Differential effects of peroxisome proliferator-activated receptor γ ligands and sulfonylurea plus statin treatment on plasma concentrations of adipokines in type 2 diabetes with dyslipidemia

WH Yin1,3,4, HL Jen1, JW Chen4, SJ Lin3,4, MS Young2

SUMMARY

Objectives: Peroxisome proliferator-activated receptor γ (PPAR-γ) is the master regulator of adipocyte differentiation and controls many adipocyte genes in response to anti-diabetic thiazolidinediones (TZDs) and lipid-lowering fibrates. We hypothesized that the combination of TZD + fibrate may be better than the sulfonylurea + statin approach regarding modifying the adipokine profile in diabetic patients with dyslipidemia.

Methods: We measured the lipid profiles and circulating levels of adiponectin, resistin, and inflammatory markers before and after treatment in 24 type 2 diabetic patients with dyslipidemia (aged 64 ± 9 years; M/F = 5/19). The study patients were randomly assigned to receive an 8-week treatment of either rosiglitazone 4 mg daily and fenofibrate 160 mg daily (PPAR group) or glibenclamide 5 mg daily and atorvastatin 10 mg daily (non-PPAR group).

Results: Even though the administration of sulfonylurea + statin can achieve a greater reduction of total cholesterol and LDL-cholesterol levels and a comparable glucose control compared to PPAR treatment, their administration did not change the plasma adipokine levels significantly. In contrast, a significant greater increase of the plasma concentrations of adiponectin (P = 0.0001), a trend to a greater decrease of the plasma resistin levels (P = 0.061), and a significant greater decrease of plasma triglycerides levels (P = 0.018) were seen in the PPAR group.

Conclusions: Considering the clinical significance of the adipokine-endothelial interaction in the progression and long-term prognosis of atherosclerosis, the differential effects of PPAR ligands and sulfonylurea + statin on plasma adipokine concentrations demonstrated in this study are interesting foci of investigation in the future.

Key-words: Adipokines · Resistin · Adiponectin · PPAR γ · Glitazones · Fibrates · Sulfonylureas · Statines · Peroxisome proliferator-activated receptor ligands · Type 2 diabetes.

RÉSUMÉ

Différence d’effet du traitement par ligand des PPAR et par sulfonylurée plus statine sur les concentrations en adipokines des diabétiques de type 2 avec dyslipidémie

Objectifs : Les PPAR sont les principaux régulateurs de la différenciation des adipocytes et contrôlent de nombreux gènes adipocytaires en réponse aux thiazolidinediones antidiabétiques (TZDs) et aux fibrates. Nous avons supposé que l’association de TZD-fibrate pouvait s’avérer plus efficace que l’association conventionnelle sulfonylurée–statine pour modifier les concentrations plasmatiques en adipokines des patients diabétiques dyslipidémiques.

Méthodes : Nous avons mesuré les paramètres lipidiques du sérum et les concentrations plasmatiques d’adiponectine, de résistine, et les marqueurs de l’inflammation avant et après traitement de 24 patients atteints de diabète du type 2 dyslipidémiques (âge 64 ± 9 ans ; M/F = 5/19). Les patients ont été randomisés en deux groupes qui récurent durant 8 semaines soit 4 mg de rosiglitazone et 160 mg de fenofibrate par jour (groupe PPAR), soit 5 mg de glibenclamide et 10 mg d’atorvastatine par jour (groupe de non-PPAR).

Résultats : À équilibre glycémique équivalent, l’association sulfonylurée–statine s’est accompagnée d’une plus grande réduction du cholesterol total et du LDL-cholestérol, mais n’a pas modifié de manière significative les concentrations plasmatiques en adiponokines. En revanche, dans le groupe PPAR comparé au groupe non-PPAR, ont été observées une élévation plus importante des concentrations plasmatiques d’adiponectine (P = 0,0001) et de HDLc (P = 0,002), une tendance à la diminution des concentrations plasmatiques de résistine (P = 0,061) et une diminution plus importante des triglycérides (P = 0,018).

