOD: Type 2 diabetes model group; LDY: Low-dose YQZMT group; MDY: Medium-dose YQZMT group; HDY: High-dose YQZMT group; ROS: Rosiglitazone group. [a]P < 0.05, [b]P < 0.01 *vs* CON group; [c]P < 0.05, [d]P < 0.01 *vs* MOD group.

Table 3 General characteristics of diabetic rats after 4 wk of treatment (mean ± SE)

	CON (n = 10)	MOD (n = 10)	LDY (n = 10)	MDY (n = 10)	HDY (n = 10)	ROS (n = 10)
Body weight (g)	496.20 ± 13.40	418.08 ± 16.06[b]	434.80 ± 13.15[b]	433.75 ± 10.99[b]	443.14 ± 13.15[a]	439.30 ± 15.27[b]
Glu (mmol/L)	3.95 ± 0.27	18.40 ± 1.63[b]	17.57 ± 0.86[b]	14.35 ± 1.60[b,c]	13.20 ± 0.64[b,d]	13.00 ± 1.29[b,d]
FINS (pg/mL)	3866.43 ± 249.23	9553.83 ± 899.22[b]	7170.76 ± 739.99[b]	7228.81 ± 480.47[a]	7114.41 ± 762.97[a]	8363.51 ± 564.91[b]
HOMA-IR	16.02 ± 1.16	191.49 ± 28.32[b]	133.39 ± 13.41[b]	99.67 ± 12.97[b,c]	98.99 ± 12.40[b,c]	107.66 ± 13.01[b,c]
TG (mmol/L)	1.38 ± 0.13	2.99 ± 0.56[b]	2.91 ± 0.47[b]	2.62 ± 0.44[a]	2.58 ± 0.77	2.46 ± 0.31[a]
TC (mmol/L)	2.06 ± 0.11	8.06 ± 0.69[b]	8.08 ± 0.80[b]	6.49 ± 1.40[b]	5.45 ± 0.64[b,c]	7.79 ± 0.78[b]
HDL-c (mmol/L)	1.02 ± 0.04	0.61 ± 0.08[b]	0.71 ± 0.07[a]	0.82 ± 0.07	0.87 ± 0.11[c]	0.84 ± 0.11
LDL-c (mmol/L)	1.04 ± 0.08	7.46 ± 0.75[b]	7.37 ± 0.82[b]	5.67 ± 1.40[b]	4.58 ± 0.70[b,d]	6.95 ± 0.85[b]

Glu: Fasting serum glucose; FINS: Fasting serum insulin; HOMA-IR: Homeostasis model assessment of basal insulin resistance; TG: Triglyceride; TC: Total cholesterol; HDL-c: High-density lipoprotein cholesterol; LDL-c: Low-density lipoprotein cholesterol; CON: Control group; MOD: Type 2 diabetes model group; LDY: Low-dose Yi-Qi-Zeng-Min-Tang (YQZMT) group; MDY: Medium-dose YQZMT group; HDY: High-dose YQZMT group; ROS: Rosiglitazone group. [a]$P < 0.05$, [b]$P < 0.01$ *vs* CON group; [c]$P < 0.05$, [d]$P < 0.01$ *vs* MOD group.

Table 4 General characteristics of diabetic rats after 8 wk of treatment (mean ± SE)

	CON (n = 10)	MOD (n = 10)	LDY (n = 10)	MDY (n = 10)	HDY (n = 10)	ROS (n = 10)
Body weight (g)	562.73 ± 12.17	424.15 ± 18.30[b]	412.60 ± 12.89[b]	444.88 ± 12.02[b]	445.71 ± 15.54[b]	470.80 ± 19.9[b,c]
Glu (mmol/L)	3.85 ± 0.33	17.65 ± 2.22[b]	14.48 ± 0.68[b]	12.76 ± 0.56[b,d]	12.16 ± 1.00[b,d]	12.70 ± 0.55[b,d]
FINS (pg/mL)	3863.25 ± 316.14	1973.70 ± 237.35[a]	3025.17 ± 296.30	2275.06 ± 256.45	1815.21 ± 187.26[a]	2087.53 ± 220.78[a]
HOMA-IR	16.59 ± 2.65	38.79 ± 9.02[b]	48.48 ± 4.74[b]	30.37 ± 3.57	22.68 ± 2.37[c]	21.66 ± 2.13[c]
TG (mmol/L)	0.83 ± 0.15	1.99 ± 0.26[b]	1.88 ± 0.31[b]	1.19 ± 0.16[c]	0.87 ± 0.15[d]	1.05 ± 0.16[d]
TC (mmol/L)	1.56 ± 0.15	6.50 ± 1.04[b]	5.80 ± 0.66[b]	4.51 ± 0.76[b]	3.31 ± 0.52[b,d]	4.71 ± 0.51[b]
HDL-c (mmol/L)	1.06 ± 0.14	0.50 ± 0.03[b]	0.69 ± 0.05[b]	0.78 ± 0.04[d]	0.84 ± 0.08[d]	0.97 ± 0.08[d]
LDL-c (mmol/L)	0.50 ± 0.05	6.00 ± 1.07[b]	5.11 ± 0.67[b]	3.73 ± 0.50[b]	2.47 ± 0.50[b,d]	3.74 ± 0.49[b]

