

PPAR- α Agonist Fenofibrate Reduces Insulin Resistance in Impaired Glucose Tolerance Patients with Hypertriglyceridemia: A Cross-Sectional Study

Xiaomeng Feng · Xia Gao · Yumei Jia · Yuan Xu

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ABSTRACT

Introduction: Peroxisome proliferator-activated receptor- α (PPAR- α) agonists can regulate metabolism and protect the cardiovascular system. This study investigated the effects of PPAR- α agonist fenofibrate on insulin resistance in patients with impaired glucose tolerance (IGT).

Methods: This research evaluated cross-sectional and interventional studies. 191 subjects with IGT were divided into a hypertriglyceridemia group (HTG group, $n = 118$) and a normal triglyceride (TG) group (NTG group, $n = 73$). 79 subjects with normal glucose tolerance were recruited as a control group. The HTG group was treated with fenofibrate (200 mg/day) for 12 weeks. The homeostatic model assessment index 2 (HOMA2) and the McAuley index (McA) were calculated.

Results: HOMA2 for β -cell function (HOMA2-%B) was 93.47 ± 26.28 , 68.47 ± 21.29 , and 79.92 ± 23.15 in HTG, NTG, and control groups, respectively. HOMA2 for insulin sensitivity (HOMA2-%S) was 48.40 (39.70, 68.70), 110.20 (62.55, 141.95), and 101.20 (79.90, 140.10) in HTG, NTG, and control groups, respectively. HOMA2 for insulin resistance (HOMA2-IR) was 2.09 (1.46, 2.52), 0.92 (0.70, 1.61), and 0.99 (0.71, 1.25) in HTG, NTG, and control groups, respectively. McA was 5.05 ± 0.76 , 7.99 ± 1.79 , and 8.34 ± 1.55 in HTG, NTG, and control groups, respectively. The HTG group had higher HOMA2-%B and HOMA2-IR, and lower HOMA2-%S and McA than NTG and control groups ($P < 0.001$ for all). Fenofibrate decreased HOMA2-%B and HOMA2-IR and increased HOMA2-%S and McA in the HTG group (HOMA2-%B: from 93.47 ± 26.28 to 89.34 ± 23.53 , $P = 0.018$; HOMA2-%S: from 48.40 (39.70, 68.70) to 56.75 (44.88, 72.53), $P < 0.001$; HOMA2-IR: from 2.07 (1.46, 2.52) to 1.76 (1.38, 2.30), $P < 0.001$; McA: from 5.05 ± 0.76 to 9.34 ± 0.88 , $P < 0.001$).

Conclusion: PPAR- α agonists improve parameters of glucoregulation in IGT patients with hypertriglyceridemia.

Keywords: β -Cell function; Insulin resistance; Hypertriglyceridemia; Impaired glucose tolerance; Peroxisome proliferator-activated receptor- α

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X. Feng · X. Gao · Y. Jia · Y. Xu (✉)
Department of Endocrinology, Beijing Chao-Yang Hospital, Capital Medical University, Beijing, People's Republic of China
e-mail: xuyuan32000@sina.com

INTRODUCTION

Impaired glucose tolerance (IGT), the major risk factor correlated with the development of both type 2 diabetes mellitus (T2DM) [1] and atherosclerotic cardiovascular diseases [2], is frequently associated with insulin resistance which is the central feature of metabolic syndrome [3]. Hypertriglyceridemia is considered as an important risk factor for insulin resistance and islet β -cell dysfunction. Lipoprotein lipase gene knockout heterozygous mice, an animal model of genetic hypertriglyceridemia, present high insulin resistance, compensatory increase of insulin secretion, and impaired glucose tolerance [4], indicating that hypertriglyceridemia could contribute to disorders of glycometabolism mediated through insulin resistance and β -cell dysfunction.

Fenofibrate, an important peroxisome proliferator-activated receptor- α (PPAR- α) agonist, is widely used in clinical as a triglyceride (TG)-lowering agent [5] which is effective at decreasing TG levels, increasing high-density lipoprotein cholesterol (HDL-C) levels, and changing low-density lipoprotein cholesterol (LDL-C) particle morphology [6]. Some large-scale clinical researches have shown that fenofibrate exerts highly beneficial effects on protecting against cardiovascular events in patients with T2DM apart from regulating lipid metabolism [7]. Thus, PPAR- α agonists may reduce cardiovascular morbidity and mortality [8] through lipid-lowering-dependent and lipid-lowering-independent mechanisms [7, 9]. Our previous studies demonstrated that fenofibrate decreased circulating irisin levels [10] and C-C chemokine ligand 5 (CCL5) levels [11] in T2DM patients with hypertriglyceridemia.

