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The effects of rosiglitazone and metformin on the plasma concentrations of resistin in patients with type 2 diabetes mellitus

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Abstract

Resistin is a protein secreted from adipose tissue that is thought to play a role in insulin sensitivity. We examined the effects of rosiglitazone and metformin on the plasma resistin levels in individuals with type 2 diabetes mellitus. Patients with type 2 diabetes mellitus who showed poor glycemic control with glimepiride (4 mg/d) were randomized to rosiglitazone (4 mg/d) and metformin (500 mg bid) treatment groups. All subjects continued glimepiride treatment as well. The plasma concentrations of resistin were measured at baseline and at 6 months of treatment for both groups. The anthropometric parameters, fasting plasma glucose, HbA1c, total cholesterol, triglyceride, high-density lipoprotein cholesterol, free fatty acids, and adiponectin concentrations were also measured. After 6 months of treatment, the reduction in plasma glucose levels was similar between the 2 groups. There were no significant changes in the lipid profiles of either group during the study period. The plasma resistin levels decreased in the rosiglitazone group (2.49 ± 1.93 vs 1.95 ± 1.59 ng/ml; $P < .05$) but increased in the metformin group (2.61 ± 1.69 vs 5.13 ± 2.81 ng/ml; $P < .05$). The plasma adiponectin concentrations were increased in the rosiglitazone group (2.91 ± 1.46 vs 4.23 ± 1.77 μg/ml; $P < .05$) but were unchanged in the metformin group. In summary, rosiglitazone treatment decreased the plasma resistin levels whereas metformin treatment increased them in patients with type 2 diabetes mellitus showing poor glycemic control with sulfonylurea therapy. These results suggest that the observed changes in plasma resistin levels are not the consequences of improved insulin resistance, nor are they consequences of glycemic control. Considering the potential role of resistin in insulin resistance, decrease in resistin levels may contribute to improving insulin action with rosiglitazone treatment.

1. Introduction

Adipose tissue was once thought of as a reservoir for surplus energy, but more recently, it has been recognized as an active endocrine organ contributing to metabolic homeostasis by secreting several adipokines such as leptin, adiponectin, tumor necrosis factor-α, interleukin-6, plasminogen activator inhibitor-1, and resistin [1]. Initially, resistin was reported as an adipose tissue-specific protein by Steppan et al [2]. They showed that the expression and release of resistin were increased during adipogenesis in vitro and that obese mice had increased serum levels of this protein. Injecting resistin into normal mice induced insulin resistance, which was reversed by antiresistin IgG. All of the findings reported by Steppan et al suggested that resistin constituted a link between obesity and insulin resistance, but ensuing studies in vitro and in vivo have showed conflicting data regarding the expression of resistin in relation to insulin resistance or obesity [3-9]. In addition, human resistin seems to be expressed mainly in macrophages, not in adipocytes, of mice [10]. However, several recent human studies support the hypothesis that resistin plays a role in insulin resistance. Although the correlations between serum resistin levels and obesity or homeostasis model assessment for insulin resistance (HOMA-IR) have been contradictory [11-18], serum resistin concentrations of patients with type 2 diabetes mellitus are significantly higher than those of subjects without type 2 diabetes mellitus in most of the studies [11-14]. Moreover, the only paper dealing with

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Table 1
Subject characteristics

	Rosiglitazone group (n = 14)	Metformin group (n = 13)
Age (y)	60 ± 8	54 ± 14
Sex (male/female)	6:8	6:7
BMI (kg/m^2)	23.3 ± 2.6	24.6 ± 2.4
Duration of diabetes (y)	9 ± 5	7 ± 6
Fasting C-peptide (nmol/L)	0.73 ± 0.26	0.63 ± 0.30
Retinopathy (n)	3	3
Proteinuria (n)	2	3
Coronary heart disease (n)	2	2
Lipid-lowering agent (n)[a]	5	3

Data are means ± SD.
[a] Statin 3, fibrate 2 in rosiglitazone group; statin 1, fibrate 2 in metformin group.

longitudinal analysis showed that serum resistin was higher in obese subjects than in lean subjects and that change in serum resistin was positively correlated with changes in body mass index (BMI), fat mass, mean glucose, and insulin levels after a weight reduction program entailing dieting and exercise [18]. Incubation of rat skeletal muscle with resistin-inhibited insulin-induced glucose uptake, glycogen synthesis, and glucose oxidation [19,20] and in vivo studies also revealed the resistin impaired insulin actions on the glucose metabolism in the skeletal muscle or liver [20-22].

