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Impact of rosiglitazone on beta-cell function, insulin resistance, and adiponectin concentrations: results from a double-blind oral combination study with glimepiride

Andreas Pfützner[a,b,*], Thomas Schöndorf[a], Daniela Seidel[c], Karl Winkler[d], Stephan Matthaei[e], Andreas Hamann[f], Thomas Forst[a]

[a]*IKFE Institute for Clinical Research and Development, Mainz, Germany*
[b]*Department of Applied Sciences, University of Applied Sciences, Rheinbach, Germany*
[c]*GlaxoSmithKline, Munich, Germany*
[d]*University Hospital, Department of Laboratory Medicine, Freiburg, Germany*
[e]*Diabetes Center, Quakenbrück, Germany*
[f]*Department of Internal Medicine, University Hospital, Heidelberg, Germany*

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Abstract

Addition of rosiglitazone to sulfonylurea has been shown to improve glycemic control in patients with type 2 diabetes previously treated with sulfonylurea monotherapy alone. This investigation was performed to assess the specific impact of rosiglitazone on insulin resistance, beta-cell function, cardiovascular risk markers, and adiponectin secretion in this treatment concept. One hundred two patients from a double-blind, 3-arm comparator trial (group 0, glimepiride + placebo, n = 30; group 4, glimepiride + 4 mg rosiglitazone, n = 31; group 8, glimepiride + 8 mg rosiglitazone, n = 41; 48 women, 54 men; age [mean ± SD], 62.8 ± 9.1 years; body mass index, 28.7 ± 4.5 kg/m^2; diabetes duration, 6.4 ± 4.8 years; HbA_{1c}, 8.1% ± 1.5%) were analyzed after 0 and 16 weeks of treatment. Observation parameters were HbA_{1c}, glucose, homeostasis model assessment for insulin resistance score, insulin, intact proinsulin, and adiponectin. Insulin resistance was defined by elevated intact proinsulin values or homeostasis model assessment for insulin resistance score of more than 2. All parameters were comparable in the 3 groups at baseline. Substantial and significant dose-dependent improvements were observed after addition of rosiglitazone for fasting glucose (group 0, −9 ± 48 mg/dL; group 4, −38 ± 47 mg/dL; group 8, −46 ± 53 mg/dL), HbA_{1c} (−0.1% ± 0.7%, −1.1% ± 1.2%, −1.3% ± 1.2%), insulin (1.4 ± 6.2, −1.2 ± 5.3, −3.7 ± 9.9 μU/mL), intact proinsulin (1.6 ± 7.1, −2.0 ± 4.6, −3.1 ± 6.1 pmol/L), and high-sensitivity C-reactive protein (0.2 ± 2.6, −1.7 ± 3.5, −2.1 ± 3.5 mg/L). After adjustment for changes in body weight, significant increases in adiponectin were detected with rosiglitazone, whereas glimepiride alone did not induce a comparable effect (−0.5 ± 5.8, 8.8 ± 22.9, 14.3 ± 19.9 mg/L). The number of insulin-resistant patients decreased in both rosiglitazone treatment groups, whereas no change was seen with glimepiride alone. Next to the reported effects on glucose control, rosiglitazone provided an additional beneficial effect on insulin resistance, beta-cell function, and cardiovascular risk markers. In conclusion, our short-term investigation of rosiglitazone action provides further experimental support for the rationale of combining rosiglitazone with sulfonylurea drugs in patients with type 2 diabetes.

1. Introduction

Peroxisome proliferator–activated receptor (PPAR) agonists have been shown to improve insulin resistance and long-term blood glucose control in patients with type 2 diabetes when used as monotherapy and also in combination with sulfonylurea drugs and metformin [1,2]. Based on the different modes of action, thiazolidinediones appear to be a logical option for use in combination with glimepiride in the treatment of type 2 diabetes. Rosiglitazone acts by directly improving the insulin sensitivity of tissues including adipose tissue, muscle, and liver [3-5] by a complementary mechanism of action to glimepiride. Addition of rosiglita-

* Corresponding author. IKFE Institute for Clinical Research and Development, D-55116 Mainz, Germany. Tel.: +49 6131 5763610; fax: +49 6131 5763611.
E-mail address: andreasp@ikfe.de (A. Pfützner).

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zone to treatment with a sulfonylurea (gliclazide, glyburide, or glipizide) has been shown to improve glycemic control without increased risk of hypoglycemia [6,7].