Conclusions : Compte tenu du rôle de l’interaction adipokines-endothélium dans l’évolution et le pronostic à long terme de l’athéroscclérose, la différence entre les effets des ligands des PPAR γ et ceux du traitement conventionnel sur les concentrations plasmatiques en adipokines mises en évidence par cette étude pourrait constituer une voie de recherche intéressante pour l’avenir.

Mots-clés : Adipokines · Résistine · Adiponectine · Dyslipidémie · PPAR γ · Glitazones · Fibrates · Sulfonylureas · Statines · Diabète de type 2.

1 Division of Cardiology
2 Department of Internal Medicine, Cheng-Hsin General Hospital,
3 Institute of Clinical Medicine,
4 Cardiovascular Research Center, National Yang-Ming University, School of Medicine, Taipei, Taiwan.

Address correspondence and reprint requests to:
MS Young, MD, Department of Internal Medicine, Cheng-Hsin General Hospital, NO. 45, Cheng-Hsin Street, Pei-Tou, Taipei, Taiwan, P.O.C.
yin.wh@msa.hinet.net

Received: June 5th, 2005; accepted: September 20th, 2005.
Introduction

Insulin resistance and its consequence, type 2 diabetes, are major causes of atherosclerosis [1]. Recently, chronic inflammation has also been postulated to play a role in the pathogenesis of type 2 diabetes and atherosclerosis [2,3]. Adipose tissue synthesizes and secretes biologically active molecules named “adipocytokines” or “adipokines” [4-7] which may represent a mechanism linking insulin resistance to atherosclerosis [8-11]. It has been suggested that the balance in the concentrations of adipokines such as resistin and adiponectin determines the inflammation status of vasculature, and in turn the progress of atherosclerosis [12].

The peroxisome proliferator-activated receptors (PPARs) are nuclear fatty acid receptors that have been implicated to play an important role in hyperlipidemia, insulin resistance and coronary artery disease [13-15]. Among the three PPAR subtypes, α, γ, and δ, PPARγ is the master regulator of adipocyte differentiation and controls many adipocyte genes in response to several structurally distinct compounds, including anti-diabetic thiazolidinediones (TZDs) and lipid-lowering fibrates [15-17]. Administration of TZDs has been shown to markedly enhance the expression and secretion of adiponectin in vitro and in vivo through the activation of its promoter [18]. However, whether the combination of TZD + fibrate is better than the sulfonylurea + statin approach regarding modifying the adipokine profile in diabetic patients with dyslipidemia is unknown.

This study measures lipid profiles and circulating levels of adiponectin, resistin, high-sensitivity C-reactive protein (hsCRP), soluble high-sensitivity tumor necrosis factor-α (TNF-α) and soluble vascular cell adhesion molecule-1 (VCAM-1) before and after these two regimens and determines which regimen is more effective than the other in affecting adipokine activity.

Materials and methods

Study Population

The study patients were recruited from a patient cohort followed up regularly at the outpatient cardiology clinic of a single local referral medical center between September 1, 2004 and December 31, 2004. Patients were included if they had type 2 diabetes and dyslipidemia. Type 2 diabetes was defined as fasting (overnight) venous plasma glucose concentration ≥126 mg/dL, triglycerides ≥150 mg/dL, or HDL cholesterol <45 mg/dL after 4 weeks on a National Cholesterol Education Panel step I or II diet. Type 2 diabetes had to have been diagnosed 12 weeks before the dietary run-in period. Patients were excluded if they had uncontrolled diabetes mellitus (fasting glucose level 160 mg/dL), uncontrolled hypertension (systolic blood pressure >160 mmHg and/or diastolic blood pressure >100 mmHg), were current tobacco smokers, had unstable angina, myocardial infarction within the previous 3 months, significant congestive heart failure (New York Heart Association more than or equal to class III), impaired renal function (creatinine (3 mg/dL)), hepatic disease, myopathy, systemic infection or inflammatory disease, malignancy or other systemic illness, alcohol/drug abuse, known hypersensitivity to oral hypoglycaemic agents or lipid-lowering agents, were pregnant or breastfeeding. Those who had had pre-scheduled coronary bypass surgery or coronary interventional therapy or who had undergone coronary intervention or bypass surgery during the 6 months prior to inclusion in the study were not recruited. Those patients who had taken regular oral hypoglycaemic agents and/or lipid-lowering agents within the 8 weeks preceding the study were also excluded. Angiotensin-converting enzyme inhibitors, angiotensin-receptor antagonists, diuretics, calcium channel blockers, and anti-platelet agents were allowed during the study. No other medications, including beta-blockers, nonsteroidal anti-inflammatory drugs, vitamins and other supplements were allowed. Patients were instructed to stop such medications upon study entry and were asked not to alter their medical treatment throughout the duration of the study. They were encouraged not to change their diet otherwise and daily dietary logs of all food and beverages consumed during the study were reviewed to assure dietary compliance. All eligible subjects gave written informed consent to participate, and the study protocol was approved by the institutional review board.

