Beneficial Effects of Combined Treatment With Rosiglitazone and Exercise on Cardiovascular Risk Factors in Patients With Type 2 Diabetes

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Physical activity attenuates metabolic and cardiovascular maladaptations in diabetes by improving glycemic control, insulin resistance, cardiorespiratory fitness, and adipocytokines levels (adiponectin, resistin, tumor necrosis factor [TNF]-α, and interleukin [IL]-6) (1,2). Likewise, thiazolidinediones favorably influence the above indexes (3,4). We hypothesized that the combination of exercise training and rosiglitazone, a thiazolidinedione, would confer additional benefits in the metabolic and cardiovascular profiles of diabetic patients, exceeding those of each treatment alone.

RESEARCH DESIGN AND METHODS

— A total of 100 Caucasian, overweight/obese (BMI> 25 kg/m^2) patients with type 2 diabetes consented to participate. They were treated with half-maximal doses of metformin (1,700 mg) and gliclazide (180 mg) for at least 6 months, with poor glycemic control eventually occurring (A1C > 7%). Smokers and patients receiving lipid-lowering medications, insulin, or thiazolidinediones were rejected. Those with vascular complications, life-threatening diseases, orthopedic problems, and heart, liver, or renal impairment were also excluded. After baseline examination, participants were randomized to one of the following age- and sex-matched groups: *1*) the control group (n = 25); *2*) the exercise group (n = 25), who underwent 8 months' exercise training; *3*) the rosiglitazone group (n = 25), who had adjunctive therapy with 8 mg/day rosiglitazone; and *4*) the rosiglitazone plus exercise (RSG + EX) group (n = 25), who participated in the 8-month exercise program (as in the exercise group) while simultaneously receiving treatment with 8 mg/day rosiglitazone.

The prescription of the exercise program was based on initial ergocycle testing results. Afterward, its workload was gradually increased until patients achieved 50–80% $V_{O_{2max}}$ during 45–60 min sessions four times a week (5). After the fourth week, the intensity and duration of each session remained constant. Patients of the control and rosiglitazone groups were instructed to maintain their habitual activities.

Laboratory and clinical measurements

Blood samples were obtained at baseline and at the end of the study. All participants avoided any severe physical activity 48 h before measurements. Plasma adiponectin (R&D Systems), resistin (BioVendor Laboratory Medicine, Modrice, Czech Republic), insulin (DRG Diagnostics, Marburg, Germany), and IL-6 and TNF-α (Assay Designs) concentrations were assayed using enzyme-linked immunosorbent assay kits. The intra- and interassay coefficients of variation are provided by manufacturers. Insulin resistance was estimated by homeostasis model assessment of insulin resistance (HOMA-IR) (6). Samples were frozen and stored (−80°C) until analysis in the same assay. Cardiorespiratory capacity was assessed at baseline and at the end of the study with a graded symptom-limited exercise test on an electronically-braked ergocycle, using a gas-exchange analyzer (COSMED K4; COSMED, Rome, Italy) (7).

Statistical analysis

Comparison between groups of baseline and final values and changes of variables was performed by one-way ANOVA and post hoc Tukey test (2 × 2 factorial design). Changes within groups were analyzed by Wilcoxon's signed-rank test. Normality of distribution was assessed by Kolmogorov-Smirnov test. A P value of <0.05 was considered statistically significant.

RESULTS

Interventions effects

Baseline values of all variables and the concomitant medications did not differ between groups. Five patients discontinued the study because of personal reasons. In the end, 95 patients were eligible for analysis. No adverse events were reported.

Compared with that at baseline and in the exercise group, rosiglitazone treatment increased BMI significantly ($P <$ 0.001). No substantial changes were noted in the other groups. Exercise training increased exercise capacity ($V_{O_{2max}}$) by 14.9% ($P <$ 0.001), while rosiglitazone induced a modest (5.46%) but significant improvement in fitness compared with that both at baseline ($P <$ 0.001) and in the control group (P = 0.031). Importantly, combined therapy remarkably increased $V_{O_{2max}}$ (26.48%; $P <$ 0.001),

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Abbreviations: HOMA-IR, homeostasis model assessment of insulin resistance; IL, interleukin; TNF, tumor necrosis factor.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Results of changes in response to treatment*