Glu: Fasting serum glucose; FINS: Fasting serum insulin; HOMA-IR: Homeostasis model assessment of basal insulin resistance; TG: Triglyceride; TC: Total cholesterol; HDL-c: High-density lipoprotein cholesterol; LDL-c: Low-density lipoprotein cholesterol; CON: Control group; MOD: Type 2 diabetes model group; LDY: Low-dose Yi-Qi-Zeng-Min-Tang (YQZMT) group; MDY: Medium-dose YQZMT group; HDY: High-dose YQZMT group; ROS: Rosiglitazone group. [a]$P < 0.05$, [b]$P < 0.01$ *vs* CON group; [c]$P < 0.05$, [d]$P < 0.01$ *vs* MOD group.

General characteristics of diabetic rats after treatment

After 4 and 8 wk of administration with YQZMT or rosiglitazone to the diabetic rats, body weight, serum glucose, insulin level, HOMA-IR value and lipids are shown in Tables 3 and 4. The levels of serum glucose, HOMA-IR, TG, TC, and LDL-c were significantly higher, while body weight and HDL-c were significantly reduced in the MOD group compared with that in the CON group, which again demonstrated that the disease animal model was established (Tables 3 and 4). At 4 wk, the MOD group had higher serum glucose levels with higher serum insulin levels compared with the CON group (Table 3), suggesting that the HFD+STZ caused insulin resistance. At 8 wk, serum insulin levels decreased in MOD group (Table 4). These results suggest that diabetes in HFD+STZ rats was the result of insulin resistance followed with relative insulin deficiency, as in human type 2 diabetes.

At 4 wk, the high-dose YQZMT (HDY) showed a significant reduction in serum glucose, HOMA-IR, TC and LDL-c, and a significant increase in HDL-c compared with MOD, while rosiglitazone (ROS) only reduced serum glucose and HOMA-IR (Table 3). After 8 wk of treatment, TG in HDY also showed a significant reduction (Table 4). The medium-dose YQZMT (MDY) also significantly reduced serum glucose and TG, and increased HDL-c. YQZMT of all oral dosage did not influence the body weight of diabetic rats. However, diabetic rats receiving rosiglitazone reduced TC and LDL-c, but without significant differences compared with the MOD group, and gained more body weight than the HDY group (Table 4). The HOMA-IR score in MOD group was 2.3 times higher than in the CON group, which markedly fell to 55.8% of ROS group and 58.5% of HDY group (Table 4).

IPGTT and ITT in diabetic rats after 8 wk treatment

IPGTT and ITT were carried out in diabetic rats after 8 wk of treatment to measure glucose tolerance and insulin sensitivity. Serum glucose levels were significantly elevated during the IPGTT in MOD compared with CON at all time points (Figure 2A). Accordingly, the AUC was roughly two-folds larger in MOD rats than in CON rats (2424.6 ± 372 mmol/L per minute *vs* 1340.1 ± 126.75 mmol/L per minute, $P < 0.01$). YQZMT and rosiglitazone attenuated the glucose intolerance, as the AUC was significantly smaller during the IPGTT in MDY (1674 ± 205.95 mmol/L per minute, $P < 0.01$), HDY (1567.8 ± 327.75 mmol/L per minute, $P < 0.01$), and ROS (1812.6 ± 134.55 mmol/L per minute, $P < 0.01$) compared with MOD rats. To investigate the differences in insulin sensitivity, we performed an ITT at different time points (Figure 2B). After insulin administration in CON group, glucose concentrations declined rapidly; however, the glucose concentrations declined slowly in MOD group. This demonstrated that MOD group presented insulin resis-