Study Design

This study was conducted in a randomized and open-label fashion. All patients underwent a full medical history, physical examination, basic laboratory screening, chest X-ray and electrocardiogram. After 4 weeks of dietary run-in period, patients underwent blood sampling for biochemical, adipokine and inflammatory marker analyses. Thereafter they were assigned, in a 1:1 ratio based on a randomization list, to receive an 8-week treatment of either rosiglitazone 4 mg once daily and fenofibrate 160 mg once daily (PPAR group) or glibenclamide 5 mg once daily and atorvastatin 10 mg once daily (non-PPAR group). The antidiabetic, anti-hypertensive and lipid-lowering treatments were left unchanged throughout the trial. Patients were followed up by an experienced dietitian throughout the study (including run-in phase) to monitor diet and exercise. After four weeks of treatment, patients returned to the laboratory for measuring of blood pressure and testing of complete blood count, fasting plasma glucose, creatine phosphokinase and liver enzymes to assess tolerability (adverse events). At the end of the 8-week treatment, patients returned to the laboratory for interview, physical examination (including blood pressure and weight measurements), routine biochemical measurements, and testing of fasting plasma glucose, glycated
hemoglobin (HbA₁c), serum lipid profile, adipokines and inflammatory markers. All adverse events were recorded. For each adverse event, the duration, frequency, severity, and relation to study treatment were assessed.

Measurement of fasting plasma glucose, HbA₁c, and lipid levels

After the dietary run-in period (baseline), and after 8 weeks of active treatment, 12-hour fasting venous blood samples were obtained and were aliquoted for serum and EDTA-plasma and centrifuged at 3000 rpm at 4°C for 20 minutes. EDTA-plasma was used immediately to measure glucose and HbA₁c with an automated analyzer (Hitachi, Japan). Serum total cholesterol, high-density lipoprotein cholesterol (HDL-C) and triglycerides were also measured immediately by an automated analyzer (Hitachi, Japan). Serum LDL-C was calculated using the Friedewald formula. The remaining serum samples were then frozen to -20°C and stored at that temperature until analysis for adipokines and inflammatory markers.

Adipokine and inflammatory marker analysis

Serum concentrations of adiponectin and resistin were measured with commercial sandwich enzyme-linked immunosorbent assays (R & D Systems, Inc., Minneapolis, MN, USA). Immunoassays were also used to measure serum concentrations of VCAM-1, TNF-α (R & D Systems, Inc., Minneapolis, MN, USA) and high-sensitivity C-reactive protein (hsCRP) (IMMAGE Immunoochemistry Systems, Beckman Coulter, Inc. California, USA). Assays for all of these factors were done concurrently to minimize any effects of repeated freeze-thaw cycles. Intra-assay and inter-assay coefficients for each factor in our laboratory were about 5% and about 10% respectively.

Statistical analysis

Data are given as mean ± SD. The changes in serum lipid levels between baseline and 8 weeks and between treatments were compared using the unpaired Student’s t test or the Mann-Whitney U test, as appropriate. Within-group tests for significance of change from baseline were performed using the paired Student’s t test. For categorical variables, the chi square or Fisher exact test was performed, as appropriate. All statistical analyses are based on two side hypothesis tests with a significance level of P<0.05.

