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Exercise training ameliorates the effects of rosiglitazone on traditional and novel cardiovascular risk factors in patients with type 2 diabetes mellitus

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Abstract

The aim of the study was to investigate the effects of rosiglitazone and/or exercise training on novel cardiovascular risk factors in patients with type 2 diabetes mellitus. One hundred overweight/obese type 2 diabetes mellitus patients, with inadequate glycemic control (hemoglobin A_{1c} >7%) despite combined treatment with gliclazide plus metformin, were randomized using a 2 × 2 factorial design to 4 equivalent (n = 25) groups, as follows: (1) CO: maintenance of habitual activities, (2) RSG: add-on therapy with rosiglitazone (8 mg/d), (3) EX: adjunctive exercise training, and (4) RSG + EX: supplementary administration of rosiglitazone (8 mg/d) plus exercise training. No participant had diabetic vascular complications or was receiving lipid-lowering therapy. Anthropometric parameters, cardiorespiratory capacity, glycemic and lipid profile, apolipoprotein (apo) A-I, apo B, interleukin (IL)-10, IL-18, insulin resistance, and blood pressure were measured before and after 12 months of intervention ($P < .05$). Both RSG and EX groups significantly reduced glycemic indexes, insulin resistance, blood pressure, and IL-18, whereas they significantly increased high-density lipoprotein, cardiorespiratory capacity, and IL-10, compared with CO group ($P < .05$). Besides this, exercise-treated patients conferred a remarkable down-regulation in the rest of lipid parameters (total cholesterol, low-density lipoprotein cholesterol, triglycerides, apo B) and body fat content ($P < .05$) in comparison with CO group. On the other hand, RSG group rather than CO group considerably increased apo A-I levels and body mass index ($P < .05$). Notably, the combined treatment group yielded pronounced beneficial changes in glycemic indexes, lipid profile, insulin resistance, blood pressure, IL-10, IL-18, apo A-I, and apo B (vs CO group, $P < .05$). Furthermore, the addition of exercise to rosiglitazone treatment counteracted the drug-related negative effects on body weight, low-density lipoprotein, and total cholesterol. Rosiglitazone plus exercise training elicited additive effects on body composition, glycemic control, and traditional and novel cardiovascular risk factors in type 2 diabetes mellitus patients, indicating complementary effects.

1. Introduction

Type 2 diabetes mellitus (T2DM) exponentially increases worldwide and highly predisposes to cardiovascular diseases [1]. With the exception of hyperglycemia, the excessive cardiovascular morbidity and mortality observed in T2DM are attributed to the clustering of comorbidities, such as insulin resistance, hypertension, dyslipidemia, and obesity [2]. Therefore, the multifaceted characteristics of T2DM entail a multimodal treatment.

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Thiazolidinediones (TZDs), a class of insulin-sensitizing, antidiabetic drugs, pose antiatherogenic role independent of their glucose-lowering effects. They favorably influence vascular function, oxidative stress, and atherosclerotic plaque morphology [3-5]. Most recently, rosiglitazone, a member of TZDs, has been suggested to increase the risk of ischemic heart events and cardiovascular mortality [6]. The precipitation of congestive heart failure by TZDs in susceptible patients has been described as a possible mechanism for their suspected adverse cardiovascular effect [7]. Moreover, the disadvantage of rosiglitazone to increase low-density lipoprotein (LDL) cholesterol levels provides another plausible explanation [8]. All the underlying mechanisms remain to be clarified.

One the other hand, physical activity has long been demonstrated to attenuate numerous metabolic and cardiovascular maladaptations in T2DM [9,10]. For instance, it increases cardiorespiratory fitness, which is inversely associated with poor cardiovascular outcomes and all-cause mortality in diabetic patients [10,11]. Furthermore, exercise training induces favorable changes in lipid profile and restricts both visceral and total body adiposity, the main resources of insulin resistance [12-17]. The multiple effects of physical activity patterns on emerging components of cardiovascular profile, so-called pleiotropic effects, provide an alternative explanation of their beneficial influence on cardiovascular function [18,19].