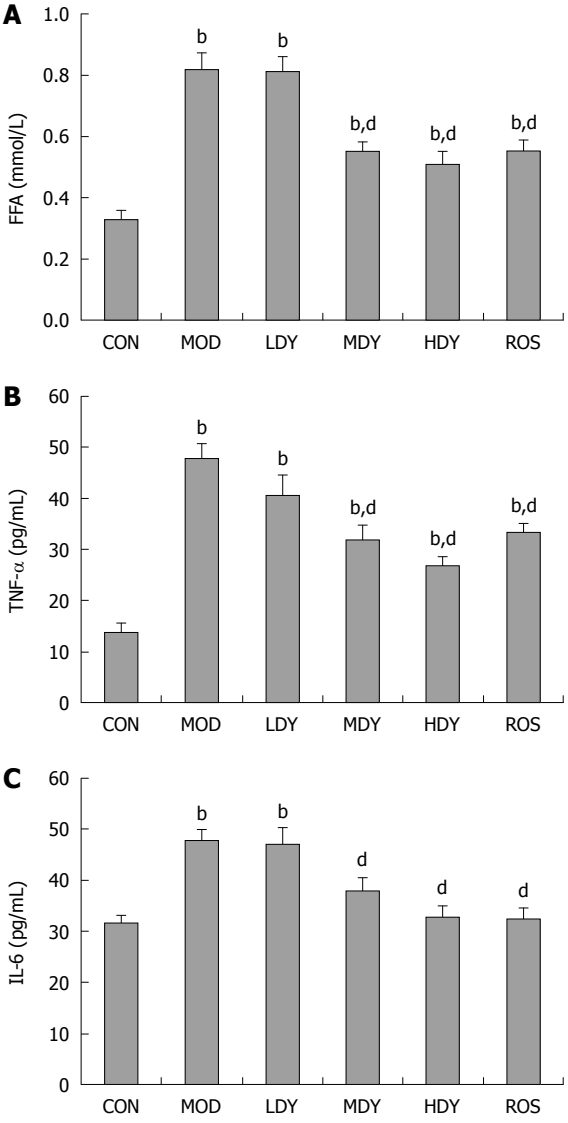

Figure 3 Free fatty acid and adipocytokines in diabetic rats after 8 wk treatment. A: Values of free fatty acid (FFA) in diabetes after 8 wk treatment; B: Values of tumor necrosis factor-α (TNF-α) in diabetes after 8 wk treatment; C: Values of interleukin-6 (IL-6) in diabetes after 8 wk treatment. CON: Control group; MOD: Type 2 diabetes model group; LDY: Low-dose Yi-Qi-Zeng-Min-Tang (YQZMT) group; MDY: Medium-dose YQZMT group; HDY: High-dose YQZMT group; ROS: Rosiglitazone group. Bar graphs indicate mean ± SE. $^{b}P < 0.01$ *vs* CON group; $^{d}P < 0.01$ *vs* MOD group.

tance. YQZMT and rosiglitazone ameliorated the insulin resistance, since the percentage of initial glucose level in LDY, MDY, HDY and ROS was shown to be significantly lower than that of MOD group during 120 min.

FFA and adipocytokines in diabetic rats after 8 wk of treatment

The serum levels of FFA, TNF-α and IL-6 in diabetic rats after 8 wk of treatment are illustrated in Figure 3. When compared with CON group, the MOD group showed significant increase in serum levels of FFA (0.82 ± 0.05 mmol/L *vs* 0.33 ± 0.03 mmol/L, $P < 0.01$, Figure 3A), TNF-α (47.98 ± 2.75 pg/mL *vs* 13.91 ± 1.74 pg/mL, $P < 0.01$, Figure 3B), and IL-6 (47.77 ± 1.92 pg/mL *vs* 31.60 ± 1.45 pg/mL, $P < 0.01$, Figure 3C).