	Control group			Exercise group			Rosiglitazone group			RSG + EX group				
	Week 0	Change	P*	Week 0	Change	P*	Week 0	Change	P*	Week 0	Change	P*	P_1	Post hoc analysis†
n (male/female)	23 (9/14)	—	—	23 (8/15)	—	—	25 (10/15)	—	—	24 (9/15)	—	—	NS	—
Age (years)	60.32 ± 9.28	—	—	56.91 ± 7.09	—	—	59.04 ± 7.35	—	—	57.83 ± 7.61	—	—	NS	—
Diabetes duration (years)	5.78 ± 2.91	—	—	6.83 ± 3.69	—	—	5.29 ± 2.63	—	—	6.33 ± 2.25	—	—	NS	—
FPG (mg/dl)	193.16 ± 25.92	10.3 ± 9.2	NS	190.32 ± 33.59	−21.7 ± 18.2	ǂ	198.59 ± 43.91	−26.2 ± 19.7	ǂ	189.64 ± 28.09	−47.6 ± 30.6	ǂ	<0.001	<0.001§¶, 0.005‖, 0.028**
A1C (%)	8.03 ± 0.91	0.34 ± 0.63	NS	8.02 ± 1.16	−0.51 ± 0.41	ǂ	8.53 ± 1.26	−0.86 ± 0.83	ǂ	8.29 ± 1.07	−1.58 ± 0.87	ǂ	<0.001	0.019††, <0.001§¶‖**
Fasting insulin (mU/l)	12.98 ± 4.68	1.34 ± 1.11	NS	12.03 ± 3.67	−2.57 ± 1.13	ǂǂ	12.97 ± 4.85	−2.83 ± 1.49	ǂ	12.78 ± 4.52	−5.33 ± 3.21	ǂ	0.001	0.048††, 0.045**, <0.001§¶‖
HOMA-IR	6.19 ± 2.72	1.02 ± 0.79	NS	5.65 ± 2.14	−1.76 ± 0.66	ǂ	6.63 ± 2.65	−2.08 ± 0.98	ǂ	6.17 ± 2.71	−3.87 ± 1.91	ǂ	<0.001	0.043ǂǂ, 0.048**, <0.001§, 0.001¶, 0.009‖
VO_{2max} (ml · kg^{-1} · min^{-1})	23.62 ± 6.32	−0.61 ± 0.7	NS	22.43 ± 4.4	3.34 ± 2.14	ǂ	23.68 ± 4.0	1.29 ± 0.39	ǂ	22.56 ± 3.13	5.97 ± 1.44	ǂ	<0.001	<0.001§‖††, 0.001**, 0.013§§, 0.031¶
Duration of exercise (min)	9.27 ± 1.77	−0.24 ± 0.3	NS	8.94 ± 1.50	0.78 ± 0.4	ǂ	9.55 ± 1.05	0.54 ± 0.26	ǂ	8.15 ± 1.52	1.37 ± 0.53	ǂ	<0.001	<0.001§‖††, 0.001¶**
Adiponectin (μg/ml)	7.90 ± 2.33	−0.60 ± 0.8	NS	8.53 ± 3.48	0.33 ± 1.15	NS	6.86 ± 2.63	5.98 ± 2.4	ǂ	7.15 ± 3.04	6.21 ± 2.5	ǂ	<0.001	0.016**, 0.001§¶, 0.011§§
Resistin (ng/ml)	18.16 ± 5.61	1.45 ± 2.82	NS	17.07 ± 6.21	−4.29 ± 2.22	ǂǂ	17.48 ± 8.12	−4.78 ± 2.65	ǂ	18.53 ± 6.8	−6.85 ± 2.03	ǂ	0.005	0.005§, 0.022¶, 0.031‖
IL-6 (pg/ml)	5.0 ± 3.42	0.21 ± 0.42	NS	4.8 ± 3.75	−0.99 ± 0.50	ǂǂ	4.7 ± 3.46	−1.38 ± 0.69	ǂǂ	4.4 ± 3.14	−2.21 ± 0.55	ǂǂ	0.040	0.009§, 0.036¶
TNF-α (pg/ml)	92.81 ± 47.05	2.2 ± 2.4	NS	91.91 ± 42.18	−5.2 ± 2.2	NS	88.61 ± 41.88	−12.3 ± 8.7	ǂǂ	94.10 ± 49.98	−18.8 ± 14.3	ǂǂ	0.048	0.011¶
BMI (kg/m^2)	28.96 ± 1.03	0.15 ± 0.85	NS	31.14 ± 3.58	−0.19 ± 0.76	NS	30.04 ± 2.99	0.93 ± 0.80	ǂ	29.91 ± 1.78	0.008 ± 0.69	NS	0.036	0.044§§
Fat mass (%)	38.8 ± 9.4	−0.3 ± 0.5	NS	37.9 ± 7.5	−1.9 ± 0.5	ǂǂ	38.6 ± 8.7	−0.7 ± 0.4	NS	39.5 ± 8.2	−2.8 ± 0.8	ǂ	NS	0.018, 0.04‖

Data are means ± SEM unless otherwise indicated. *Levels of variables between baseline and the end of the study within groups; †post hoc analysis of changes of variables between groups; ǂ$P < 0.001$; §RSG + EX vs. control group; ¶rosiglitazone vs. control group; ‖exercise vs. control group; **RSG + EX vs. exercise group; ††RSG + EX vs. rosiglitazone group; ǂǂ$P < 0.05$; §§rosiglitazone vs. exercise group. P_1, ANOVA of changes of variables between groups. FPG, fasting plasma glucose; NS, not significant.

which exceeded the complementary effects of both interventions.