Both rosiglitazone and metformin are insulin-sensitizing agents, but the mechanism and main target organ of each seem to be different. Rosiglitazone is a thiazolidinedione (TZD) derivative that activates the peroxisome proliferator–activated receptor gamma of adipocytes. The main mechanism of its antidiabetic effect is to increase the glucose disposal rate in muscle and adipose tissue, but it also decreases endogenous glucose production [23]. Metformin is a biguanide with an insulin-sensitizing action. Recently, adenosine monophosphate–activated protein kinase activation has been suggested as a unified explanation for the pleiotropic beneficial effects of this drug [24]. In contrast to rosiglitazone, metformin works mainly by decreasing the hepatic glucose production [25].

Recently, 2 separate reports were published concerning the effects of these 2 different insulin sensitizers on the circulating adiponectin levels [26,27]. However, there has been only one human study showing the changes in the circulating resistin levels induced by insulin sensitizers (ie, showing pioglitazone treatment decreased serum resistin levels, liver fat content, and endogenous glucose production and increased peripheral glucose disposal) [28]. In this study, to see whether improving insulin resistance can modulate circulating resistin levels in human beings, we evaluated the effects of 2 different insulin sensitizers, rosiglitazone and metformin, on plasma resistin concentrations in Korean subjects with type 2 diabetes mellitus failing sulfonylurea treatment.

2. Subjects and methods

2.1. Human subjects and treatment protocol

Thirty Korean patients with type 2 diabetes mellitus (13 men and 17 women) were recruited from the Diabetes Clinic of the Seoul National University Hospital. The enrollment criteria were as follows: age between 20 and 70 years, secondary treatment failure (HbA1c >8% on glimepiride 4 mg/d or equivalent dose of other sulfonylureas), no other severe illnesses including liver failure, renal failure, heart failure, etc. They were randomized to rosiglitazone (4 mg/d; 15 subjects) and metformin (1000 mg/d; 15 subjects) treatment groups. The number of men and women in each group is shown in Table 1.

The baseline anthropometric parameters were height, weight, waist circumferences, hip circumferences, and BMI.

Table 2
Effects of each agent on clinical parameters and plasma adipokines

	Rosiglitazone (n = 14)		Metformin (n = 13)	
	Baseline	6 mo	Baseline	6 mo
BMI (kg/m^2)	23.3 ± 2.6	24.5 ± 3.0*	24.6 ± 2.4	24.8 ± 2.5
Waist circumference (cm)	87.0 ± 5.4 (M)	88.7 ± 5.6 (M)	89.0 ± 4.5 (M)	88.5 ± 3.7 (M)
	86.6 ± 11.8 (F)	88.4 ± 9.4 (F)	87.0 ± 10.5 (F)	87.3 ± 9.7 (F)
Fasting glucose (mmol/L)	11.4 ± 2.1	8.8 ± 2.3*	10.3 ± 2.7	9.1 ± 1.6**
Fasting Insulin (pmol/L)	85 ± 39	77 ± 32	68 ± 20	70 ± 25
HbA1c (%)	9.3 ± 0.9	7.8 ± 1.1*	9.0 ± 0.8	8.0 ± 1.1**
HOMA-IR	7.3 ± 3.3	5.0 ± 2.4**	5.3 ± 2.4	4.6 ± 1.9
FFA (mmol/L)	0.66 ± 0.22	0.55 ± 0.18	0.66 ± 0.28	0.66 ± 0.20
Total cholesterol (mmol/L)	5.07 ± 0.72	5.22 ± 0.91	5.30 ± 1.29	5.07 ± 0.96
TG (mmol/L)	1.88 ± 0.81	1.97 ± 1.18	2.17 ± 0.79	2.14 ± 0.89
HDL (mmol/L)	1.09 ± 0.18	1.14 ± 0.23	1.14 ± 0.28	1.14 ± 0.26
Adiponectin (μg/ml)	2.91 ± 1.46	4.23 ± 1.77**	3.80 ± 2.50	4.10 ± 2.60
Resistin (ng/ml)	2.49 ± 1.93	1.95 ± 1.59** †	2.61 ± 1.69	5.13 ± 2.81*

M indicates male; F, female.
* $P < .01$ vs baseline.
** $P < .05$ vs baseline.
† $P < .05$ vs metformin group at 6 months.