During the past years, new markers have been identified for the assessment of insulin resistance and overall cardiovascular risk. These include intact proinsulin, the insulin precursor molecule that is secreted by the beta cell only in case of clinically relevant insulin resistance and is regarded as independent cardiovascular risk factor [8,9], and adiponectin, a hormone actively secreted by the white adipose tissue that is considered to be the link among insulin resistance, inflammation, and arteriosclerosis [10,11]. Until today, the role of proinsulin as a laboratory marker and risk factor for cardiovascular disease has been very diversely discussed [12-15]. However, the development of specific assays for intact proinsulin [16] triggered new investigations and led to new insights into the interactive correlation between beta-cell dysfunction and insulin resistance [8]. Based on the fasting morning values of intact proinsulin, insulin, and glucose, a beta-cell secretion–oriented staging of type 2 diabetes has been suggested as a model to describe the beta-cell secretion status and as a helpful tool for the identification of the most beneficial antidiabetic therapeutic approach. It could be shown that reduction of insulin resistance, for instance by thiazolidinedione intervention, is associated with a reduction of fasting intact proinsulin secretion, overall beta-cell protection, and an increase of adiponectin levels within 3 months [17,18]. Adiponectin is a 30-kd serum protein derived exclusively from the adipose tissue and accounts for about 0.01% of the total plasma protein [19]. Adiponectin concentrations are negatively associated with obesity, insulin resistance, oxidative stress [20], and endothelial dysfunction [10] and it is considered to be useful as a predictive biomarker for insulin resistance and cardiovascular risk [19,21].

A dose-dependent additional positive effect of treatment with rosiglitazone on long-term glycemic control (as measured by HbA_{1c} assessment) when added to glimepiride monotherapy has recently been demonstrated in a prospective randomized, double-blind, 3-arm parallel study over 6 months (glimepiride + placebo vs glimepiride + 4 mg rosiglitazone vs glimepiride + 8 mg rosiglitazone) in 174 patients with type 2 diabetes [7]. The presented investigation was performed to analyze the dose-dependent effect of rosiglitazone given for 4 months in addition to glimepiride on beta-cell function, insulin resistance, and cardiovascular risk, as assessed by insulin, intact proinsulin, adiponectin, and high-sensitivity C-reactive protein (hsCRP) concentrations in patient samples derived from this investigation.

2. Patients and methods

The samples were derived from a double-blind, randomized, parallel study comparing the effect of different doses of rosiglitazone (Avandia; GlaxoSmithKline, Munich, Germany) provided in addition to an antidiabetic treatment with 3 mg of glimepiride (Amaryl, Sanofi-Aventis, Berlin, Germany) [7]. Patients were recruited to this study from 32 centers in Germany. At screening, eligible patients stopped taking their current antidiabetic monotherapy medication and entered a maximum 4-week open-label titration period, during which the dose of glimepiride was up-titrated to 3 mg/d, followed by a 4-week single-blind run-in period with glimepiride 3 mg/d plus placebo. At the end of the run-in period, patients were randomized to a double-blind treatment with glimepiride 3 mg/d plus rosiglitazone-matched placebo, glimepiride 3 mg/d plus rosiglitazone 4 mg/d, or glimepiride 3 mg/d plus rosiglitazone 8 mg/d. All treatments were dosed once daily, which means 2 tablets per day per patient. The samples taken for this analysis were drawn at week 0 (before randomization) and after 16 weeks of treatment.

After approval for the additional analyses was obtained from the responsible ethical review board, 204 samples from 102 patients (visit 5 = baseline and visit 9 = 16 weeks) with complete data sets could be included into this analysis (54 males, 48 females; age [mean ± SD], 64 ± 9 years; diabetes duration, 6.4 ± 4.8 years; HbA_{1c}, 8.1% ± 1.5%; glimepiride + placebo, n = 30; glimepiride + 4 mg rosiglitazone, n = 31; glimepiride + 8 mg rosiglitazone, n = 41). The patient characteristics are given in Table 1. They were not different from the original treatment cohorts regarding the mean clinical or laboratory values at baseline

Table 1
Patient characteristics and clinical parameters (mean ± SD) at baseline and end point in the different treatment groups

	Glim + placebo (n = 30)		Glim + 4 mg RSG (N = 31)		Glim + 8 mg RSG (N = 41)	
Sex						
Male	15		15		22	
Female	13		16		19	
Age (y)	63.7 ± 9.0		59.8 ± 10.2		62.2 ± 8.6	
Disease duration (y)	7.3 ± 5.6		5.9 ± 6.2		6.4 ± 3.9	
	Baseline	End point	Baseline	End point	Baseline	End point
Systolic RR	142 ± 13	140 ± 14	139 ± 16	137 ± 17	141 ± 82	141 ± 81
Diastolic RR	83 ± 7	83 ± 9	82 ± 9	82 ± 7	82 ± 9	82 ± 9
BMI	30.0 ± 3.4	29.8 ± 3.4	27.7 ± 4.1	27.7 ± 4.1	29.3 ± 4.8	29.5 ± 4.8

RR indicates blood pressure (as measured with the method of Riva and Rocci); BMI=body mass index.