In our study, we tested the hypothesis that exercise training enhances the beneficial effects of rosiglitazone on novel cardiovascular risk factors and simultaneously attenuates its negative effects on lipids and body weight in overweight/obese patients with T2DM. This study constitutes the second part of an ongoing prospective project, and data from the first part have been already published elsewhere [20].

2. Research design and methods

2.1. Subjects

A total of 100 white patients (39 men and 61 women) with T2DM, aged 50 to 70 years, were recruited from our outpatient diabetic clinic. All eligible patients were overweight or obese (body mass index [BMI] >25 kg/m^2); and they were receiving combined antidiabetic treatment with metformin (1700 mg) plus gliclazide (180 mg), for at least 6 months, but with inadequate glycemic control (hemoglobin A_{1c} [HbA_{1c}] >7%). Our study cohort was sedentary, without reporting systemic (>1 time/wk) sport activities before. Patients with clinical or laboratory evidence of diabetic vascular complications, chronic heart failure, liver or renal impairment, uncontrolled hypertension, arrhythmias, orthopedic problems, or life-threatening diseases were excluded. Moreover, lipid-lowering medication, hormone replacement therapy, insulin, or TZDs treatment and active smoking were also considered as exclusion reasons. The duration of the study was 12 months; and patients were asked to maintain dietary habits and antidiabetic and antihypertensive medications throughout the study, unless deemed medically appropriate.

At baseline, participants were randomly assigned to the following age- and sex-matched groups: (1) CO (n = 25): maintenance of habitual activities (control group), (2) RSG (n = 25): add-on therapy with rosiglitazone (8 mg/d), (3) EX (n = 25): adjunctive exercise program, and (4) RSG + EX (n = 25): adjunctive exercise program (as in EX group) and supplementary administration of rosiglitazone (8 mg/d). A password-protected database and computer generated random list were used for patients' assignment. Only the statistician of our team had access to the database until the randomization was actually done. We used random block sizes to ensure close balance of the numbers in each group at any time during the study.

The study was approved by the local ethics committee, and it was conducted in accordance with the Declaration of Helsinki. All participants provided a written informed consent before enrolment.

2.2. Physical fitness and body composition

We assessed cardiorespiratory capacity of all participants at baseline and at the end of the study using an electronically braked ergocycle. The workload was initially set at 25 W for 2 minutes and thereafter was increased by 25 W every 2 minutes until patients were unable to either continue or retain a constant rate of pedal revolutions. Oxygen uptake and carbon dioxide output were measured continuously by a gas exchange analyzer (COSMED K4, Rome, Italy) using facemask and breath-by-breath technique. Peak oxygen consumption (Vo_2peak) achievement was considered by one of the following criteria: (1) respiratory exchange ratio greater than 1.1, (2) heart rate within 10 beats per minute of the age-predicted maximal heart rate, and (3) no significant increase of Vo_2 (<1 mL kg^{-1} min^{-1}) despite the increase of work rate. There was continuous electrocardiographic recording during the test, and the whole procedure was closely supervised by an experienced physician. The heart rate response to the aforementioned test was used to prescribe exercise training program. A prior familiarization ergospirometry testing of short duration and constant, low intensity was performed 1 week before study beginning.

Body composition (percentage of fat mass and total body water) was analyzed using bioelectrical impedance (Bodystat 1500, Douglas, British Isles). The standard errors of the estimate of percentage body fat and body water were 3.1% and 4.4%, respectively, whereas the test-retest reliability has been found to be r = 0.987. Blood pressure (BP) was measured twice after keeping participants at a sitting position for 15 minutes. There was a 5-minute interval between the 2 measurements, and the mean value was calculated. All assessments were performed at least 48 hours after the last exercise session to assess the true training effects.