Although both rosiglitazone treatment and exercise training alone ameliorated glycemic indexes, fasting insulin, and HOMA-IR ($P < 0.05$), the RSG + EX group elicited a more pronounced decrease of the aforementioned parameters compared with that of all of the other groups ($P < 0.05$) (Table 1).

Adipocytokines

We observed considerable reduction of resistin and IL-6 levels in all of the interventions groups ($P < 0.05$), but greater alterations were found in the RSG + EX group. Both combined therapy and rosiglitazone treatment alone elicited significant increments of adiponectin in comparison with baseline values and the changes elicited by other groups ($P < 0.05$). Similarly, TNF-α was also downregulated significantly in the latter groups, and, compared with that in the control group, the change was significant only after combined treatment. Patients in the exercise group demonstrated a slight increase of adiponectin ($P = 0.39$) and a less marked decrease of TNF-α ($P = 0.45$). No adipocytokines were affected significantly in the control group.

CONCLUSIONS — In this 8-month study, we demonstrated for the first time that simultaneous treatment with rosiglitazone plus exercise attenuated adipocytokine levels, counteracted rosiglitazone-induced weight gain, and extended improvements of insulin sensitivity, glycemic control, and fitness beyond those expected by their complementary actions in patients with type 2 diabetes.

The most pronounced results of glucose regulation were observed in the RSG + EX group (A1C −19.1%). After completion of the study, 78% of patients in the RSG + EX, 37.9% in the rosiglitazone, and 21.82% in the exercise group had achieved glycemic target (A1C <7%). This is a striking finding in that our patients had inadequate glycemic control notwithstanding the double antidiabetes treatment. Furthermore, combined treatment considerably ameliorated insulin resistance (change of HOMA-IR [δHOMA-IR] −68.1%), exceeding the expected results from the addition of rosiglitazone (δHOMA-IR −30.8%) to exercise (δHOMA-IR −23.08%). We hypothesized that the latter synergistic effects might be ascribed to multiple interactions be-

tween insulin signaling and muscle glucose uptake (8,9).

Poor metabolic control, physical inactivity, and muscle abnormalities are determinants of impaired exercise capacity in type 2 diabetes (1,10). To our knowledge, this is the first study demonstrating a robust increase of fitness in the RSG + EX group, outlining synergism between thiazolidinediones and exercise training. Trying to explain these results, we observed that the $V_{O_{2max}}$ increment was correlated with HOMA-IR and A1C reduction in all active groups (data not shown). We then postulated that metabolic control improvement after combined treatment might amplify $V_{O_{2max}}$ elevation. Alternatively, thiazolidinediones and physical activity have been demonstrated to ameliorate endothelial dysfunction and induce mitochondrial biogenesis and thereby could facilitate oxygen delivery and muscle performance (1,11,12).

Adiponectin modulates insulin sensitivity with significant antiatherogenic properties (13). Our lifestyle intervention left adiponectin levels almost unaltered, while rosiglitazone treatment doubled adiponectin levels (14). Therefore, the increment of adiponectin in the RSG + EX group was predominantly ascribed to rosiglitazone administration.

Up to now, limited studies have provided conflicting data about the influence of thiazolidinediones and prolonged exercise on human plasma adipocytokines (5,15–19). We demonstrated that all interventions suppressed resistin and IL-6 levels, while both combined therapy and rosiglitazone treatment alone decreased TNF-α levels significantly. Those effects were independent of insulin resistance modulation. Among all groups, the greatest magnitude of anti-inflammatory impact was found in the RSG + EX group, which raises the prospect of reduced cardiovascular risk.

Weight gain, the most common side effect of thiazolidinediones, is predominantly attributed to fluid retention (3). In the RSG + EX group, body weight remained stable. Perhaps the addition of exercise counterbalanced the rosiglitazone-related body weight increase by remarkably decreasing fat mass content.

The principal limitation of our study was the small number of patients. However, the sample cohort was adequately homogeneous. Another limitation was the usage of the HOMA-IR index. Although it is dependent on both peripheral and hepatic insulin sensitivity, it highly correlates with estimation derived from the euglycemic clamp test (6). The combination of rosiglitazone and exercise favored remarkable benefits on traditional and novel cardiovascular risk factors. Further research will confirm the aforementioned promising results.

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