Results

Baseline data of the study population (table I)

Of the 31 consecutive patients initially screened, 24 (5 men and 19 women; mean age 64±9 years, range 55 to 73 years)
fulfilled the inclusion criteria and were eligible for the study. Seven were excluded (1 withdrew and 6 dropped out for uncontrolled fasting glucose level ≥160 mg/dL) owing to a lack of available post-baseline efficacy data. Twenty-four patients therefore remained in the study population. Of these, 12 patients were randomized to TZD + fibrate treatment and 12 patients to sulfonylurea + statin treatment. The baseline characteristics are displayed in table I. There were no differences in baseline characteristics between the two treatment groups. Mean values of fasting plasma glucose, HbA1c, total cholesterol, LDL-C, HDL-C, triglycerides, adiponectin, resistin and inflammatory markers were all comparable between the two treatment groups.

**Tolerability**

Both treatments were well tolerated and no significant changes in serum creatine phosphokinase, liver enzyme activities, haemogram or blood pressure were observed. Although not significant, the increase in mean body weight was higher in the PPAR group compared to non-PPAR group, with mean body weight being increased by 0.4 kg in the PPAR group and by 0.1 kg in the non-PPAR group. The adverse events diagnosed as possibly, probably or related were considered as treatment-related adverse events. No major adverse events were reported and there were no treatment discontinuations or interruptions due to adverse events. During the study period, 9 events in 8 patients in the PPAR group and 8 events in 8 patients in the non-PPAR group were reported; all of these were mild. The frequency of adverse events was comparable between the two treatments. The treatment-related adverse events after PPAR ligand treatment were dizziness (3 patients, 25%), atypical chest pain (3 patient, 25%), mild edema (1 patient, 8.3%), epigastralgia (1 patient, 8.3%), and insomnia (1 patient, 8.3%). The treatment-related adverse events after sulfonylurea + statin treatment were lower abdominal pain (2 patients, 17%), myalgia (1 patients, 8.3%), hypoglycaemia (1 patients, 8.3%), diarrhea (1 patient, 8.3%), palpitations (1 patient, 8.3%), dry mouth (1 patient, 8.3%), and insomnia (1 patient, 8.3%).

**Effects of treatment on fasting plasma glucose, HbA1c, and lipid levels (tables II and III)**

Both the TZD + fibrate and sulfonylurea + statin treatments improved fasting plasma glucose, although the difference was not statistically significant (P=0.233 after PPAR treatment and P=0.339 after non-PPAR treatment, respectively). Mean HbA1c levels were also decreased with the two treatment groups. Patients receiving PPAR treatment showed a mean non-significant decrease in HbA1c from 8.6% at baseline to 7.7% at week 8 (P=0.170). Patients receiving sulfonylurea + statin treatment showed a non-significant decrease from 7.9% at baseline to 7.4% at week 8 (P=0.125). Differences in % glycated haemoglobin were not significantly different in the 2 groups (0.9 vs 0.5).

| Table II |
| Changes of lipid profiles, adipocytokines and inflammatory markers before and after treatment. |

<table>
<thead>
<tr>
<th></th>
<th>PPAR (N=12)</th>
<th>Non-PPAR (N=12)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>End</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>69.6±17</td>
<td>70.0±17</td>
</tr>
<tr>
<td>Fasting plasma glucose, mg/dL</td>
<td>159±36</td>
<td>152±39</td>
</tr>
<tr>
<td>Glycated hemoglobin, %</td>
<td>8.6±1.6</td>
<td>7.7±1.3</td>
</tr>
<tr>
<td>Lipid profile</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>233±22</td>
<td>198±24</td>
</tr>
<tr>
<td>LDL-C, mg/dL</td>
<td>140±18</td>
<td>113±23</td>
</tr>
<tr>
<td>HDL-C, mg/dL</td>
<td>52±10</td>
<td>66±10</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>203±107</td>
<td>96±38</td>
</tr>
<tr>
<td>Adipocytokines</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adiponectin (ng/mL)</td>
<td>5911±2700</td>
<td>14688±7797</td>
</tr>
<tr>
<td>Resistin (ng/mL)</td>
<td>13.6±8.7</td>
<td>11.9±10.1</td>
</tr>
<tr>
<td>Inflammatory markers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VCAM-1 (ng/mL)</td>
<td>670±275</td>
<td>541±181</td>
</tr>
<tr>
<td>TNF-α (pg/mL)</td>
<td>4.8±4.7</td>
<td>4.5±3.9</td>
</tr>
<tr>
<td>hsCRP (mg/dL)</td>
<td>0.3±0.2</td>
<td>0.4±0.4</td>
</tr>
</tbody>
</table>