The insulin-sensitizing effects of fenofibrate, which can improve glycometabolism and protect the cardiovascular system, have remained controversial. Most studies have indicated the insulin-sensitizing actions of fenofibrate, although the actions have been questioned by other studies. Some studies have demonstrated that fenofibrate exerted protective effects on hypertriglyceridemic patients with prediabetes [12], and ameliorated insulin resistance in

hypertriglyceridemic patients with normal glucose tolerance (NGT) [13]. On the contrary, other studies have found that fenofibrate has no effects on the insulin sensitivity in insulin-resistant nondiabetic subjects [14] or in subjects with T2DM [15, 16]. Thus, we aimed to examine whether treatment with the PPAR- α agonist fenofibrate affected insulin resistance in patients with IGT in this study.

METHODS

Subjects

A total of 270 subjects (both genders) ranging in age from 30 to 70 years were recruited from July 2014 to June 2016 from a group of outpatients at the Department of Endocrinology, Beijing Chao-Yang Hospital, Capital Medical University, Beijing, China. The 75 g oral glucose tolerance test was performed at a screening visit for all subjects.

The subjects diagnosed with IGT, as defined by the American Diabetes Association criteria [17], were eligible for the study. The following exclusion criteria for IGT subjects were applied: normal glucose tolerance, impaired fasting glucose, and diabetes. Hypertriglyceridemia was defined by TG levels of at least 1.7 mmol/L according to the guideline of National Cholesterol Education Program Adult Treatment Panel III and the Endocrine Society [18, 19]. On the basis of TG levels, all IGT subjects were divided into a hypertriglyceridemia group (HTG group, $n = 118$) and a normal TG group (NTG group, $n = 73$).

Seventy-nine subjects with NGT were recruited as the control group. None of them had a history of prediabetes (including impaired glucose tolerance and impaired fasting glucose), diabetes, or hypertriglyceridemia.

People with hypertension, coronary artery disease, endocrine disease, systemic inflammatory disease, infectious disease, cancer, chronic kidney disease [i.e., creatinine (CR) greater than 120 μ mol/L], hepatic enzymes [i.e., aspartate aminotransferase (AST) and alanine aminotransferase (ALT)] greater than 1.5 times the

upper normal limits, creatine kinase (CK) greater than 1.5 times the upper normal limit, a history of alcohol abuse, pregnancy, and lactation were excluded. People taking agents known to influence glucose or insulin metabolism, and/or people being treated with lipid-lowering drugs were also excluded.

Study Design

Subjects in the HTG group were required to attend three study visits: the screening visit, visit 1, and visit 2 (spaced 12 weeks apart), while subjects in NTG and control groups attended the screening visit. Starting at visit 1, subjects in the HTG group who fulfilled the inclusion criteria (without any exclusion criteria) were treated with fenofibrate at 200 mg/day for 12 weeks. The drugs were counted at visit 2, and compliance was considered to be satisfactory if more than 90% of capsules were taken.

Blood samples and the data on the medical history, height, weight, and blood pressure were collected at the screening visit (all three groups) and at visit 2 (HTG group) (under fasting conditions, as described below). At visit 1, each subject in the HTG group received instructions to maintain his/her usual nutritional and exercise habits. Subjects in the HTG group were asked to immediately report the development of unusual muscle soreness or pain throughout the study. In addition, any adverse event in the HTG group was recorded at visit 2.

Compliance with Ethics Guidelines

The study protocol was approved by the Medicine and Pharmacy Ethics Committee of Beijing Chao-Yang Hospital, Capital Medical University. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964, as revised in 2013. Informed consent was obtained from all patients for being included in the study.

Data Collection and Laboratory Tests

A standard questionnaire was used to collect information about the subjects' health status and medications. Height and weight were measured without shoes and in light clothing to the nearest 0.1 cm and 0.1 kg, respectively, by the same trained group. Body mass index (BMI) was calculated as $\text{weight (kg)}/[\text{height (m)}]^2$. Blood pressure was measured using a calibrated standard mercury sphygmomanometer. All readings were measured from the non-dominant arm after a 5-min resting period with the patients in the sitting position.

Fasting blood samples were collected in the morning after an 8-h overnight fast. Total cholesterol (TC), HDL-C, LDL-C, TG, free fatty acids (FFA), CR, AST, ALT, CK, fasting blood glucose (FBG), 2-h postchallenge glucose (2hPG), glycosylated hemoglobin (HbA1c), fasting insulin (FINS), and high sensitivity C-reactive protein (hsCRP) were measured in the central laboratory of Beijing Chao-Yang Hospital, Capital Medical University.