2.3. Exercise training protocol

Patients allocated to the group of exercise alone and the group of combined treatment with rosiglitazone plus exercise underwent 12-month aerobic exercise training program. They attended the same fitness center to perform 4 sessions per week. Each session included 10 minutes of warm-up, 30 to 45 minutes of aerobic exercise, and 5 minutes of cooldown. The intensity was individualized according to the initial ergocycle test. Heart rate was assessed continuously by a portable heart rate monitor. The initial workload was low and increased gradually until the subjects were able to achieve exercise training at 50% to 80% Vo_2peak for 45 minutes. After the first month, the duration of each session remained constant, whereas the intensity of exercise was further adapted. Structured exercise consisted mainly of walking or running on treadmill, cycling, and calisthenics involving large muscles groups. From the eighth month of exercise, subjects received written instructions to continue the exercise on their own by performing a self-controlled lifestyle program. The latter conformed to American Diabetes Association recommendations including moderate-intensity aerobic activity such as brisk walking, jogging, and daily activities (household work, bicycling, etc) for more than 150 min/wk [21]. Patients were frequently encouraged to continue, and their compliance was estimated every 2 weeks by examining their personal diary of activity records.

2.4. Blood analyses

At baseline and at the end of the study, blood samples were obtained between 8:00 and 10:00 AM after an overnight fast. Patients were instructed to refrain from caffeine, alcohol, and any intensive body activity for at least 48 hours before all measurements. Biochemical parameters (glucose, total cholesterol, triglycerides, high-density lipoprotein [HDL] cholesterol, creatinine, urea) were enzymatically measured (Roche/Hitachi 912 analyzer; Roche Diagnostics, Basel, Switzerland). Low-density lipoprotein cholesterol was calculated from the Friedewald equation. Measurement of HbA_{1c} was made by high-performance liquid chromatography (Menarini Diagnostics, Rome, Italy). Plasma interleukin (IL)-10 was assayed using quantikine immunoassay (R&D Systems, Minneapolis, MN). The inter- and intraassay coefficients of variance were 8.1% and 6.6%, respectively. Plasma IL-18 and insulin were quantified using commercially available enzyme-linked immunosorbent assay kits (Bender MedSystems, Vienna, Austria, and Mercodia, Uppsala Sweden, respectively). The intra- and interassay coefficients of variance were 5.6% and 7.6% for IL-18 and 4% and 3.6% for insulin, respectively. Insulin resistance was estimated by homeostasis model assessment (HOMA-IR) [22]. Apolipoprotein (apo) A-I and apo B concentrations were determined by immunonephelometry (Olympus AU640; Medicon, Watford, United Kingdom). Nephelometric assay (Dade Behring, BNII, Marburg, Germany) was used for high-sensitivity C-reactive protein (hsCRP) determination. Samples were frozen and stored (−80°C) until analysis in the same assay. The quality control of the lipid laboratory was in compliance with Clinical Laboratory Improvement Amendments of 1988.

2.5. Statistical analysis

The 2 × 2 factorial design of the study allows the interaction of different treatments to be assessed. Normality of distribution was assessed by Shapiro-Wilk test. Concerning the normal distribution of all continuous variables, comparison between groups of baseline, final values, and changes of variables was performed by 1-way analysis of variance (ANOVA) and post hoc Tukey test. Changes over time within groups were analyzed by paired-samples t test. For missing values handling, we excluded patients with incomplete data. At baseline, we performed Fisher exact test for comparison of categorical data between groups. Pearson correlation and multiple regression analysis quantified the relationship between changes of variables and their independent predictors, respectively. For all calculations, we used SPSS 16.0 (SPSS, Chicago, IL). A 2-tailed P value < .05 was considered as statistically significant.

3. Results

Clinical and biochemical variables are listed in Tables 1 and 2 and in Fig. 1. All groups did not differ at baseline. Eleven patients discontinued the study. Two patients stopped training because of time constraints, 2 patients declined repeated measurements, and 7 patients withdrew because of personal reasons. At the end, 89 patients were eligible for analysis. All exercise-treated patients showed high compliance to either structure exercise (attendance 88% ± 4% of exercise sessions) or self-directed exercise (89.2% achieved the target of exercise >150 min/wk). The concomitant medications were similar among groups, and no adverse events were referred throughout the study.