PPAR = Peroxisome proliferator-activated receptor, LDL-C = Low-density lipoprotein cholesterol, HDL-C = High-density lipoprotein cholesterol, VCAM-1 = Vascular cellular adhesion molecule-1, TNF-α = Tumor necrosis factor-alpha, hsCRP = High-sensitivity C-reactive protein.
In the PPAR group after 8 weeks of treatment, mean total cholesterol decreased from 233±22 to 198±24 mg/dL (P=0.001), mean LDL-cholesterol decreased from 140±18 to 113±23 mg/dL (p=0.004), mean triglycerides decreased from 203±107 to 96±58 mg/dL (P=0.004) and mean HDL-cholesterol increased from 52±10 to 66±10 mg/dL (P=0.002). In the non-PPAR group after 8 weeks of treatment, mean total cholesterol decreased from 224±33 to 176±28 mg/dL (P=0.0009), mean LDL-cholesterol decreased from 129±32 to 87±20 mg/dL (P=0.0008), mean triglycerides decreased from 206±118 to 156±52 mg/dL (P=0.02) and mean HDL-cholesterol increased from 54±15 to 58±14 mg/dL (P=0.53). Mean changes in total cholesterol (-48±22 vs -35±13 mg/dL; P=0.079) and LDL-cholesterol (-42±27 vs -27±21 mg/dL; P=0.148) were greater in the non-PPAR group than in the PPAR group, but they did not reach statistical significance. However, the mean changes in HDL-cholesterol (14±5.4 vs -0.3±2.3 mg/dL; P=0.061) and triglycerides (-106±92 vs -49±79 mg/dL; P=0.018) were significantly greater in the PPAR group than in the non-PPAR group.

Table III
Comparison of changes of lipid profile and adipocytokines between PPAR and non-PPAR groups.

<table>
<thead>
<tr>
<th>Lipid profile</th>
<th>PPAR (N=12)</th>
<th>Non-PPAR (N=12)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>-35±13</td>
<td>-48±22</td>
<td>NS</td>
</tr>
<tr>
<td>Low density lipoprotein-cholesterol, mg/dL</td>
<td>-27±21</td>
<td>-42±27</td>
<td>NS</td>
</tr>
<tr>
<td>High density lipoprotein-cholesterol, mg/dL</td>
<td>14±9</td>
<td>4±4</td>
<td>0.002</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>-106±92</td>
<td>-49±79</td>
<td>0.018</td>
</tr>
</tbody>
</table>

Adipocytokines

<table>
<thead>
<tr>
<th></th>
<th>PPAR</th>
<th>Non-PPAR</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adiponectin (ng/mL)</td>
<td>8777±5709</td>
<td>381±1662</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Resistin (ng/mL)</td>
<td>-1.7±5.4</td>
<td>-0.3±2.3</td>
<td>0.061</td>
</tr>
</tbody>
</table>

PPAR = Peroxisome proliferator-activated receptor.

In the PPAR group after 8 weeks of treatment, mean total cholesterol decreased from 233±22 to 198±24 mg/dL (P=0.001), mean LDL-cholesterol decreased from 140±18 to 113±23 mg/dL (p=0.004), mean triglycerides decreased from 203±107 to 96±58 mg/dL (P=0.004) and mean HDL-cholesterol increased from 52±10 to 66±10 mg/dL (P=0.002). In the non-PPAR group after 8 weeks of treatment, mean total cholesterol decreased from 224±33 to 176±28 mg/dL (P=0.0009), mean LDL-cholesterol decreased from 129±32 to 87±20 mg/dL (P=0.0008), mean triglycerides decreased from 206±118 to 156±52 mg/dL (P=0.02) and mean HDL-cholesterol increased from 54±15 to 58±14 mg/dL (P=0.53). Mean changes in total cholesterol (-48±22 vs -35±13 mg/dL; P=0.079) and LDL-cholesterol (-42±27 vs -27±21 mg/dL; P=0.148) were greater in the non-PPAR group than in the PPAR group, but they did not reach statistical significance. However, the mean changes in HDL-cholesterol (14±5.4 vs -0.3±2.3 mg/dL; P=0.061) and triglycerides (-106±92 vs -49±79 mg/dL; P=0.018) were significantly greater in the PPAR group than in the non-PPAR group.