Table 2
Laboratory parameters (mean ± SD) at baseline and end point in the different treatment groups

	Glim + placebo			Glim + 4 mg RSG			Glim + 8 mg RSG		
	Baseline	End point	Δ (%)	Baseline	End point	Δ (%)	Baseline	End point	Δ (%)
HbA_{1c} (%)	7.7 ± 1.4	7.7 ± 1.5	0	8.3 ± 1.4	7.1 ± 1.7***	−14	8.0 ± 1.4	6.7 ± 1.0***	−16
Glucose (mmol/L)	10.2 ± 2.6	9.7 ± 2.1	−5	10.6 ± 2.5	8.4 ± 2.1***	−21	10.3 ± 2.7	7.7 ± 1.9***	−25
HOMA-IR score	2.6 ± 2.0	3.2 ± 3.2	23	3.0 ± 1.6	1.9 ± 1.4*	−37	4.1 ± 1,7	1.7 ± 1.2**	−59
Intact proinsulin (pmol/L)	6.4 ± 4.1	8.0 ± 5.1	25	6.5 ± 3.9	4.5 ± 2.9	−31	7.9 ± 5.7	4.8 ± 3.0**	−39
Insulin (μU/mL)	5.7 ± 4.0	7.1 ± 6.0	25	6.2 ± 5.0	5.0 ± 3.1	−19	8.6 ± 9.1	4.9 ± 3.0*	−43
Adiponectin (μg/L) adjusted for BMI changes	8.4 ± 5.1	11.9 ± 6.2*	42, −6	12.1 ± 13.5	20.8 ± 15.2*	72, 73	10.2 ± 8.5	20.5 ± 17.9**	101, 143
hsCRP (mg/L)	3.0 ± 2.5	3.2 ± 2.0	7	5.0 ± 3.9	3.3 ± 3.3*	−34	5.0 ± 3.6	2.9 ± 2.5	−42

* $P < .05$ vs baseline.
** $P < .005$ vs baseline.
*** $P < .001$ vs baseline.

and end point. Observation parameters were insulin, intact proinsulin, and adiponectin. Further information available for the current analysis from previous reports were the results for glucose, HbA_{1c}, and body mass index.

2.1. Laboratory analysis

The observation parameters were tested at the IKFE laboratory in accordance with the guidelines of the College of American Pathologists. All determinations were performed in duplicate. No irregularities or deviations from the SOPs of IKFE laboratory occurred during the measurements. Intact proinsulin was measured by a specific enzyme-linked immunosorbent assay method (Linco, St. Charles, MO) as described previously [16]. Insulin was determined by means of the MLT chemiluminescence assay (MLT, Cardiff, UK), and adiponectin was measured with radioimmunoassay (Linco). HbA_{1c} was measured by automated cation exchange high-performance liquid chromatography (Tosoh Biosep, Stuttgart, Germany; reference range, 3.4%-6.0%). Fasting plasma glucose was assessed using an enzymatic hexokinase method on a MODULAR analyzer (Roche Diagnostica, Mannheim, Germany).

2.2. Analysis of insulin resistance

Insulin resistance was estimated by a combination of 2 methods: prevalence of fasting intact proinsulin and the homeostasis model assessment for insulin resistance (HOMA-IR) score. Fasting intact proinsulin is only elevated when insulin resistance has increased the insulin demand to such an extent that the cleavage capacity of the beta cells is exhausted, that is, when an increasing demand of insulin really leads not to an increase in insulin but to a cosecretion of proinsulin or other proinsulinlike molecules [22]. It is therefore a direct marker for beta-cell dysfunction and a highly specific indirect marker for insulin resistance [8,15]. In case of normal fasting intact proinsulin values, an increased demand for insulin leads indeed to insulin secretion, which is the situation where HOMA-IR may be applied by means of the following formula: HOMA-IR = [glucose (mmol/L) × insulin (μg/mL)]/22.5. As published by Hedblad and coworkers [23] for a nondiabetic population, values exceeding 2.0 were regarded as being insulin-resistant.