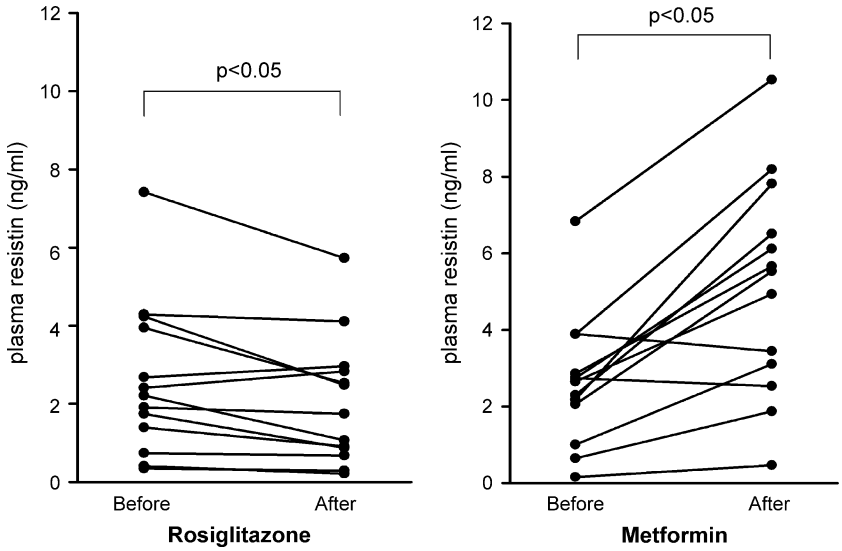

Fig. 1. Effects of rosiglitazone and metformin on individual plasma resistin levels in subjects with type 2 diabetes mellitus. Samples were obtained in the fasting state before and after the indicated treatment.

Height and weight were measured with subjects in light clothing but no shoes. Body mass index was calculated and expressed in kilograms per meter squared. Waist circumference was measured with a soft tape on standing subjects midway between the lowest rib and the iliac crest. Hip circumference was measured at the level of the greater trochanter. The baseline laboratory studies included plasma glucose level, HbA1c, free fatty acids (FFAs), insulin, C-peptide, total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglyceride (TG), resistin, and adiponectin and were performed in the morning at 8 AM after a 10-hour overnight fast. Subjects were asked not to smoke, not to take their morning medication, and not to perform any strenuous exercise the day before the tests. Blood samples for plasma glucose and lipid profiles were taken every 2 months.

After 6 months of combined treatment with sulfonylurea and one of the 2 insulin sensitizers, the anthropometric values, fasting plasma glucose, HbA1c, lipid profiles, plasma resistin, and adiponectin levels were measured again in each group.

The characteristics of the subjects are summarized in Table 1. The institutional review board of the Clinical Research Institute of the Seoul National University Hospital approved the study protocol, and informed consent was obtained from each subject.

2.2. Assay methods

The fasting plasma glucose, total cholesterol, TG, and HDL cholesterol concentrations were measured enzymatically using an autoanalyzer (Hitachi 747, Hitachi, Ltd, Tokyo, Japan). Inter- and intraassay coefficients of variations