Insulin resistance was measured with the following surrogates: homeostatic model assessment index 2 for β -cell function (HOMA2-%B, a marker of insulin secretion), homeostatic model assessment index 2 for insulin sensitivity (HOMA2-%S), and homeostatic model assessment index 2 for insulin resistance (HOMA2-IR) were calculated with the homeostatic model assessment index 2 (HOMA2) calculator version 2.2 (www.dtu.ox.ac.uk/homacalculator/index.php). The McAuley index (McA) = $\exp[2.63 - 0.28 \ln \text{FINS (mIU/L)} - 0.31 \ln \text{TG (mmol/L)}]$.

Adverse events were recorded throughout the study. The safety parameters included CR, AST, ALT, and CK.

Statistical Analysis

All analyses were performed with Statistical Package for Social Sciences version 19.0 (SPSS, Inc., Chicago, IL, USA). The normality of data distribution was verified using the Kolmogorov–Smirnov test. Normally distributed data were expressed as the means \pm standard

deviations. Non-normally distributed data were given as medians (25th and 75th percentiles). Comparisons of the baseline clinical and biochemical markers among three groups were performed using one-way ANOVA and Kruskal–Wallis *H* test. Comparisons of the pretreatment and posttreatment (with fenofibrate) clinical and biochemical markers in HTG group were performed with paired *t* test and Wilcoxon test. Proportions were analyzed using the Chi-squared test. The associations between anthropometric parameters and lipid profile and HOMA2-%B, HOMA2-%S, HOMA2-IR, or McA were examined using Pearson's and Spearman's correlation coefficient analyses. HOMA2-%S and HOMA2-IR did not follow a normal distribution. After logarithmic transformation, the data of HOMA2-%S and HOMA2-IR were fitted to a normal distribution. Variables with a *P* value less than 0.05 in Pearson's and Spearman's correlation coefficient analyses were retained for the multiple stepwise regression analyses. All tests were two-sided, and a *P* value less than 0.05 was used to indicate statistical significance for the results. However, given the multiple comparison performed, statistical significance at the 0.017 (0.05 divided by the number of comparisons) should be used.

RESULTS

Baseline Clinical Characteristics in Study Subjects

The baseline clinical characteristics of the study subjects are listed in Table 1. The subjects in the three groups were similar in sex, age, systolic blood pressure (SBP), diastolic blood pressure (DBP), and TC ($P > 0.05$ for all). A significant trend was observed for BMI, HDL-C, LDL-C, TG, FFA, FBG, 2hPG, HbA1c, FINS, and hsCRP among the three groups (BMI, HDL-C, FBG, 2hPG, HbA1c, and FINS: $P < 0.01$; LDL-C, TG, FFA, and hsCRP: $P < 0.05$). The HTG group had significantly increased levels of BMI, TG, FFA, FBG, and FINS and significantly decreased levels of HDL-C compared with the control and NTG groups ($P < 0.01$ for all). The levels of FBG were significantly elevated in the NTG group

compared to those in control group ($P < 0.01$). Both HTG and NTG groups exhibited significantly higher levels of 2hPG and HbA1c than the control group ($P < 0.01$ for both). The HTG group had higher levels of LDL-C and hsCRP than the control group ($P < 0.017$ for both).

Baseline Values of HOMA2-%B, HOMA2-%S, HOMA2-IR, and McA in Study Subjects

The baseline values of HOMA2-%B, HOMA2-%S, HOMA2-IR, and McA in study subjects are exhibited in Table 2. The baseline values of HOMA2-%B were 93.47 ± 26.28 , 68.47 ± 21.29 , and 79.92 ± 23.15 in HTG, NTG, and control groups, respectively. The baseline values of HOMA2-%S were 48.40 (39.70, 68.70), 110.20 (62.55, 141.95), and 101.20 (79.90, 140.10) in HTG, NTG, and control groups, respectively. The baseline values of HOMA2-IR were 2.09 (1.46, 2.52), 0.92 (0.70, 1.61), and 0.99 (0.71, 1.25) in HTG, NTG, and control groups, respectively. The baseline values of McA were 5.05 ± 0.76 , 7.99 ± 1.79 , and 8.34 ± 1.55 in HTG, NTG, and control groups, respectively. The values of HOMA2-%B and HOMA2-IR in the HTG group were significantly higher than those in the NTG and control groups ($P < 0.001$ for all), and a significant decrease in HOMA2-%S and McA was observed in the HTG group compared with the NTG and control groups ($P < 0.001$ for all). No statistically significant differences were observed in HOMA2-%B, HOMA2-%S, HOMA2-IR, and McA between NTG and control groups.