2.3. Statistical methods

Predominantly, methods of descriptive analysis were applied. The data were tabulated, and the means and SDs were calculated for the different groups. Baseline to end point comparison and comparison between the groups were performed by appropriate parametric and nonparametric methods. Comparison of mean values of normally distributed values was done by means of Student t test. Nonnormally distributed values were compared by Mann-Whitney U test. Contingency tests were used to compare the prevalence of insulin resistance between the groups at baseline and end point. Statistical significance was assumed for P values of less than .05.

3. Results

A summary of the mean ± SD values for all observation parameters at baseline and end point for all 3 treatment groups is provided in Table 2. Although glimepiride monotherapy showed no improvement of long-term glucose control or fasting glucose values, a significant reduction of both values was observed after addition of rosiglitazone in both respective treatment arms after 4 months. In addition, a trend for a further deterioration of beta-cell function and insulin resistance was seen with glimepiride monotherapy, as shown by a nonsignificant increase in insulin, intact proinsulin, and HOMA-IR values. In contrast, PPARγ activation by addition of rosiglitazone resulted in a dose-dependent improvement of both conditions, as given in the absolute values and values from baseline and end point and in the percentage of changes in Table 2.

A significant increase was observed for the adiponectin concentrations in all 3 groups. It had been shown in the

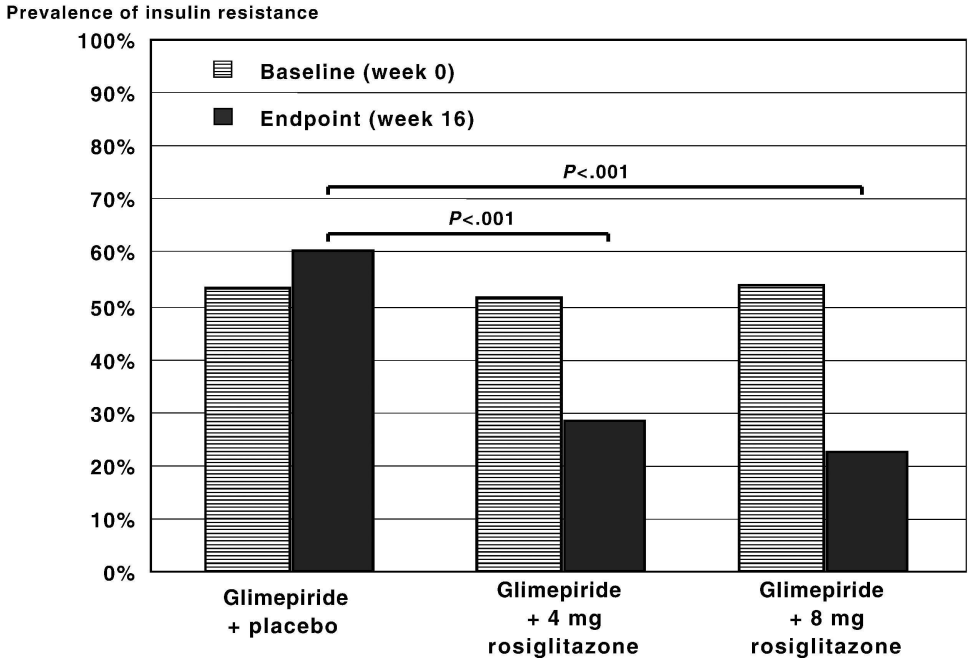

Fig. 1. Prevalence of insulin resistance at baseline and after 16 weeks of treatment with glimepiride alone or in combination with 4 or 8 mg of rosiglitazone as assessed by intact proinsulin and HOMA-IR determination.

literature that adiponectin values are inversely correlated with changes in body weight [24]. After adjustment for changes in the body weight, an increase in adiponectin concentrations could only be seen in the rosiglitazone treatment arms (Table 2).

Insulin resistance as defined by elevated intact proinsulin values or by HOMA-IR score values above 2.0 [23] (or both conditions) was comparably prevalent in all 3 treatment groups at baseline. There was a significant reduction in the prevalence of insulin resistance in the 2 rosiglitazone arms at end point, whereas more patients became insulin-resistant when being treated with glimepiride only. The percentage of insulin resistance prevalence at baseline and end point in all 3 treatment groups is given in Fig. 1.