3.1. Lipid profile and body composition

The results are presented in Table 2 and Fig. 1. Exercise training alone significantly improved lipid profile by reducing total cholesterol, triglycerides, LDL, apo B, and apo B/apo A-I levels, whereas it increased HDL levels, as compared with CO (P < .05). Notably, exercise program appeared superior to rosiglitazone add-on therapy in reducing total cholesterol and LDL (P < .05).

Rosiglitazone treatment resulted in a significant increase in HDL and apo A-I levels (P < .05). We also observed a slight, nonsignificant increment in total cholesterol and LDL levels after 12 months of rosiglitazone treatment. No effect was detected on triglycerides and apo B concentrations.

In the group of combined treatment, all lipid parameters were altered favorably throughout the study. In particular,

Table 1
Baseline values of variables

Variable	Group				*P* overall
	CO	RSG	EX	RSG + EX	
n (M/F)	21 (8/13)	23 (8/15)	22 (8/14)	23 (9/14)	NS
Age (y)	60.32 ± 9.28	59.04 ± 7.35	56.91 ± 7.09	57.83 ± 7.61	NS
DD (y)	5.78 ± 2.91	5.29 ± 2.63	6.83 ± 3.69	6.33 ± 2.25	NS
BMI (kg/m^2)	29.96 ± 1.03	30.04 ± 2.99	31.14 ± 3.58	28.96 ± 1.03	NS
Fat mass (%)	38.8 ± 9.4	38.6 ± 8.7	37.9 ± 7.5	39.5 ± 8.2	NS
BW (%)	48.8 ± 9.1	49.1 ± 7.9	47.3 ± 8.2	50.4 ± 8.9	NS
FPG (mg/dL)	193.16 ± 25.92	198.59 ± 43.91	190.32 ± 33.59	189.64 ± 28.09	NS
HbA_{1c} (%)	8.03 ± 0.91	8.53 ± 1.26	8.02 ± 1.16	8.29 ± 1.07	NS
TC (mg/dL)	239.42 ± 31	235.65 ± 51.25	230.76 ± 38.13	220.31 ± 56.87	NS
HDL (mg/dL)	55.33 ± 11.21	52.24 ± 13.13	49.95 ± 14.9	46.77 ± 13.14	NS
LDL (mg/dL)	154.95 ± 29.6	148.93 ± 46.93	153.66 ± 31.13	142.77 ± 49.14	NS
TG (mg/dL)	147.21 ± 64.8	150.25 ± 68.67	146.57 ± 56.87	171.77 ± 79.43	NS
Insulin (mU/L)	12.98 ± 4.68	12.97 ± 4.85	12.03 ± 3.67	12.78 ± 4.52	NS
HOMA-IR	6.19 ± 2.72	6.63 ± 2.65	5.65 ± 2.14	6.17 ± 2.71	NS
SBP (mm Hg)	140.53 ± 14.71	144.48 ± 18.91	134.81 ± 17.42	136.15 ± 16.98	NS
DBP (mm Hg)	78.95 ± 8.09	85 ± 9.64	79.86 ± 10.67	78.85 ± 12.77	NS
hsCRP (mg/L)	4.2 ± 1.2	3.9 ± 1.5	4.1 ± 1.1	4.1 ± 1.8	NS

Data are means ± SD. M/F indicates male/female; DD, duration of diabetes; BW, body water; TC, total cholesterol; TG, triglycerides; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; NS, not significant; *P* overall, *P* value for ANOVA.

total cholesterol (P = .042), LDL (P = .022), triglycerides (P = .006), apo B (P = .036), and apo B/apo A-I (P = .014) levels were considerably down-regulated compared with CO group. Among all active groups, combined treatment induced the most pronounced elevation in HDL and apo A-I levels at the end of the study (RSG + EX vs CO, P < .001). In comparison with rosiglitazone alone, simultaneous treatment with rosiglitazone plus exercise further reduced LDL cholesterol (RSG + EX vs RSG, P = .021) and apo B levels (RSG + EX vs RSG, P = .010) (Table 2, Fig. 1).