Effects of treatment on circulating adipokine concentrations (tables II and III)

Administration of glibenclamide and atorvastatin did not affect circulating levels of adiponectin and resistin. However, the administration of rosiglitazone and fenofibrate for 8 weeks markedly increased the plasma adiponectin concentrations (5911±2700 ng/mL vs 14688±7797 ng/mL; P=0.0002). The mean change in adiponectin concentration was significantly greater in the PPAR group than in the non-PPAR group (8777±5709 ng/mL vs 381±1662 ng/mL; P<0.0001). The administration of rosiglitazone and fenofibrate for 8 weeks also significantly decreased the plasma resistin concentrations (13±2.7±9.7 ng/mL vs 11.9±10.1 ng/mL; P=0.03), even though the mean change in resistin concentrations was not different in the PPAR group compared to the non-PPAR group (-1.7±5.4 ng/mL vs -0.3±2.3 ng/mL; P=0.061).

Effects of treatment on circulating levels of inflammatory markers (table II)

Neither the administration of rosiglitazone and fenofibrate or glibenclamide and atorvastatin significantly affected circulating levels of hsCRP, TNF-α or VCAM-1. A trend of decrease of VCAM-1 was observed in the TZD+fibrate treatment group; however, the difference was not statistically significant (670±275 ng/mL vs 541±181 ng/mL; P=0.157).

Discussion

This study showed that 8-week treatment with rosiglitazone and fenofibrate markedly increased the plasma concentrations of adiponectin and significantly decreased the plasma concentrations of resistin, both being adipose-specific proteins, in type 2 diabetic patients with dyslipidemia. A significantly greater increase of HDL-cholesterol and a significantly greater reduction of triglycerides level were also seen in the PPAR group. Even though the administration of glibenclamide and atorvastatin can achieve a greater reduction of mean total cholesterol and LDL-cholesterol levels and a comparable glucose control, their administration did not change the plasma adipokine levels significantly in the study patients.

Over the past few years, much effort has been made to understand the interaction between insulin resistance and endothelial dysfunction, with particular emphasis on adipocyte-derived hormones (adipokines) and their effects on vascular homeostasis [4-7,12]. Although their precise mechanisms of action remain to be elucidated, adipokines play important roles in the development of diabetes and atherosclerosis and may represent a mechanism linking insulin resistance to atherosclerosis [8-11]. For example, adipokine
resistin, which is expressed in white adipose tissue specifically, antagonizes insulin-stimulated glucose metabolism and inhibits adipocyte differentiation and has a direct proinflammatory effect on vascular endothelial cells [12]. An increase of serum resistin concentrations in obese and diabetic animal models has been reported [11]. In contrast, adiponectin, another adipose-specific plasma protein, possesses anti-atherogenic properties [19-21], can suppress TNF-α- and resistin-induced adhesion molecule expression in vascular endothelial cells [12,19] and cytokine production from macrophages [21], and plays an important role in improving insulin resistance and atherosclerosis [8-10]. Plasma adiponectin concentrations are decreased in patients with coronary artery disease and type 2 diabetes mellitus, and hypoadiponectinemia may play a role in the development of atherosclerotic vascular disease in those patients [22-24]. Therefore, a regimen that could increase plasma adiponectin and/or decrease plasma resistin might hinder the development of atherosclerosis in patients with insulin resistance and type 2 diabetes.

