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ORIGINAL ARTICLE

Fenofibrate Has Beneficial Effects on Lipid Profile But Has No Effect on Glucose Metabolism in Type 2 Diabetic Patients with Hyperlipidemia: A Randomized, Double-Blinded, Placebo-Controlled Trial

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Hypolipidemic agent fenofibrate has recently been demonstrated to improve carbohydrate metabolism in animal and cell models. The purpose of this study was to determine its clinical effects on glycemic control and the relationship with its hypolipidemic action in type 2 diabetic patients with hyperlipidemia.

Materials and Methods: Forty-eight type 2 diabetic patients with hyperlipidemia were recruited from the Endocrine Division's outpatient clinic of a tertiary-care university-affiliated centre and randomly assigned micronised fenofibrate 200mg daily or placebo in a double-blinded, placebo-controlled study for three months. A total of 44 patients completed the study. Main outcome measured were changes from the baseline in fasting and postprandial lipid and glycemic variables.

Results: Treatment with micronised fenofibrate resulted in a significant decrease in fasting (3.81 ± 1.86 to 1.90 ± 0.77 mmol/L, p< 0.0001) and postprandial triglyceride (5.36±2.640 to 2.30±1.33 mmol/L, p< 0.0001), total cholesterol (6.18±1.17 to 5.23±0.97 mmol/L, p<0.0001) and non-HDL cholesterol (5.09±1.12 to 3.96±1.11 mmol/L, p<0.0001). After treatment the placebo group showed no significant changes in serum lipid levels. Both groups did not alter in fasting and postprandial plasma glucose, mean HbA1c, fasting insulin, QUICKI index and proinsulin-to-insulin ratio.

Conclusion: Micronised fenofibrate significantly improved both fasting and postprandial lipid profiles, but did not affect glycemic variables, insulin resistance, and β cell function in patients with type 2 diabetes.

Key Words: Fenofibrate; Type 2 diabetes mellitus; Insulin resistance; Proinsulin-to-insulin ratio

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Introduction

Drugs of the fibric acid derivatives have been recommended for use in diabetic dyslipidemia,[1,2] as they reduce triglycerides and increase HDL-cholesterol levels,[3] which are the most common lipid abnormalities among these patients.[4] Fenofibrate, one of the new fibric acid derivatives, has been shown to be effective in diabetic dyslipidemia in many

clinical trials.[2,5,6,7] Recently, the micronised form of fenofibrate has been introduced, because its efficacy is similar to that of the standard formulation of fenofibrate at a lower daily dosage.[8-11] In addition, fenofibrate has also been demonstrated to improve carbohydrate metabolism in animal and cell models.[12-14] However, this beneficial effect on human beings has been controversial and never been properly evaluated in a controlled clinical trial. The present study was conducted to assess the effect of micronised fenofibrate on lipid and carbohydrate metabolism over a 12-week treatment period in type 2 diabetic individuals with hyperlipidemia.

Materials and Methods

Subjects

Patients were recruited from the Endocrine Division's outpatient clinic of the National Cheng-Kung University Hospital, Tainan, Taiwan. Based upon clinical characteristics, including the absence of ketoacidosis, age at diagnosis of diabetes of over 20 years, or a fasting C-peptide level > 0.30 nmol/L, all patients were diagnosed as type 2 diabetes mellitus. They were found to be associated with hyperlipidemia defined by fasting serum cholesterol >5.1mmol/L and/or fasting serum triglycerides >2.3 mmol/L that could not be normalized with diet therapy for at least 3 months. They were clinically stable and had moderately well-controlled type 2 diabetes mellitus and did not take any lipid-lowering drugs for at least two months.

Exclusion criteria included (1) pregnancy (or child bearing potential) or nursing females; (2) concomitant medications such as oral contraceptives, probucol, statins, oral anticoagulants, and any medical treatment (e.g., thiazides, ß-blockers, metformin, alpha-glucosidase inhibitors, and thiazolidinediones) capable of interfering with lipid metabolism; (3) a medical history of hypothyroidism, pancreatitis, cholestasis, nephrotic syndrome, chronic alcoholism, myocardial infarction, cerebrovascular stroke, cardiovascular surgery, unstable or recent angina pectoris, gastric or peptic ulcer within three months prior to the study; (4) hypersensitivity to any drug in the clinical trial; (5) hyperglycemia (FPG>16.7mmol/L) on two successive visits, unstable diabetes mellitus; (6) poorly-controlled hypertension (systolic BP>200mmHg or diastolic BP>115mmHg), and (7) elevated liver enzymes (>2.5 times the upper normal limit) or serum creatinine > 160 mmol/L.