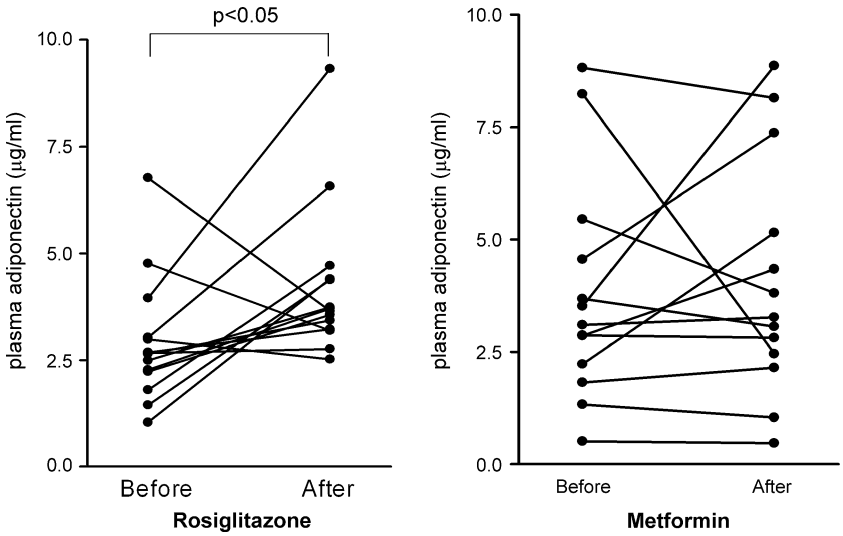

Fig. 2. Effects of rosiglitazone and metformin on individual plasma adiponectin levels in subjects with type 2 diabetes mellitus. Samples were obtained in the fasting state before and after the indicated treatment.

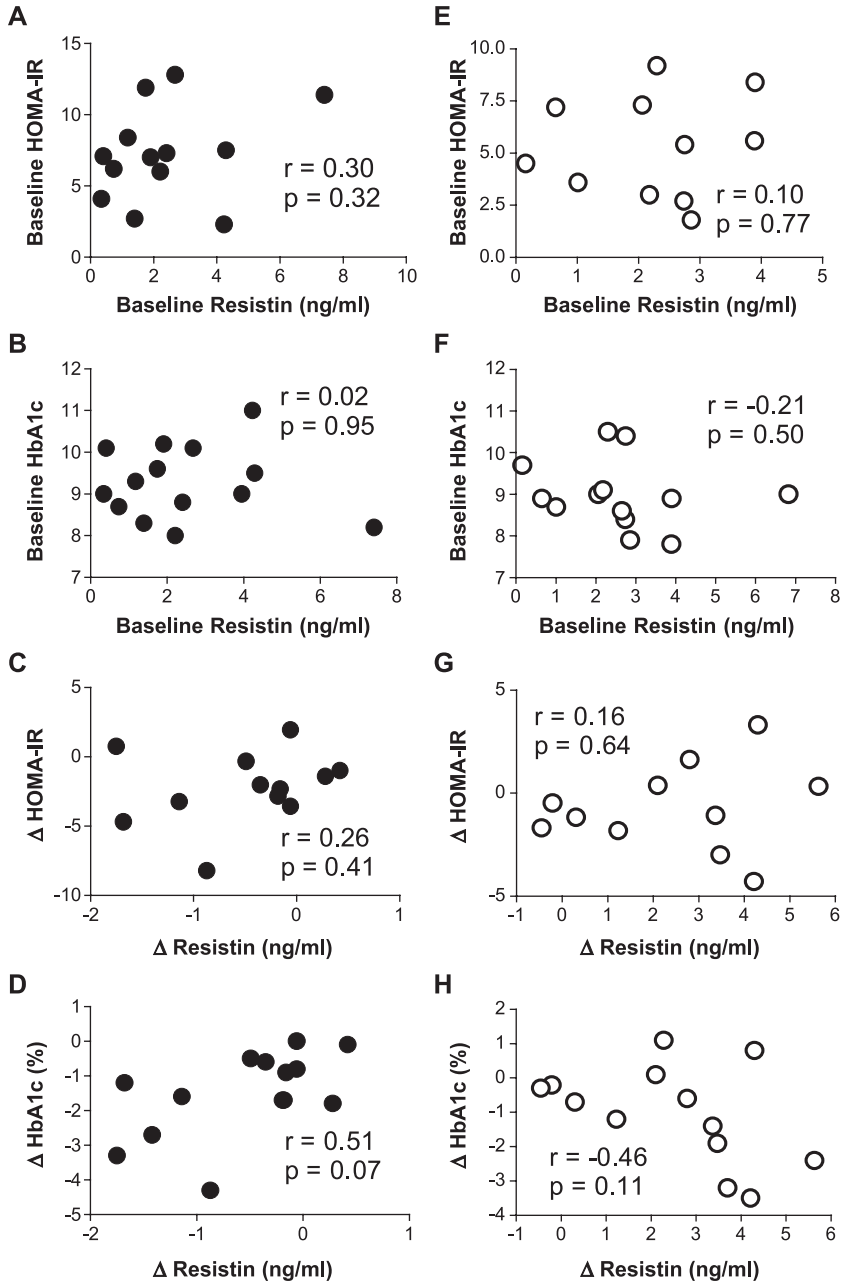

Fig. 3. Relationship between the resistin levels and either HOMA-IR or HbA1c in rosiglitazone-treated subjects (closed circles in A, B, C, D) and metformin-treated subjects (open circles in E, F, G, H) with type 2 diabetes mellitus. Samples were obtained in the fasting state before and after the indicated treatment and Pearson's correlation coefficient was used for the statistical analysis.