The diabetic rats treated with medium- and high-dose YQZMT (MDY and HDY group) and rosiglitazone (ROS group) showed significant reduction of the following parameters when compared with the untreated diabetic group (MOD group): serum levels of FFA (MDY *vs* MOD: 0.55 ± 0.03 mmol/L *vs* 0.82 ± 0.05 mmol/L; HDY *vs* MOD: 0.51 ± 0.04 mmol/L *vs* 0.82 ± 0.05 mmol/L; ROS *vs* MOD: 0.55 ± 0.04 mmol/L *vs* 0.82 ± 0.05 mmol/L, $P < 0.01$, respectively, Figure 3A), TNF-α (MDY *vs* MOD: 32.18 ± 2.88 pg/mL *vs* 47.98 ± 2.75 pg/mL; HDY *vs* MOD: 26.76 ± 1.94 pg/mL *vs* 47.98 ± 2.75 pg/mL; ROS *vs* MOD: 33.49 ± 1.75 pg/mL *vs* 47.98 ± 2.75 pg/mL, $P < 0.01$, respectively, Figure 3B), and IL-6 (MDY *vs* MOD: 37.84 ± 2.65 pg/mL *vs* 47.77 ± 1.92 pg/mL; HDY *vs* MOD: 32.74 ± 2.27 pg/mL *vs* 47.77 ± 1.92 pg/mL; ROS *vs* MOD: 32.54 ± 2.08 pg/mL *vs* 47.77 ± 1.92 pg/mL, $P < 0.01$, respectively, Figure 3C).

DISCUSSION

The therapeutic effects for type 2 diabetes are limited due to unavailability of effective medications. TCM has demonstrated a good practice in the treatment of diabetes mellitus and its complications[17,20,23,24]. The present study was undertaken to investigate the effect of Chinese herbal decoction YQZMT on insulin resistance in high-fat diet and low-dose STZ-induced diabetic rats.

The chronic consumption of a high-fat diet is strongly associated with development of obesity[25] and can induce insulin resistance in human and animals[26-28]. The high-fat diet and low-dose STZ induced type 2 diabetic rat model mimicks the natural history of the disease events (from insulin resistance to β cell dysfunction) as well as metabolic features of human type 2 diabetes[21,29]. In the present work, the model group of type 2 diabetes showed significant increase in serum levels of glucose, HOMA-IR value, TC, TG, LDL-c and decrease in HDL-c, coupled with impaired glucose tolerance and insulin sensitivity when compared with the normal control group. Insulin secretion of the model group rats, which was maintained initially, gradually declined but was not depleted at the end of the study. These results indicated the successful development of type 2 diabetes rat model with insulin resistance.

Administration of YQZMT induced dose- and time-dependent changes in biochemical parameters in the type 2 diabetic rats. In general, high-dose YQZMT exhibited the best effect. Treatment for 8 wk with high-dose YQZMT was found to significantly decrease the high serum glucose concentration, HOMA-IR, TC, TG, LDL-c, FFA, TNF-α, IL-6, and increase HDL-c compared with the model group, with a similar effect of rosiglitazone. However, rosiglitazone group reduced TC and LDL-c without significant differences. And a trend towards a decrease in serum insulin concentration could be found in the high-dose YQZMT group compared with the model group, while no change was seen in rosiglitazone group. IPGTT and ITT also verified that high-dose YQZMT

markedly improved glucose tolerance and insulin resistance. Like other studies[30], we identified an increase in body weight in the group receiving rosiglitazone, and this was not found in groups administrated with YQZMT.

Dyslipidemia contributes directly to development of type 2 diabetes mellitus as lipolytic products may induce gluconeogenesis in the liver, thus contributing to hyperglycemia[31]. Well-established relationship of LDL-c levels with cardiovascular risk and the availability of proven treatments support LDL-c as the primary target[32]. Furthermore, multiple epidemiologic studies have established a low level of HDL-c as an independent risk factor for CVD[33]. While LDL-c-lowering strategies have consistently reduced cardiovascular risk, currently available options to increase low HDL-c levels are only moderately effective and associated with tolerance issues. In our study, reduction of serum TG (56.3%), TC (49.1%), LDL-c (58.8%) and increase of HDL-c (68%) were achieved after 8-wk treatment with high-dose YQZMT compared with the model group. However, diabetic rats receiving rosiglitazone treatment reduced TC and LDL-c, but without significant differences. It demonstrates that YQZMT may be a promising new strategy to address diabetic dyslipidemia and to reduce cardiovascular risk.

In accordance with the significant decrease of serum glucose, TG, TC and LDL-c, increase of HDL-c, amelioration of insulin resistance, and significant decrease of FFA, TNF-α and IL-6 levels were also observed in the high-dose YQZMT group compared with the model group. Chronically elevated FFA may impair insulin secretory function through the "lipotoxicity hypothesis" and can also induce or aggravate insulin resistance and contribute to the development of type 2 diabetes[34-39]. The fact that TNF-α impairs insulin signaling, has been proven to be due to stimulation of serine phosphorylation of IRS (*via* activity of the serine kinase inhibitor of nuclear factor-κβ kinase), leading to both degradation of IRS and inhibition of tyrosine phosphorylation which is essential to insulin signaling and action[8,40,41]. IL-6 plays a direct role in insulin resistance at the cellular level by inhibiting insulin receptor signal transduction through induction of suppressor of cytokine signaling-3[42] and insulin metabolic actions including inhibition of insulin-induced glycogen synthesis[43]. Our study confirmed again that the circulating FFA, TNF-α and IL-6 are elevated in established type 2 diabetes[44-47] and rosiglitazone has the property of reducing levels of FFA, TNF-α and IL-6[30,48,49]. Significant reduction of serum FFA, TNF-α and IL-6 was achieved after 8-wk treatment with medium- and high-dose YQZMT, similarly with rosiglitazone.