Correlation Between Anthropometric Parameters and Lipid Profile and Values of HOMA2-%B, HOMA2-%S, HOMA2-IR, and McA

HOMA2-%B was positively correlated with TG ($r = 0.359$, $P < 0.001$) and BMI ($r = 0.215$, $P < 0.001$) and inversely related to HDL-C ($r = -0.198$, $P = 0.001$) (Table 3). After adjusting for the confounders, the multiple stepwise regression analysis showed that the increased levels of TG ($\beta = 8.055$, $P < 0.001$) and BMI

Table 1 Baseline clinical characteristics of the study subjects

Parameters	HTG group (<i>n</i> = 118)	NTG group (<i>n</i> = 73)	Control group (<i>n</i> = 79)	<i>P</i> for trend
Sex (M/F)	71/47	39/34	40/39	0.382
Age (years)	56.12 ± 8.51	58.23 ± 7.14	56.68 ± 7.70	0.198
BMI (kg/m ²)	26.47 ± 4.68 ^{a,b}	24.78 ± 3.65	24.28 ± 3.50	0.001
SBP (mmHg)	127.51 ± 6.04	126.03 ± 6.81	126.29 ± 6.81	0.235
DBP (mmHg)	75.50 ± 6.49	74.42 ± 7.17	74.10 ± 7.45	0.335
TC (mmol/L)	5.13 ± 1.04	4.99 ± 0.95	4.87 ± 0.92	0.189
HDL-C (mmol/L)	1.34 ± 0.28 ^{a,b}	1.56 ± 0.38	1.56 ± 0.35	<0.001
LDL-C (mmol/L)	3.10 ± 0.74 ^a	2.92 ± 0.78	2.83 ± 0.77	0.041
TG (mmol/L)	2.37 (1.99, 2.81) ^{a,b}	1.18 (0.73, 1.51)	1.03 (0.69, 1.45)	0.015
FFA (mmol/L)	0.67 ± 0.18 ^{a,b}	0.49 ± 0.15	0.44 ± 0.14	0.023
hsCRP (mg/L)	1.64 (1.04, 2.57) ^a	1.47 (0.64, 2.63)	1.15 (0.34, 2.38)	0.048
FBG (mmol/L)	6.33 ± 0.49 ^{a,b}	6.06 ± 0.50 ^a	5.49 ± 0.39	<0.001
2hPG (mmol/L)	9.34 ± 0.88 ^a	9.31 ± 0.89 ^a	6.34 ± 0.73	<0.001
HbA1c (%)	6.30 (6.00, 6.40) ^a	6.20 (6.00, 6.30) ^a	5.90 (5.50, 6.10)	<0.001
FINS (mIU/L)	15.50 (10.78, 18.60) ^{a,b}	6.80 (5.20, 11.70)	7.53 (5.30, 9.40)	0.001

HTG group impaired glucose tolerance patients with hypertriglyceridemia, *NTG group* impaired glucose tolerance patients without hypertriglyceridemia; control group, control subjects; *BMI* body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *TC* total cholesterol, *HDL-C* high-density lipoprotein cholesterol, *LDL-C* low-density lipoprotein cholesterol, *TG* triglycerides, *FFA* free fatty acids, *hsCRP* high sensitivity C-reactive protein, *FBG* fasting blood glucose, *2hPG* 2-h postchallenge glucose, *HbA1c* glycosylated hemoglobin, *FINS* fasting insulin

^a *P* < 0.017 (0.05 divided by the number of comparisons), significantly different compared with control group

^b *P* < 0.017 (0.05 divided by the number of comparisons), significantly different compared with the NTG group

($\beta = 0.920$, $P = 0.011$) were independently related to high HOMA2-%B. The model had an adjusted R^2 of 0.143, $F = 23.464$, and $P < 0.001$.

HOMA2-%S was negatively associated with TG ($r = -0.623$, $P < 0.001$), BMI ($r = -0.314$, $P < 0.001$), and LDL-C ($r = -0.132$, $P = 0.030$) and positively related to HDL-C ($r = 0.344$, $P < 0.001$) (Table 3). After controlling for confounders, the multiple stepwise regression analysis showed that the decreased levels of TG ($\beta = -0.242$, $P < 0.001$) and BMI ($\beta = -0.020$, $P = 0.001$) and the increased levels of HDL-C ($\beta = 0.243$, $P = 0.002$) were independently correlated with high HOMA2-%S. The model had

an adjusted R^2 of 0.382, $F = 56.485$, and $P < 0.001$.

HOMA2-IR was positively correlated with TG ($r = 0.622$, $P < 0.001$), BMI ($r = 0.306$, $P < 0.001$), LDL-C ($r = 0.136$, $P = 0.025$), and FFA ($r = 0.129$, $P = 0.034$) and negatively related to HDL-C ($r = -0.346$, $P < 0.001$) (Table 3). After adjusting for the confounders, the multiple stepwise regression analysis showed that the high levels of TG ($\beta = 0.241$, $P < 0.001$) and BMI ($\beta = 0.020$, $P = 0.002$) and the low levels of HDL-C ($\beta = -0.252$, $P = 0.001$) were independently related to increased HOMA2-IR. The model had an adjusted R^2 of 0.380, $F = 55.919$, and $P < 0.001$.