After the completion of the study, a significant increase in BMI was observed only in the RSG group (0.91 ± 0.71 kg/m^2, P = .036), which was accompanied with significant body water accumulation (P = .048) as compared with CO group. Among all groups, RSG + EX (P = .01) and EX groups (P =

Table 2
Changes of variables from baseline to the end of the study

Variable	Group				*P* overall	*P* post hoc
	CO	RSG	EX	RSG + EX		
BMI (kg/m^2)	0.25 ± 0.89	0.91 ± 0.71	−0.28 ± 1.75	0.007 ± 0.09	.036	.036[d], .044[e]
Fat mass (%)	−0.4 ± 0.1	−0.5 ± 0.2	−1.6 ± 0.6	−2.4 ± 1.1*	.011	.010[c], .040[f]
BW (%)	0.3 ± 0.8	2.4 ± 1.4*	0.6 ± 0.5	1.6 ± 1.2	.045	.048[e]
FPG (mg/dL)	10.09 ± 18.29	−31.38 ± 30.69*	−16.39 ± 35.21*	−32 ± 25.86*	<.001	<.001[c,e], .013[f], .043[d]
HbA_{1c} (%)	0.51 ± 0.61	−0.83 ± 0.89*	−0.29 ± 0.57*	−1.42 ± 0.91*	<.001	.044[a], <.001[b,c,e], .010[f]
TC (mg/dL)	1.47 ± 29.6	1.52 ± 33.35	−19.48 ± 15.44*	−18.15 ± 41.23*	.035	.042[c], .033[d], .039[f]
HDL (mg/dL)	−2.33 ± 7.58	3.93 ± 8.12*	5.29 ± 5.13*	11 ± 4.87*	<.001	.015[a], <.001[c], .017[e], .001[f]
LDL (mg/dL)	7.53 ± 4.62	−6.89 ± 5.61	−15.14 ± 6.35*	−32.39 ± 12.02*	.019	.021[a], .022[c], .027[d], .028[f]
TG (mg/dL)	7.53 ± 4.62	−6.89 ± 5.61	−15.14 ± 6.35*	−32.39 ± 12.02*	.019	.006[c], .022[f]
Insulin (mU/L)	0.61 ± 5.36	−2.58 ± 4.04	−1.13 ± 5.01	−5.63 ± 5.15*	.024	.008[b], <.001[c,e]
HOMA-IR	2.12 ± 2.16	−1.87 ± 2.44*	−0.85 ± 0.85*	−3.25 ± 2.81*	.008	.018[b], <.001[c], .009[e], .047[f]
SBP (mm Hg)	0.79 ± 2.54	−6.38 ± 3.22*	−6.29 ± 4.25*	−13.08 ± 6.28	.001	.001[c], .034[e], .038[f]
DBP (mm Hg)	0.89 ± 8.48	−3.45 ± 4.45*	−2.86 ± 4.29	−7.31 ± 3.35*	.004	.002[c], .033[e]
hsCRP (mg/L)	0.1 ± 0.05	−1.6 ± 0.9	−0.9 ± 0.7	−2.5 ± 1.2	<.001	<.001[c], .036[e], .048[f]

Data are means ± SD.

P values of changes of variables between groups:

[a] RSG + EX vs RSG.
[b] RSG + EX vs EX.
[c] RSG + EX vs CO.
[d] RSG vs EX.
[e] RSG vs CO.
[f] EX vs CO.
* P < .05 values within groups.