Study design and assessment

Patients deemed eligible at screening were asked to withdraw all lipid lowering agents and to adhere to diet and hypoglycemic agents with fasting plasma glucose (FPG) <13.9 mmol/L and HbA1c<11% without ketosis. During the diet run-in period, the recommended diet and hypoglycemic agents were held constant. After completion of the 4-week diet run-in period, the participants were randomized to either micronised fenofibrate 200mg daily (Fenolip Micronised^{TM}) or placebo (in similar form) taken with the first mouthful of food in the morning. When entering the study, all patients were requested to have the appropriate diet (Therapeutic lifestyle changes diet recommended as the National Cholesterol Education Program guidelines[15]) throughout the entire period. All other treatments were kept constant throughout the study. The study protocol was approved by the Clinical Trial Committee of the National Cheng Kung University Hospital before the study was initiated. All eligible patients gave written informed consent prior to participation in the trial.

Venous blood sampling

Blood samples were collected from all patients in the morning after an overnight fasting for 12 hours. Blood was drawn from the antecubital vein, with the patient in a seated position, for serum total and HDL cholesterol, triglycerides, glucose, HbA1c, insulin, proinsulin and safety parameters before, and monthly during, the treatment. Each patient

was then given a standard fat tolerance meal consisting of 260 g skimmed milk and a sandwich. The energy content of the test meal was 282 kcal; skimmed milk (46 kcal) and sandwich (236 kcal). It contained 30% of calories from fat, 55% from carbohydrates, and 15% from protein. Venous blood for postprandial lipid profiles and plasma glucose was taken 2-h after a standard fat meal. The meal tolerance test was performed before and 12 weeks after the beginning of treatment.

Assays

Serum total cholesterol, triglycerides, HDL-cholesterol, and safety parameters (including liver function tests and renal function test) were determined in the central laboratory of National Cheng Kung University Hospital with an auto analyzer Hitachi 747E. Blood glucose was measured by a hexokinase method (Roche Diagnostic GmbH, Mannheim, Germany) with an auto analyzer Hitachi 747E. HbA1c was measured by HPLC method (Tosoh Automated Glycohemoglobin Analyzer HLC-723GHbV A1c 2.2; Intra-assay CV 0.5%, Inter-assay CV 2.0%). Immunoreactive plasma insulin was measured by Coat-A-Count Insulin, a solid-phase ^{125}I radioimmunoassay (Diagnostic Products Corporation, Los Angles, USA) which is with an intraassay and interassay CV of 5.0-9.3% and 4.9-10%, respectively. We estimated insulin resistance (IR) by using the QUICKI index. In diabetics, the correlation between such an index and the gold standard index derived from glucose clamp study is much better than that of fasting insulin. QUICKI index is defined as $1/[\log(I_0)+\log(G_0)]$, where I_0 is the fasting insulin (μU/mL) and G_0 is the fasting glucose (mmol/L).[16] Proinsulin was determined using the DRG Proinsulin ELISA KIT (DRG International Inc., USA), which has a laboratory sensitivity of 0.5 pmol/l and an intraassay and interassay CV of 2.9-7.4% and 5.5-6.8%, respectively. The proinsulin-to-insulin ratio was calculated to be an indicator of the degree of reduced β cell secretory capacity.[17] The QUICKI index and proinsulin-to-insulin ratio were determined only in patients not on insulin therapy.

Statistical analysis

The unpaired t-test was used to compare demographic data between treatment groups. Efficacy parameters were analyzed by the intent-to-treat population in this study for all patients. The observed parameters were compared within each group by paired t-test and by unpaired t-test or Wilcoxon rank sum test between groups. Statistical significance is fixed at $p< 0.05$ as indicated (two tailed test).