(CVs) were less than 2% for glucose, total cholesterol, and TG and 4.7% for HDL cholesterol. HbA1c was measured by affinity chromatography using the Bio-Rad Variant II system (Bio-Rad Laboratories, Hercules, Calif, USA) with a CV of 3%. Plasma insulin was measured by radioimmunoassay (BioSource SA, Nivelles, Belgium) with inter- and intra-assay CVs of 6.3% and 1.9%, respectively. Plasma C-peptide was measured by radioimmunoassay (Daiichi, Tokyo, Japan) and the CV was 3.5%. The low-density lipoprotein cholesterol level was calculated using the Friedewald equation. Homeostasis model assessment for insulin resistance was calculated as previously described [29].

2.3. Quantitative assay for plasma resistin and adiponectin

Plasma resistin and adiponectin were measured using enzyme-linked immunosorbent assay kits developed by the KOMED Institute for Life Science, Korea [11]. The plasma samples were diluted 1:10 before performing the assay. All samples were assayed in duplicate. The lower limit of detection with the resistin assay was 100 pg/ml.

The inter- and intraassay CVs were 5.3% and 5.4%, respectively. The lower limit of detection with the adiponectin assay was 500 pg/ml. The inter- and intraassay CVs were 2.7% and 7.2%, respectively.

2.4. Statistical analysis

Statistical analysis was performed using SPSS 10.0 software (SPSS, Inc, Chicago, Ill). Statistical significance was evaluated with the Student t test. For correlation analysis, Pearson's correlation coefficients were used. Data are presented in the form of mean ± SD and significance was accepted at the $P < .05$ level.

3. Results

3.1. Baseline characteristics

Among the 30 patients, a total of 3 dropped out, including one from the metformin group because of acute hepatitis and two owing to follow-up loss (one from each group). As a result, a total of 27 patients completed the study. There were no significant differences between the groups in terms of the baseline characteristics such as age, sex distribution, fasting C-peptide levels, and the severity of diabetic complications as shown in Table 1. Body mass index of the subjects was between 23 and 25 kg/m^2, which is the overweight range for people from the Asia Pacific region [30].

3.2. Regulation of plasma resistin levels in rosiglitazone- and metformin-treated subjects with diabetes mellitus

In both groups, the fasting plasma glucose and HbA1c levels were significantly decreased after 6 months of therapy (Table 2). The magnitude of plasma glucose reduction was not optimal, but it was sufficient for us to show the 2 insulin sensitizers come into action. The rosiglitazone-treated group also displayed decreased HOMA-IR and increased BMI (Table 2). There were no significant changes in LDL, HDL, or TG levels in either group.

The baseline plasma adiponectin and resistin concentrations did not differ between the 2 groups. After 6 months of therapy, the plasma resistin levels decreased significantly in the rosiglitazone-treated subjects and increased significantly in the metformin-treated subjects ($P < .05$ in both cases; Fig. 1). The plasma adiponectin levels increased significantly in the rosiglitazone-treated subjects ($P < .05$; Fig. 2), whereas they were unchanged in the metformin-treated subjects. The increase in adiponectin values showed no correlation with the reduction in resistin levels in the rosiglitazone group.

3.3. Plasma resistin levels and response to insulin sensitizers

According to Pearson's correlation coefficients, the changes in HbA1c correlated with those in HOMA-IR in both groups ($r = 0.667$, $P < .05$ in the rosiglitazone group and $r = 0.720$, $P < .05$ in the metformin group). They also correlated negatively with the baseline FFA in the rosiglitazone group ($r = -0.653$; $P < .05$). The baseline and the changes of plasma resistin levels were not correlated with those of HOMA-IR or HbA1c in either group significantly (Fig 3), but there was a tendency of correlation between change of plasma resistin and that of HbA1c with marginal P value in the rosiglitazone treatment group ($r = 0.51$, $P = .07$; Fig 3D).