Table 2 Baseline HOMA2-%B, HOMA2-%S, HOMA2-IR, and McA in the study subjects

Parameters	HTG group (<i>n</i> = 118)	NTG group (<i>n</i> = 73)	Control group (<i>n</i> = 79)	<i>P</i> for trend
HOMA2-%B	93.47 ± 26.28 ^{a,b}	68.47 ± 21.29	79.92 ± 23.15	<0.001
HOMA2-%S	48.40 (39.70, 68.70) ^{a,b}	110.20 (62.55, 141.95)	101.20 (79.90, 140.10)	<0.001
HOMA2-IR	2.09 (1.46, 2.52) ^{a,b}	0.92 (0.70, 1.61)	0.99 (0.71, 1.25)	<0.001
McA	5.05 ± 0.76 ^{a,b}	7.99 ± 1.79	8.34 ± 1.55	<0.001

HTG group impaired glucose tolerance patients with hypertriglyceridemia, *NTG group* impaired glucose tolerance patients without hypertriglyceridemia; control group, control subjects; *HOMA2-%B* homeostasis model assessment index 2 for β -cell function, *HOMA2-%S*, homeostasis model assessment index 2 for insulin sensitivity, *HOMA2-IR* homeostasis model assessment index 2 for insulin resistance, *McA* McAuley index

^a $P < 0.017$ (0.05 divided by the number of comparisons), significantly different compared with control group

^b $P < 0.017$ (0.05 divided by the number of comparisons), significantly different compared with the NTG group

Table 3 Correlation between the anthropometric parameters and lipid profile associated with HOMA2-%B, HOMA2-%S, HOMA2-IR, or McA

Parameters	HOMA2-%B (<i>n</i> = 270)		HOMA2-%S (<i>n</i> = 270)		HOMA2-IR (<i>n</i> = 270)		McA (<i>n</i> = 270)	
	<i>r</i>	<i>P</i> value	<i>r</i>	<i>P</i> value	<i>r</i>	<i>P</i> value	<i>r</i>	<i>P</i> value
Age (years)	−0.092	0.131	0.080	0.189	−0.088	0.150	0.089	0.146
BMI (kg/m ²)	0.215	<0.001	−0.314	<0.001	0.306	<0.001	−0.341	<0.001
SBP (mmHg)	0.060	0.326	−0.119	0.052	0.110	0.067	−0.080	0.193
DBP (mmHg)	−0.038	0.530	−0.057	0.348	0.067	0.271	−0.040	0.516
TC (mmol/L)	0.010	0.872	−0.031	0.606	0.038	0.536	−0.108	0.074
HDL (mmol/L)	−0.198	0.001	0.344	<0.001	−0.346	<0.001	0.424	<0.001
LDL (mmol/L)	0.036	0.551	−0.132	0.030	0.136	0.025	−0.295	<0.001
TG (mmol/L)	0.359	<0.001	−0.623	<0.001	0.622	<0.001	−0.797	<0.001
FFA (mmol/L)	0.093	0.123	−0.120	0.051	0.129	0.034	−0.214	0.001
hsCRP (mg/L)	0.063	0.300	−0.029	0.632	0.031	0.613	−0.003	0.965

HOMA2-%B homeostasis model assessment index 2 for β -cell function, *HOMA2-%S* homeostasis model assessment index 2 for insulin sensitivity, *HOMA2-IR* homeostasis model assessment index 2 for insulin resistance, *McA* McAuley index, *BMI* body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *TC* total cholesterol, *HDL-C* high-density lipoprotein cholesterol, *LDL-C* low-density lipoprotein cholesterol, *TG* triglycerides, *FFA* free fatty acids, *hsCRP* high sensitivity C-reactive protein

McA was inversely associated with TG ($r = -0.797$, $P < 0.001$), BMI ($r = -0.341$, $P < 0.001$), LDL-C ($r = -0.295$, $P < 0.001$), and FFA ($r = -0.214$, $P < 0.001$) and positively related to HDL-C ($r = 0.424$, $P < 0.001$) (Table 3).

After adjusting for the confounders, the multiple stepwise regression analysis showed that the reduced levels of TG ($\beta = -1.323$, $P < 0.001$), BMI ($\beta = -0.067$, $P < 0.001$), and LDL-C ($\beta = -0.256$, $P = 0.006$) and the elevated levels

of HDL-C ($\beta = 1.107$, $P < 0.001$) were independently related to increased McA. The model had an adjusted R^2 of 0.701, $F = 158.586$, and $P < 0.001$.