Results

Patient disposition and characteristics

Table 1 shows the baseline clinical and metabolic characteristics of the two treatment groups. A total of 48 patients were randomized at the end of the run-in period, 24 in the micronised fenofibrate group and 24 in the placebo group. No significant difference was observed between the two treatment groups. Of the 48 patients enrolled, 44 (92%) (22 in each group) completed treatment and were analyzed for efficacy variables. The reasons for withdrawal from the study included protocol deviation (one in the micronised fenofibrate group), adverse events (two in the placebo group), and loss to follow-up (one in the micronised fenofibrate group).

Therapeutic efficacy

Table 2 shows the effect of treatment on fasting and postprandial lipid and lipoprotein concentrations. After a 12-week treatment period, the patients treated with micronised fenofibrate had a significant decrease in both fasting and postprandial triglyceride, total cholesterol, and non-HDL cholesterol. They also had a significant increase in HDL-cholesterol. There were no significant changes from baseline on the fasting and postprandial parameters in the placebo group.

Table 1. Baseline clinical and metabolic characteristics

	Statistics	Placebo	Micronised fenofibrate
Patients	N	24	24
Age (years)	Median (Range)	66 (36-76)	60 (22-74)*
Gender	M/F	10/14	13/11
DM history (years)	Median (Range)	5.5 (1-29)	5.5 (1-21)
BMI	Mean (SD)	26.6 (3.1)	25.3 (3.0)
WHR	Mean (SD)	0.91 (0.06)	0.91 (0.06)
Systolic BP (mmHg)	Mean (SD)	142 (18)	138 (17)
Diastolic BP (mmHg)	Mean (SD)	85 (10)	83 (11)
FPG (mmol/L)	Mean (SD)	9.17 (2.72)	9.25 (3.33)
HbA1c (%)	Mean (SD)	7.7 (1.6)	8.4 (1.8)
Triglyceride (mmol/L)	Mean (SD)	3.16 (1.58)	3.97 (1.98)
Triglyceride-postprandial (mmol/L)	Mean (SD)	4.48 (1.84)	5.60 (2.62)
Total cholesterol (mmol/L)	Mean (SD)	5.95 (0.90)	6.44 (1.68)
HDL cholesterol (mmol/L)	Mean (SD)	1.16 (0.25)	1.11 (0.31)
Non-HDL cholesterol (mmol/L)	Mean (SD)	4.80 (0.82)	5.33 (1.66)
Uric acid (µmol/L)	Mean (SD)	378 (114)	396 (90)

Abbreviations: WHR= Waist circumference/Hip circumference ratio; FPG=fasting plasma glucose; * $p<0.05$

Table 2. Effect of treatment on fasting and 2-h postprandial lipid concentrations

	Statistics	Placebo (n=22)			Micronised fenofibrate (n=22)			Placebo-micronised fenofibrate		
		Baseline	12 weeks	p-value	Baseline	12 weeks	p-value	Mean	(95% CI)	p-value
Total cholesterol, fasting (mmol/L)	Mean (SD)	5.99 (0.94)	6.15 (0.94)	NS	6.18 (1.17)	5.23 (0.97)	<0.0001	1.10	0.65-1.55	<0.0001
HDL cholesterol, fasting (mmol/L)	Mean (SD)	1.16 (0.27)	1.18 (0.26)	NS	1.09 (0.30)	1.27 (0.36)	0.001	-0.16	-0.29- -0.03	<0.001
Non-HDL cholesterol, fasting (mmol/L)	Mean (SD)	4.83 (0.85)	4.97 (0.94)	NS	5.09 (1.12)	3.96 (1.11)	<0.0001	1.26	0.24-0.79	<0.0001
Triglyceride, fasting (mmol/L)	Mean (SD)	3.35 (1.52)	3.94 (2.81)	NS	3.81 (1.86)	1.90 (0.77)	<0.0001	2.51	1.30-3.72	<0.0001
Triglyceride, postprandial (mmol/L)	Mean (SD)	4.48 (1.84)	4.48 (2.75)	NS	5.36 (2.40)	2.30 (1.13)	<0.0001	3.13	0.59-1.93	<0.0001

Table 3 shows the effect of treatment on glycemic variables. No differences in fasting plasma glucose or HbA1c were observed for week 12 compared with the baseline in both treatment groups. Fasting insulin levels and the estimate of insulin resistance QUICKI index were unchanged after treatment in both treatment groups. The serum proinsulin/ insulin ratio remained the same before and after treatment in both groups.