4. Discussion

Resistin is a recently identified adipokine that has been proposed as a potential link between obesity and insulin resistance [2]. In this study, we found that the plasma resistin levels decrease with rosiglitazone treatment, whereas they increase with metformin treatment in subjects with type 2 diabetes mellitus failing sulfonylurea therapy.

Our observation that rosiglitazone decreased the plasma resistin levels in patients with type 2 diabetes mellitus is consistent with the initial report of Steppan et al, which showed that the serum concentrations of resistin in mice were decreased by treatment with TZDs [2], and with another human study by Bajaj et al [28]. The expression of resistin in the adipocytes of mice treated with TZDs has also been shown to be decreased, and it has been suggested that TZD reduces resistin gene expression, at least in part, by reducing the histone acetylation associated with the binding of CCAAT enhancer-binding protein-α (C/EBPα) in mature adipocytes [31,32].

Interestingly, the plasma resistin levels in patients with type 2 diabetes mellitus increased with metformin treatment in our study. The mechanism of metformin's effect on resistin expression is currently unclear. Fujita et al [33] showed that the administration of a high dose of metformin to obese, diabetic mice increased the expression of resistin in adipose tissue and decreased the plasma levels of insulin and glucose. The same amount of glucose reduction was observed after an insulin injection, but in this case, resistin expression was not increased. Therefore, the authors concluded that the increase in resistin expression caused by metformin was brought about indirectly by a decrease in the insulin level. In other words, they concluded that hyperinsulinemia suppressed resistin expression in obese diabetic mice. In this study, however, metformin treatment for 6 months reduced the fasting plasma glucose and HbA1c levels but not the fasting plasma insulin levels. Moreover, we recently observed that the log-transformed plasma resistin levels were increased in patients with type 2 diabetes mellitus and that these patients had higher fasting plasma insulin levels than their age- and sex-matched nondiabetic control subjects [11]. On the other hand, it is possible that the increased plasma resistin may not be from adipose tissue but could be from other sources such as macrophages that were suggested to express human resistin [10].

There has been much controversy surrounding the relation between resistin and insulin resistance [2-9]. In

our study, the baseline plasma resistin concentrations did not show any relationship with the indices of obesity or HOMA-IR. The magnitude of the changes in glycemic control was not correlated with the plasma resistin levels, whereas it was correlated with the changes in HOMA-IR in both groups and with the circulating FFA levels in the rosiglitazone group. Moreover, the fact that rosiglitazone and metformin have opposite effects on the plasma resistin levels suggests that the observed changes in plasma resistin levels are not the result of improved insulin resistance or reduced hyperglycemia. Regarding the role of circulating resistin on insulin resistance, Rajala et al [22] showed that the 2- to 15-fold elevation of serum resistin impaired hepatic insulin sensitivity, whereas it did not affect peripheral glucose disposal in rats. There are also reports showing that recombinant resistin impaired glucose uptake in rat skeletal muscle [19,20]. Thus, we could not exclude the possibility that circulating resistin might have a modest effect on peripheral or hepatic insulin resistance, which was not precisely estimated in this study. Further studies will be needed to explore the role of circulating resistin levels on insulin resistance or glucose homeostasis in human beings.

We found that rosiglitazone increased the plasma adiponectin levels, whereas metformin had no effect. This observation is in agreement with previous studies involving TZD treatment [26,27,34,35]. Although both adiponectin and resistin appear to be modulated by peroxisome proliferator-activated receptor gamma, the increase in adiponectin values showed no correlation with the reduction in resistin levels in the rosiglitazone group. The only other paper that reported on the relationship between metformin and adiponectin showed the same result as ours (ie, the absence of effect of metformin on plasma adiponectin levels in patients with type 2 diabetes mellitus) [26]. The observed differences between these 2 agents provide additional evidence for their having distinct action mechanisms and target organs.

In summary, rosiglitazone treatment decreased the plasma resistin levels and increased the plasma adiponectin levels, whereas metformin treatment increased the resistin levels without affecting the adiponectin levels in patients with type 2 diabetes mellitus showing poor glycemic control with sulfonylurea therapy. The magnitude of the changes in the plasma resistin levels was not associated with that of either glycemic control or insulin resistance in either group. However, there was a potential correlation between the decrease of plasma resistin and that of HbA1c in the rosiglitazone group, which might become significant if the sample size were larger. Further studies are needed to determine the mechanism of modulation of resistin expression with insulin sensitizers and the causal relationship between resistin and insulin resistance.

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