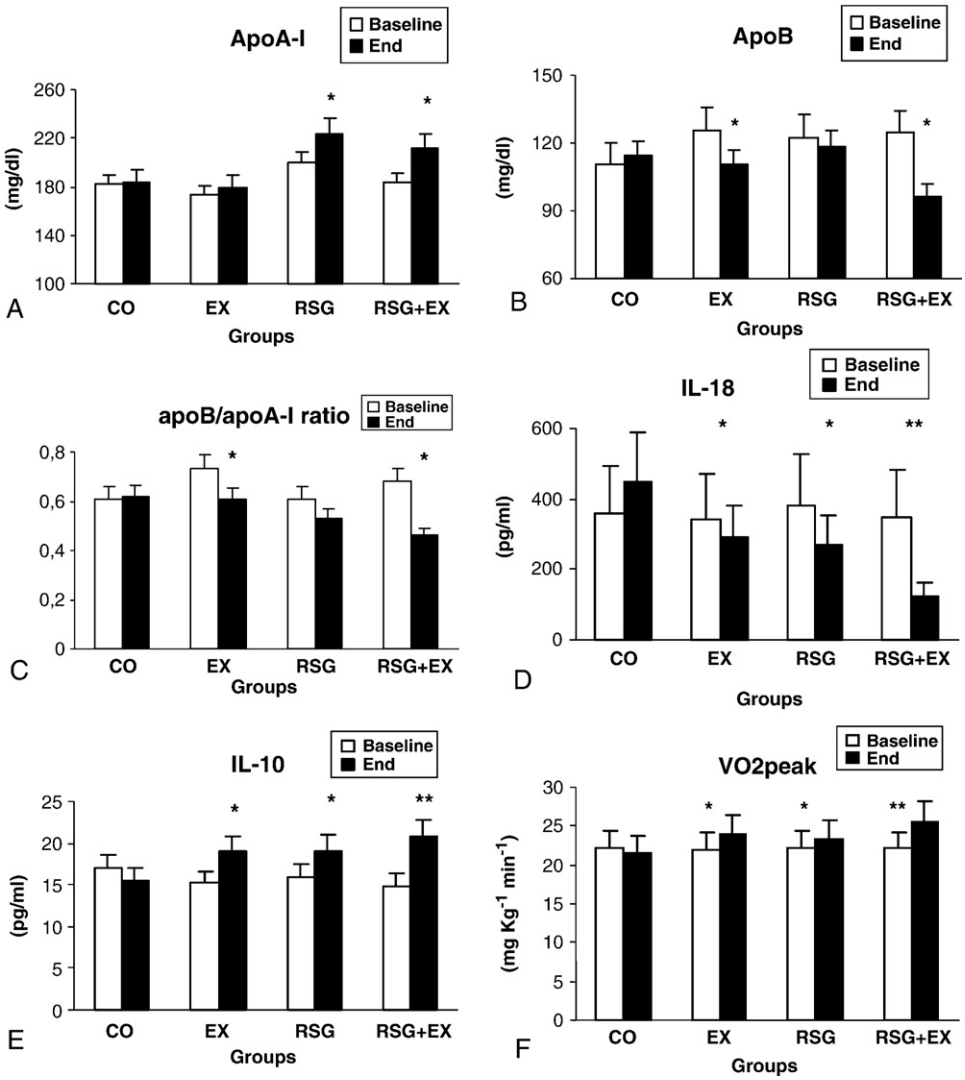

Fig. 1. Effects of treatment on (A) apo A-I, (B) apo B, (C) apo B/apo A-I ratio, (D) IL-18, (E) IL-10, and (F) V_{O_2}max. Values are means ± SD.*$P < .05$ and **$P < .001$; changes of variables compared with CO group.

.040) significantly reduced the percentage of fat mass in comparison with control patients.

3.2. Glycemic control, insulin resistance, exercise capacity, and BP

Exercise training exerted beneficial effects on HbA_{1c}, fasting plasma glucose (FPG), insulin resistance (HOMA-IR), and systolic BP compared with controls ($P < .05$). As expected, exercise training increased exercise capacity (V_{O_2}peak) by 10.8% (EX vs CO group, $P < .001$). Similarly, rosiglitazone treatment attenuated hyperglycemia, insulin resistance, and both systolic and diastolic BP ($P < .05$). Importantly, rosiglitazone alone induced a modest (4.06%) but significant improvement in V_{O_2}peak vs baseline ($P = .015$) and the exercise ($P < .001$) and control ($P = .008$) groups. The addition of exercise training to rosiglitazone exerted greater benefits on glycemic control than all the other groups ($P < .05$). Besides this, the latter treatment modality further decreased HOMA-IR as compared with CO ($P < .001$) and EX ($P = .018$) groups and significantly down-regulated BP vs CO ($P < .01$), whereas it remarkably increased V_{O_2}peak ($P < .001$) vs CO and RSG groups (Table 2, Fig. 1).