Effects of Fenofibrate on Clinical Characteristics in HTG Group

The pretreatment and posttreatment (with fenofibrate) clinical parameters in the HTG group are summarized in Table 4. No statistically significant changes were observed in BMI, SBP, DBP, AST, ALT, CK, FBG, 2hPG, and HbA1c after 12 weeks of fenofibrate treatment compared with the baseline in HTG group ($P > 0.05$

for all). Compared with the baseline, at visit 2, the patients in the HTG group presented significantly lower levels of TC, LDL-C, TG, FFA, FINS, and hsCRP ($P < 0.01$ for all), but significantly higher levels of HDL-C and CR ($P < 0.01$ for both).

Effects of Fenofibrate on HOMA2-%B, HOMA2-%S, HOMA2-IR, and McA in HTG Group

Fenofibrate treatment significantly decreased the values of HOMA2-%B and HOMA2-IR and increased the values of HOMA2-%S and McA after 12 weeks compared with the baseline in

Table 4 Pretreatment and posttreatment characteristics of IGT patients with hypertriglyceridemia treated with fenofibrate

Parameters	Pretreatment ($n = 118$)	Posttreatment ($n = 118$)	P value
BMI (kg/m^2)	26.47 \pm 4.68	26.43 \pm 4.59	0.176
SBP (mmHg)	127.51 \pm 6.04	127.94 \pm 6.58	0.158
DBP (mmHg)	75.50 \pm 6.49	75.59 \pm 6.53	0.806
TC (mmol/L)	5.13 \pm 1.04	4.85 \pm 0.86	0.001
HDL-C (mmol/L)	1.34 \pm 0.28	1.44 \pm 0.33	<0.001
LDL-C (mmol/L)	3.10 \pm 0.74	2.91 \pm 0.67	0.003
TG (mmol/L)	2.37 (1.99, 2.81)	1.62 (1.16, 1.97)	<0.001
FFA (mmol/L)	0.67 \pm 0.18	0.45 \pm 0.16	<0.001
hsCRP (mg/L)	1.64 (1.04, 2.57)	1.28 (0.53, 2.05)	0.004
CR ($\mu\text{mol}/\text{L}$)	67.56 \pm 17.26	72.03 \pm 16.42	0.001
AST (IU/L)	21.00 (17.00, 24.00)	20.00 (18.00, 25.00)	0.446
ALT (IU/L)	22.00 (18.75, 28.00)	22.00 (17.00, 28.00)	0.351
CK (IU/L)	84.00 (66.00, 114.50)	78.00 (63.00, 111.50)	0.911
FBG (mmol/L)	6.33 \pm 0.49	6.27 \pm 0.49	0.123
2hPG (mmol/L)	9.34 \pm 0.88	9.18 \pm 0.74	0.092
HbA1c (%)	6.30 (6.00, 6.40)	6.30 (6.00, 6.40)	0.777
FINS (mIU/L)	15.50 (10.78, 18.60)	13.10 (9.90, 16.43)	<0.001

IGT impaired glucose tolerance, BMI body mass index, SBP systolic blood pressure, DBP diastolic blood pressure, TC total cholesterol, HDL-C high-density lipoprotein cholesterol, LDL-C low-density lipoprotein cholesterol, TG triglycerides, FFA free fatty acids, hsCRP high sensitivity C-reactive protein, CR creatinine, AST aspartate aminotransferase, ALT alanine aminotransferase, CK creatine kinase, FBG fasting blood glucose, 2hPG 2-h postchallenge glucose, HbA1c glycosylated hemoglobin, FINS fasting insulin

Table 5 Pretreatment and posttreatment parameters of gluoregulation in IGT patients with hypertriglyceridemia treated with fenofibrate

Parameters	Pretreatment (<i>n</i> = 118)	Posttreatment (<i>n</i> = 118)	<i>P</i> value
HOMA2-%B	93.47 ± 26.28	89.34 ± 23.53	0.018
HOMA2-%S	48.40 (39.70, 68.70)	56.75 (44.88, 72.53)	<0.001
HOMA2-IR	2.07 (1.46, 2.52)	1.76 (1.38, 2.30)	<0.001
McA	5.05 ± 0.76	9.34 ± 0.88	<0.001

IGT impaired glucose tolerance, *HOMA2-%B* homeostasis model assessment index 2 for β -cell function, *HOMA2-%S* homeostasis model assessment index 2 for insulin sensitivity, *HOMA2-IR* homeostasis model assessment index 2 for insulin resistance, *McA* McAuley index

HTG group (*HOMA2-%B*: from 93.47 ± 26.28 at pretreatment to 89.34 ± 23.53 at posttreatment, $P = 0.018$; *HOMA2-%S*: from 48.40 (39.70, 68.70) at pretreatment to 56.75 (44.88, 72.53) at posttreatment, $P < 0.001$; *HOMA2-IR*: from 2.07 (1.46, 2.52) at pretreatment to 1.76 (1.38, 2.30) at posttreatment, $P < 0.001$; *McA*: from 5.05 ± 0.76 at pretreatment to 9.34 ± 0.88 at posttreatment, $P < 0.001$) (Table 5).