PPARs are transcription factors recognized as important mediators in regulating lipid and glucose homeostasis [13-17]. PPARα potentiates fatty acid catabolism in the liver and is the molecular target of the lipid-lowering fibrates (e.g. fenofibrate and gemfibrozil), whereas PPARγ is essential for adipocyte differentiation and mediates the activity of the insulin-sensitizing thiazolidinediones (e.g. rosiglitazone, etc.) [13-17]. Recently, PPAR activators have also been recognized as important mediators in the inflammatory response, and the modulation of PPAR pathway may exert anti-inflammatory and vascular protective effects [15,16]. Our results show that the administration of PPAR ligands rosiglitazone (a TZD) and fenofibrate (a PPARα activator also possessing weak PPARγ activating activity) for 8 weeks markedly increases the plasma concentrations of adiponectin in type 2 diabetic patients with dyslipidemia, which is compatible with a previous report [18]. Although statins can also suppress resistin-induced adhesion molecule expression in vascular endothelial cells [12] as adiponectin does, our study demonstrates that they may not affect the plasma adiponectin levels significantly. The exact mechanism of action responsible for these differential effects on plasma adiponectin levels of both treatments is unknown and is an interesting focus of investigation.

In the present study, the administration of glibenclamide and atorvastatin also did not affect circulating levels of resistin significantly. In contrast, administration of PPAR ligands rosiglitazone and fenofibrate for 8 weeks significantly decreased the plasma concentrations of resistin in the study patients. Administration of TZDs to mice has controversial (increase or decrease) effects on resistin gene expression [11,25,26]. Our results suggest that the use of PPAR ligand treatment can have beneficial effects on circulating resistin levels.

Although TZDs, PPAR agonists and statins have all been reported to exert anti-inflammatory and vascular protective effects [13-16,27], the present study demonstrates that neither administration of TZD + fibrate nor sulfonylurea + statin significantly affects circulating levels of hsCRP, TNF-α or VCAM-1. Even though a trend of decrease of VCAM-1 was observed in the PPAR group, the difference was not statistically significant. While glucose levels and lipid profiles of study patients were only mildly elevated, their serum levels of inflammatory markers were also comparable to that of healthy volunteers reported recently from our laboratory [28,29]. Thus, vascular inflammation could be minimal in the study patients and there may have been too little room left for improvement by both treatments.

Improved glucose control and cholesterol- and triglyceride-lowering therapy can reduce risk for micro- and macrovascular complications of diabetes [30]. Although the concentrations of adipokines were not evaluated, a comparison between TZD and sulfonylurea on blood glucose control and lipid profiles has already been presented in the “Quartet” study [31]. It revealed that TZD therapy was equivalent to sulfonylurea in reducing HbA1c, with specific differences between treatments in terms of mechanism of action, plasma lipid profiles and adverse events [31]. Our study showed that even though the administration of sulfonylurea + statin can achieve a comparable glycaemic control compared to PPAR therapy, the difference in the glycated hemoglobin value is higher in the PPAR group. This could suggest that at least some of the differences observed are related to a better glycaemic control rather than to a direct effect on lipids and adipokines.

For many years, sulfonylurea drugs were considered first-line oral hypoglycemics and TZDs more appropriately as the second add-in drug for persons with diabetes [30]. The results of recent clinical trials now favor the use of statins before fibrates in most diabetic persons with dyslipidemia [30,32]. Glibenclamide and atorvastatin were chosen as the comparators for this study as they are two of the most commonly prescribed sulfonylureas and statins in Taiwan. The mean body mass index of the study population in the present study was 26±4 kg/m². To treat diabetic patients with dyslipidemia of this weight, most physicians in Taiwan would choose sulfonylurea and statin as the first-line drugs. However, considering the favorable effects of PPAR ligand therapy on blood glucose control and lipid profiles, and the clinical significance of adipokine-endothelial interaction and vascular inflammation in the progression as well as long-term prognosis of atherosclerotic disease, our finding of a marked increase of plasma adiponectin concentrations and decrease of resistin levels is clinically relevant. Nevertheless, further and larger studies will be required to determine whether PPAR ligand therapy is comparable to or even better than conventional sulfonylurea + statin treatment in managing these patients.
Conclusions

In this study, both the TZD + fibrate and sulfonylurea + statin treatments were able to achieve acceptable glucose control and significantly reduce mean serum levels of cholesterol and triglyceride in patients with type 2 diabetes and dyslipidemia. However, only TZD + fibrate treatment significantly increased circulating levels of adiponectin and decreased plasma resistin levels. The differential effects of PPAR ligands and sulfonylurea + statin treatment on plasma concentrations of adipocytokines and the complex vascular protective mechanism of these drugs in type 2 diabetic patients with dyslipidemia are interesting topics worth studying in the future.

References