3.3. Inflammatory markers

In comparison with CO group, exercise training considerably suppressed hsCRP ($P = .048$) and IL-18 ($P = .041$) levels, whereas it increased IL-10 concentration ($P = .028$). Similarly, the rosiglitazone group showed a significant reduction in IL-18 ($P = .030$) and hsCRP levels ($P = .036$) and a considerable elevation in IL-10 levels ($P = .042$). Most importantly, the combined treatment group yielded a pronounced reduction in IL-18 (vs CO group, $P < .001$) and hsCRP levels (vs CO group, $P = .005$), whereas IL-10 levels were significantly up-regulated (vs CO group, $P = .003$) (Table 2, Fig. 1).

Table 3
Pearson correlations between changes in Vo_2peak and selected variables in the RSG + EX group

	ΔVo2peak	
	r	*P*
ΔHOMA-IR	−0.886	.036
ΔHbA_{1c}	−0.404	.009
ΔhsCRP	−0.337	.032
ΔApo A-1	0.435	.012
ΔIL-10	0.595	.007
ΔIL-18	−0.480	.005

Δ = difference from baseline to the end of the study. $P < .05$.

3.4. Correlations

We next examined the changes of Vo_2peak, inflammatory markers, apo B, and apo A-I in relation to the changes of the other variables in the RSG + EX group (Table 3). The increment of Vo_2peak correlated with the changes in HOMA-IR, HbA_{1c}, hsCRP, IL-10, IL-18, and apo A-I ($P < .05$). Alterations in IL-10 showed additionally a significant relationship with systolic BP ($r = −0.240$, $P = .004$). Apart from Vo_2peak, IL-18 changes correlated with HbA_{1c} ($r = 0.365$, $P = .017$) and hsCRP changes ($r = 0.299$, $P = .008$). Moreover, apo A-I changes were related to HDL ($r = 0.585$, $P < .001$) and HbA_{1c} alterations ($r = −0.349$, $P = .017$), whereas apo B changes were positively associated with changes in HOMA-IR ($r = 0.353$, $P = .044$), hsCRP ($r = 0.334$, $P = .043$), IL-18 ($r = 0.398$, $P = .016$), and triglycerides ($r = 0.349$, $P = .025$). Multiple regression analysis demonstrated changes in HOMA-IR, HbA_{1c}, and IL-18 to independently correlate with Vo_2peak alterations in the RSG + EX group ($R^2 = 0.576$, $P = .005$).

4. Discussion

In our 12-month study, either exercise training or rosiglitazone treatment alone altered favorably numerous cardiovascular risk factors in diabetic patients. Most importantly, the combined intervention (rosiglitazone plus exercise) yielded additive effects on glycemic profile and novel cardiovascular risk factors, which are of clinical importance. On the other hand, exercise training counteracted the negative effects of rosiglitazone on body weight and lipid metabolism. The present results extend those from our previous 8-month study because, after the cessation of the structured exercise program, patients were encouraged to follow a self-controlled lifestyle program [20]. The present study showed sustainability of improvements at 1 year in terms of glycemic control, insulin sensitivity, and exercise capacity.