Table 3. Effect of fenofibrate treatment on glycemic variables

	Statistics	Placebo (n=22)			Micronised fenofibrate (n=22)			Placebo – micronised fenofibrate		
		Baseline	12 weeks	p-value	Baseline	12 weeks	p-value	Mean	(95% CI)	p-value
FPG (mmol/L)	Mean (SD)	9.37 (2.74)	10.12 (3.13)	NS	9.10 (3.56)	8.70 (3.69)	NS	0.88	(-1.22 to 2.98)	NS
PPG (mmol/L)	Mean (SD)	12.67 (4.68)	13.60 (5.14)	NS	11.68 (3.99)	11.46 (5.02)	NS	1.15	(-1.92 to 4.22)	NS
HbA1c	Mean (SD)	7.80 (1.56)	8.43 (2.18)	NS	8.47 (1.88)	8.67 (2.16)	NS	0.44	(-0.48 to 1.35)	NS
Insulin-ac (pmol/L)	Mean (SD)	133.08 (55.13)	119.40 (65.03)	NS	107.66 (45.29)	114.42 (51.83)	NS	- 20.43	(-45.82 to 4.95)	NS
QUICKI index	Mean (SD)	0.29 (0.01)	0.30 (0.02)	NS	0.30 (0.02)	0.30 (0.03)	NS	0.00	(-0.01 to 0.01)	NS
Proinsulin (pmol/L)	Mean (SD)	46.44 (18.41)	49.64 (14.29)	NS	42.87 (16.39)	42.58 (14.42)	NS	3.49	(-9.52 to 16.50)	NS
Proinsulin/Insulin	Mean (SD)	41.38 (24.00)	51.00 (26.04)	NS	48.96 (34.48)	42.83 (31.78)	NS	10.74	(-10.58 to 32.06)	NS

Abbreviations: FPG= Fasting plasma glucose; PPG= Postprandial plasma glucose

Discussion

The Adult Treatment Panel III of the National Cholesterol Education Program[15] has concluded that diabetes should be considered a coronary heart disease risk equivalent and the identification of non-HDL cholesterol (total-cholesterol-HDL-cholesterol) be made a secondary target of therapy in diabetic patients with metabolic syndrome. In a recent study on type 2 diabetic patients, non-HDL cholesterol was proven to be a good alternative to expensive apoB assay in hypertriglyceridemic patients.[18] Besides lowering of triglycerides and total cholesterol, our study revealed that micronised fenofibrate can produce a significant reduction of 22% in non-HDL cholesterol. The Diabetes Atherosclerosis Intervention Study, which treated diabetic patients with mild dyslipidemia with fenofibrate for a mean duration of three years, revealed improved lipid profiles and also demonstrated improved angiography.[19]

Postprandial lipemia has been associated with cardiovascular disease.[20] Type 2 diabetes results in exaggerated postprandial lipemia.[21] The mechanisms by which the postprandial period may induce an atherogenic state depend on the generation of potentially atherogenic triglyceride-rich lipoprotein remnants, the effect on coagulation and fibrinolysis, and the effect of oxidative stress on endothelial function.[20] Generally, fibrates are more effective than statins in reducing either fasting or postprandial triglycerides. In a randomized, double-blind, placebo-controlled trial, Syvanne et al showed that gemfibrozil reduced the postprandial lipemia by 34% in 20 type 2 diabetic patients with moderate hypertriglyceridemia.[22] In another open-labeled study on type 2 diabetic patients, bezafibrate reduced fasting and postprandial lipemia by 43% and 53% respectively.[23] Our work reveals that micronised fenofibrate might have a comparable effect on reducing fasting (-

50%) and postprandial triglycerides (-57%) in diabetes.