YQZMT may mediate glucose and lipid metabolism *via* ameliorating insulin resistance by down-regulating adipocytokines and fatty acids metabolism.

In conclusion, YQZMT has beneficial effects in insulin resistance, glycaemic control, dyslipidemia, FFA and adipocytokines in type 2 diabetes mellitus. Our findings demonstrate that YQZMT displays the insulin sensitization characteristic of rosiglitazone, but unlike rosiglitazone, does not cause any increase in body weight. Administration of YQZMT may be a suitable adjunct for the treatment of insulin resistance patients. Further studies will be required to identify the ingredients and chemicals in YQZMT responsible for the beneficial effects observed in the present study.

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COMMENTS

Background

The prevalence of type 2 diabetes is dramatically increasing throughout the world. Insulin resistance is a hallmark of type 2 diabetes, and it most often precedes the onset of hyperglycemia and predicts development of type 2 diabetes. At present, thiazolidinediones (TZD), the agonists of the peroxisome proliferators-activated receptor γ, are the main agents to improve insulin sensitivity in the liver, adipose tissue, and skeletal muscle, thus improving glycaemic control in patients with type 2 diabetes. Despite the efficacy, some deleterious side effects of TZDs, including rosiglitazone and pioglitazone, have been noted, such as increasing body weight and aggravating heart failure through fluid retention. Therefore, development of new agents may be helpful in the treatment of type 2 diabetic patients with insulin resistance. Yi-Qi-Zeng-Min-Tang (YQZMT), a traditional Chinese compound recipe consisting of 10 medicinal herbs, is considered to be a useful medicine for the amelioration of insulin resistance of type 2 diabetes.

Research frontiers

Insulin resistance is a hallmark of type 2 diabetes, characterized by a decreased response of the peripheral tissues to insulin action. Insulin resistance produces elevations in glucose and lipid levels. It has become increasingly evident that obesity and the concomitant development of inflammation are major components of insulin resistance. Studies have revealed a clear association between pro-inflammatory signaling pathways and decreased insulin sensitivity. Pro-inflammatory adipokines including tumor necrosis factor-α, interleukin-6, as well as free fatty acids (FFAs), have been implicated to play important roles in inflammation, insulin resistance, and type 2 diabetes. The results of this study indicate that YQZMT has beneficial effect in insulin resistance, glycaemic control, dyslipidemia, FFA and adipocytokines, and does not cause any increase in body weight in high-fat diet and low-dose streptozotocin induced type 2 diabetic rats.

Innovations and breakthroughs

This study has established a model of type 2 diabetes with insulin resistance, and the beneficial effect of YQZMT was observed on insulin resistance, glycaemic control, dyslipidemia, FFA and adipocytokines in type 2 diabetes mellitus. YQZMT displays the insulin sensitization characteristic of rosiglitazone, but unlike rosiglitazone, does not cause any increase in body weight.

Applications

YQZMT, which ameliorates insulin resistance and does not cause increase in body weight, can be used as an adjunct for the treatment of type 2 diabetes.

Terminology

YQZMT, a traditional Chinese decoction, consisting of *Radix Astragali*, *mung bean coating*, *Folium Perillae*, *Phellodendron amurense Rupr*, *Pollen Typhae*, *Serissa foetida*, *Ramulus Cinnamomi*, *Radix Aconiti Lateralis Preparata*, *Coptis Chinensis Franch*, *and Rhizoma Alismatis*.

Peer review

Work by Zhang *et al*, described in the present manuscript, generates data indicating a therapeutical effect of an herbal extract of Chinese medicinal plats in a rat model of insulin resistance and diabetes mellitus. The therapeutic effect is shown as changes in plasma markers of metabolic alterations and inflammation related to insulin resistance and diabetes, as well as whole body tests such as intraperitoneal glucose tolerance test and insulin tolerance test.

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