4. Discussion

In this study, addition of rosiglitazone to an underlying sulfonylurea treatment resulted in additional beta-cell protective and anti-inflammatory therapeutic effects and an overall improvement of long-term glycemic control. These results are in line with the current knowledge on thiazolidinedione effects in vitro and in animal experiments. However, this is the first study to show that rosiglitazone is able to completely prevent the negative effects of sulfonylurea drugs on beta-cell dysfunction, insulin resistance, and cardiovascular risk markers in a dose-dependent fashion.

Thiazolidinediones activate PPARγ and exert short-term anti-inflammatory effects, which can accumulate into anti-atherogenicity [25]. Numerous in vitro experiments with adipocytes, monocytes, and endothelial cell cultures have demonstrated the capabilities of pioglitazone and rosiglitazone to induce anti-inflammatory and anti-artherogenetic effects in adipose and muscle tissue [26-31]. In animal studies, rosiglitazone monotherapy increased plasma adiponectin levels in rodents independently from changes in glycemic control [32,33].

Recent publications give evidence of the transferability of the in vitro and animal results into clinically important findings, as indicated by the improvement of established and newly defined biochemical and clinical surrogate markers for insulin resistance, beta-cell function, and cardiovascular risk. In a randomized, parallel study of 173 patients with type 2 diabetes, pioglitazone in comparison to glimiperide has been shown to reduce biomarkers for cardiovascular risk, such as hsCRP, matrix metalloproteinase-9 (MMP-9), or monocyte chemoattractant protein 1, independently from glycemic control [34]. These effects were accompanied by a reduction in carotid intima-media thickness [35], reduction of insulin resistance scores and intact proinsulin levels, and an increase in adiponectin concentrations [18,34]. The hsCRP reduction observed was comparable to the reduction achieved in our actual study.

The anti-inflammatory actions of rosiglitazone were investigated in 11 nondiabetic obese subjects and 11 obese diabetic subjects who received 4 mg of rosiglitazone daily for a period of 6 weeks. A decrease in nuclear factor κB–binding activity in mononuclear cell nuclear extract and a reduction in plasma monocyte chemoattractant

protein 1 and CRP was seen in both groups, whereas plasma tumor necrosis factor α and serum albumine A (SAA) concentrations were inhibited significantly in the obese group, but not in the obese diabetic subjects [36]. In a randomized, double-blind study with 20 drug-naive patients with type 2 diabetes, 8 mg of rosiglitazone but not 2 g of metformin significantly increased insulin clearance (by 20%) and insulin-stimulated glucose uptake, whereas hepatic insulin sensitivity in the basal state increased similarly in both groups after 4 months of treatment. Serum adiponectin concentrations increased by 123% with rosiglitazone, a value comparable to our current results, but remained unchanged during metformin treatment. In addition, rosiglitazone but not metformin significantly increased expression of PPARγ and lipoprotein lipase in adipose tissue [37]. Smith et al [38] described the results of a double-blind parallel comparator study between rosiglitazone monotherapy (4 or 8 mg) and sulfonylurea treatment (glyburide 2 mg) in 446 patients with type 2 diabetes. Treatment with rosiglitazone, but not with glyburide, was associated with significant decreases in plasma proinsulin and the proinsulin-insulin ratio.

All the above-mentioned studies give evidence about the beneficial effects of thiazolidinediones on insulin resistance, beta-cell dysfunction, and cardiovascular risk markers when used in monotherapy. Although sulfonylurea treatment alone seems to exert a further deteriorating effect on both principal underlying causes of type 2 diabetes, activation of PPARγ by rosiglitazone (in our study) or pioglitazone [17] has been shown to supercede those effects when both kind of drugs are used in a combination treatment.

Whether these surrogate findings may finally influence the overall cardiovascular mortality is still subject to speculation. An extensive program of outcome studies with hard end points is currently under way (DREAM, RECORD, ADOPT, BARI-2D, PROACTIVE, etc), which may be able to provide the evidence whether the observed anti-inflammatory and beta-cell protective actions of thiazolidinediones will finally translate into a significant lower cardiovascular risk for patients with impaired glucose tolerance [39-41].

In conclusion, the dose-dependent positive effects of rosiglitazone on biomarkers for glucose control, insulin resistance, beta-cell function, and cardiovascular risk have been observed independently from the underlying sulfonylurea treatment. The results of our short-term investigation of rosiglitazone action provide further experimental support for the rationale of combining rosiglitazone with sulfonylurea drugs in patients with type 2 diabetes.

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