In recent years, fenofibrate had been shown to improve carbohydrate metabolism as well. It was postulated that fenofibrate may improve insulin sensitivity by several distinct mechanisms. First, as an agonist of peroxisome proliferator-activated receptor α (PPAR α), fenofibrate improves insulin sensitivity, reduces adiposity and alleviates the fatty acid-mediated inhibition of insulin-mediated glucose disposal.[12,13,23] Second, triglyceride reduction also resulted in increased sensitivity to insulin in some studies.[14,24-26] Finally, fenofibrate may decrease production of cytokines, such as interleukin-6 and TNF-α, which have been implicated in the development of insulin resistance.[13,26-29]

Most evidence on the beneficial effect of fenofibrate benefit on carbohydrate metabolism comes from animal studies. Fenofibrate treatment prevents sequential hypertrophy and atrophy of pancreatic islet in obese diabetes-prone OLETF rats,[12] and improved insulin secretion and lowered plasma glucose in insulin-resistant rat or hamster model.[13,30-34] Similar effect on insulin sensitivity has been shown in the obese non-diabetic primate model,[35] indicating potential beneficial effects on type 2 diabetic patients.

However, clinical effect of fenofibrate on human beings has been studied only in some clinical trials. In a study on 37 overweight male patients with metabolic syndrome (including 11 with impaired glucose tolerance and 7 with diabetes), the authors reported reduced fasting serum insulin and insulin response after oral glucose load, indicating an improvement of insulin sensitivity after a 3-month treatment.[36] Damci conducted another study on 31 obese diabetics (mean BMI 30.3, disease duration 7.7 years) with hypertriglyceridemia and showed that fenofibrate treatment resulted in better glycemic control and insulin sensitivity, as evidenced by lower fasting and postprandial blood glucose, HbA_1c and fasting serum insulin.[37] Despite these encouraging results in diabetics, there are some pitfalls in interpretation. First, both these study designs are not randomized and there are no placebo-control groups. Second, fasting insulin only might not be a reasonable index of insulin sensitivity due to inadequate insulin secretion inherent in diabetes. Third, as patients with type 2 diabetes are associated with the dual defects of insulin resistance and secretion,[38] studying the effects on carbohydrate metabolism should include these two mechanisms. To our knowledge, our work is the first randomized, double-blinded, placebo-controlled study to investigate the global effect of fenofibrate treatment on carbohydrate metabolism in type 2 diabetics. Our result, showed no effect of fenofibrate treatment on fasting plasma glucose, insulin levels, and hence the QUICKI index in spite of significant reduction in fasting and postprandial serum triglyceride. As the proinsulin or proinsulin/insulin ratio indicates β-cell strain or insult on insulin secretion,[39] our observations also suggest that micronised fenofibrate had no effect on the β cell capacity of secretion in these diabetic patients. Taken together, we conclude that micronised fenofibrate had no effect on carbohydrate metabolism.

What are the possible explanations for the lack of effect of fenofibrate on glycemic variables in our study? Based upon the data from United Kingdom Prospective Diabetes Study, only 52 % and 28 % β-cell function remains 6 years following diagnosis of diabetes in intensive and conventional therapy group, respectively.[40,41] In addition, our patients are less obese (mean BMI 25.8 vs 30.3) than those enrolled in Damci's study.[37] Therefore in our patients, with a mean duration of diabetes for 5 years, defective insulin secretion might play a more important role than insulin resistance so that the improvement in insulin resistance may be too subtle to be detected. A larger scale, longer study would be helpful in addressing this issue. Meanwhile, despite human PPAR-α being similar to that of rodents in lipid lowering upon activation, in other responses such as hepatomegaly the ef-

hepatomegaly the effect is species-specific for rodents.[42] Whether the effects of PPAR-α agonist on insulin sensitivity differ between species is still unknown. More in vitro studies on human cells in the future may answer this question.

Regarding limitations of the current study, the numbers studied are relatively small and the duration is relatively short. In addition, BMI in the fenofibrate group is relatively lower than placebo group (although not statistically significant) during randomization. These might cause some results, such as proinsulin/insulin ratio, statistically insignificant. Following the Helsinki Heart Study[43] and VA-HIT,[44] a study enrolling more patients, enough for stratification by sex, lipid profile, BMI or waist circumference, over a longer period, may be needed to elucidate the possible subtle effect of fenofibrate on carbohydrate metabolism. Finally, the current study was performed in non-obese Taiwanese patients with moderately well-controlled type 2 diabetes and the results may not be applicable to other ethnic groups.

In conclusion, micronised fenofibrate, a well-tolerated fibric acid derivative, effectively improves both fasting and postprandial lipid and lipoprotein profile similar to previous RCT studies, but it has no effect on glycemic variables, insulin resistance, and β cell function in patients with coexisting type 2 diabetes mellitus and dyslipidemia.

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