Correlation Between Change in TG and Change in HOMA2-%B, HOMA2-%S, HOMA2-IR, or McA

No statistically significant correlation was observed between the change in TG and the change in *HOMA2-%B*, *HOMA2-%S*, or *HOMA2-IR*. However, the change in TG were inversely related to the change in *McA* ($r = -0.768$, $P < 0.001$).

DISCUSSION

In the present study, the HTG group exhibited significantly higher values of FINS, *HOMA2-%B*, and *HOMA2-IR* and significantly lower values of *HOMA2-%S* and *McA* compared with the control and NTG groups. The increased levels of TG and BMI were independently related to high *HOMA2-%B*; the decreased levels of TG and BMI and the increased levels of HDL-C were independently correlated with increased *HOMA2-%S*; the high levels of TG and BMI and the low levels of HDL-C were independently related to increased

HOMA2-IR; and the reduced levels of TG, BMI, and LDL-C and the increased levels of HDL-C were independently associated with high *McA*. Importantly, fenofibrate treatment administered to the IGT patients with hypertriglyceridemia for 12 weeks resulted in the significant decrease in FINS, *HOMA2-%B*, and *HOMA2-IR* and the significant increase in *HOMA2-%S* and *McA*; the change in TG was inversely related to the change in *McA*. Our findings are similar to the previous studies in hypertriglyceridemic patients with prediabetes [12] or with NGT [13]. However, our findings are in contrast to some recent studies in nondiabetic individuals with insulin resistance [14] or in subjects with T2DM [15, 16]. It is possible that these conflicting data are caused by the poly-pharmacotherapy and other confounding variables of the study populations.

Although there are some studies linking diabetes to defects in beta cell mass and insulin secretion [20], most studies have supported that a compensatory period (i.e., a compensatory increase in insulin production that is secondary to high insulin resistance and the elevated secreting load of islet β -cells with subtle changes in glucose levels) has been identified before diabetes, and insulin production decreases after the diagnosis of diabetes [21]. Insulin resistance might be considered to be responsible for the increase in the secreting load of islet β -cells and insulin secretion during the compensatory period. *HOMA2-%B* reflects insulin secretion rather than β -cell "health" [22]. Hence, the decrease of *HOMA2-%B* and *HOMA2-IR* and the increase of *HOMA2-%S* and *McA* after 12 weeks of fenofibrate therapy in

our study indicated the reduction of the secreting load of β -cells and insulin secretion, with the decreased insulin resistance, through fenofibrate treatment. However, the exact mechanism involved in these effects of fenofibrate has not been fully elucidated.

Evidence accumulated has shown that hypertriglyceridemia causes an excess of FFA, which could increase insulin resistance and the secreting load of β -cells [23], with “lipotoxicity” that is an important pathogenetic factor directly associated with peripheral tissue insulin resistance and islet β -cell dysfunction [24]. On the other hand, hyperinsulinemia increases triglycerides and closes the vicious circle eventually [25]. When insulin secretion is insufficient and blood glucose levels rise, prediabetes become overt. Therefore, insulin resistance and β -cell dysfunction might be the result of chronic exposure to hypertriglyceridemia [26]. PPAR- α agonists might increase insulin sensitivity and protect β -cell function through decreasing hypertriglyceridemia. PPAR- α agonists significantly attenuate muscle TG, total liver TG content, and visceral fat weight [27], indicating that PPAR- α agonists ameliorate insulin resistance and the secreting load of islet β -cells through reducing ectopic lipid storage. In addition, PPAR- α agonists reduce the levels of FFA [28], especially when TG levels are markedly increased [9], which has been identified by our study. Therefore, PPAR- α agonists could promote insulin sensitivity in IGT patients with hypertriglyceridemia through inhibiting “lipotoxicity”.

Additionally, HDL-C, an anti-atherogenic lipoprotein, decreases insulin resistance and β -cell dysfunction. HDL-C may activate the phosphorylation of adenosine 5'-monophosphate-activated protein kinase to induce glucose uptake [29]. Moreover, HDL-C removes cholesterol from β -cells, which regulates islet β -cell function [30]. Low HDL-C has been documented to promote the progression of diabetes [31]. In our study, the fenofibrate treatment significantly increased HDL-C levels, which might exert favorable effects on alleviating insulin resistance and β -cell dysfunction.

Furthermore, our finding that BMI is positively related to HOMA2-%B and HOMA2-IR

and negatively associated with HOMA2-%S and McA is consistent with the previous study showing that a reduction in BMI was associated with a decrease in HOMA- β and an improvement in insulin sensitivity in obese individuals [32]. Thus, the reduction of BMI may lead to improving β -cell function, reducing insulin resistance, and decreasing the needs for compensatory hyperinsulinemia. PPAR- α agonists have been reported to elicit brown adipocytes and to induce weight loss in diet-induced obese mice [33], which might cause the protection of insulin sensitivity and islet β -cell function. However, no significant change was observed in BMI after 12 weeks of fenofibrate treatment compared with the baseline in the HTG group in our study, since observation time might not be long enough.

Recent evidence has also suggested that inflammation might be crucial for the development of insulin resistance and β -cell dysfunction [34]. Inflammatory cytokines and acute-phase reactants are positively related to insulin resistance in patients with metabolic syndrome [35]. It has been reported that PPAR- α agonists have anti-inflammatory effects [36]. In our previous study, PPAR- α agonist fenofibrate suppressed the levels of hsCRP and CCL5 in T2DM patients with hypertriglyceridemia [11]. In the present study, fenofibrate also reduced the levels of hsCRP in IGT patients with hypertriglyceridemia. It is possible that PPAR- α agonists prevent insulin resistance and β -cell dysfunction through anti-inflammation.

On the basis of previous research, insulin resistance is involved in the increasing risk of cardiovascular events [37]. Therefore, our present results indicated that the HTG group, with higher HOMA2-%B and HOMA2-IR and lower HOMA2-%S and McA, was at higher risk for the progression of cardiovascular diseases not only than the control group but also the NTG group. Furthermore, our findings that treatment with the PPAR- α agonist fenofibrate decreased HOMA2-%B and HOMA2-IR and increased HOMA2-%S and McA in the IGT patients with hypertriglyceridemia may partially explain the beneficial effects of PPAR- α agonist treatment in clinical trials in which the favorable effects only partly correlated with lipid changes [7]. Our

results support that PPAR- α agonists may protect against the cardiovascular complications of prediabetes and diabetes, at least in part, through improving insulin sensitivity and β -cell function, although further animal and clinical studies are still needed to investigate the mechanism.

The limitations of our study are identified as follows. Firstly, our study population was limited to Chinese subjects. Therefore, our findings may not be directly applicable to other populations. Secondly, our sample size was relatively small so that our findings were not powerful enough to account for potentially confounding factors in our analyses, and our results could be improperly influenced by some outliers as a result of the sample size. Thirdly, our study was not a randomized controlled trial. Considering ethics guidelines, we chose a self-control study and compared pretreatment and posttreatment (with fenofibrate) parameters in the HTG group. However, it might introduce some bias. Fourthly, our study estimated insulin resistance by HOMA2 and McA. Although the updated HOMA2 model accounts for variations in hepatic and peripheral glucose resistance, allows for an increase in insulin secretion in response to a plasma glucose concentration of greater than 10 mmol/L, incorporates an estimate of proinsulin secretion into the model and thus allows the use of either total [radioimmunoassay (RIA)] or specific insulin assays, and includes renal glucose losses in hyperglycemic subjects [22], and some studies have shown that the log-transformed values for fasting insulin and fasting triglycerides are accurate predictors of insulin sensitivity in the general population [38], they are still surrogates of the precise methods such as the hyperglycemic and hyperinsulinemic clamp technique. Finally, one should acknowledge that long-term follow-up will be necessary to evaluate whether fenofibrate delays disease progression eventually.

CONCLUSION

We report the significant increases in HOMA2-%B and HOMA2-IR and the significant decreases in HOMA2-%S and McA in the IGT patients with hypertriglyceridemia. More importantly, we

present data that fenofibrate treatment significantly reduced HOMA2-%B and HOMA2-IR and elevated HOMA2-%S and McA in the IGT patients with hypertriglyceridemia. These results indicate that PPAR- α agonists might improve parameters of gluco-regulation in IGT patients with hypertriglyceridemia.

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All authors had full access to all of the data in this study and take complete responsibility for the integrity of the data and accuracy of the data analysis.

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Compliance with Ethics Guidelines. The study was approved by the Medicine and Pharmacy Ethics Committee of Beijing Chao-Yang Hospital, Capital Medical University, Beijing, China. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964, as revised in 2013. Informed consent was obtained from all subjects for being included in the study.

Data Availability. The datasets during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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