Up to now, the influence of rosiglitazone on lipid parameters is a subject of controversy [23]. Although rosiglitazone increases HDL cholesterol, it concomitantly increases total and LDL cholesterol [24]. Our study confirmed the latter unfavorable effects of rosiglitazone, which have been previously attributed to increases in apo C-III and a delayed clearance of smaller very low-density lipoprotein and intermediate-density lipoprotein particles [24,25]. On the other hand, our exercise program improved all lipid parameters. Thereby, the combination of exercise training and rosiglitazone treatment counteracted the aforementioned negative impact on lipid parameters; and it further ameliorated triglycerides and HDL concentrations. Moreover, combined treatment improved apo A-I, apo B, and apo B/apo A-I ratio, which constitute more clinically relevant indexes of cardiovascular risk than traditional lipid values, in diabetic patients [26,27]. The favorable influence of exercise on lipid profile has been ascribed to alterations in intravascular enzyme activities, such as lipoprotein lipase activity, hepatic lipase activity, lecithin-cholesterol acyltransferase activity, and cholesterol ester transfer protein concentration [28]. Besides this, both exercise and TZDs have been suggested to enhance adipose tissue sensitivity to the antilipolytic action of insulin and to reduce hepatic triglycerides content, free fatty acids, and insulin resistance in muscle, liver, and adipose tissues [29,30]. Therefore, we hypothesized that our combined intervention stimulated complementary mechanisms and thereby retrieved insulin resistance–related lipid disorders. This hypothesis requires further investigation.

In our study, rosiglitazone administration significantly increased body weight and total body water. Thiazolidinediones have been hypothesized to increase extracellular volume through renal sodium retention and fluid accumulation, but the pathogenetic mechanisms are poorly characterized [3,31]. Regarding in vitro and animal data, TZDs seem to stimulate sodium reabsorption in the distal nephron by up-regulating the expression and the translocation of the collecting duct epithelial sodium channel [32]. On the other hand, our exercise program reduced fat mass, but increased total body water; so the net weight loss was negligible. Available data indicate that exercise training expands mainly intravascular volume. Increased amount of intravascular proteins or volume regulatory hormones and enhanced renal tubular sodium reabsorption through sensitization of aldosterone receptors predominantly contribute to exercise-stimulated hypervolemia [33-35]. Paradoxically, rosiglitazone in conjunction with exercise increased total body water to a lesser extent than rosiglitazone alone. Nevertheless, no patient reported peripheral edema or congestive heart failure. We hypothesized that exercise-induced hypervolemia was completed within 10 to 14 days from exercise initiation, fairly earlier than TZDs influence [35]. As a result, the exercise-triggered sensitivity of aldosterone receptors might have limited the expression and the translocation of the collecting duct epithelial sodium channel from rosiglitazone, through negative feedback, leading to less water retention by TZDs. In the RSG + EX group, body water increased whereas fat mass decreased, compensating for the rosiglitazone-induced weight gain. Further work will elucidate the

effects of simultaneous exercise and TZDs treatment on body water homeostasis.

Consistently with previous studies, rosiglitazone therapy and long-term exercise alone improved glycemic control [36,37]. Among all groups, the RSG + EX group conferred the most pronounced hypoglycemic effects, regarding the substantial proportion of patients (76.7%) that achieved the glycemic target (HbA_{1c} <7%) at the end of the study. This finding is of clinical importance because all patients were already receiving simultaneously 2 antidiabetic agents (metformin plus gliclazide). Concerning our previous study, it seems that exercise-treated patients maintained the majority of exercise-related benefits, despite the transformation of structured to self-controlled exercise program. Thus, the sustained lifestyle improvement provides persistent benefits in glycemic control in the diabetic population.

Thiazolidinediones and physical activity are well-documented insulin-sensitizing agents. In the present study, all active groups attenuated insulin resistance. However, combined therapy conferred additive results because HOMA-IR was remarkably down-regulated compared with the CO and EX groups. We postulated several interactions between exercise and rosiglitazone in insulin signaling stimulation. Indeed, the "energy charge hypothesis" indicates that muscle contraction (exercise) and inhibition of cell respiration (TZDs) activate adenosine monophosphate–activated protein kinase and augment insulin sensitivity in the long term [38]. Another plausible explanation is that rosiglitazone enhances the interplay between exercise and insulin on muscle glucose uptake [39]. Hevener et al [40] illustrated that troglitazone, a withdrawn member of TZDs, combined with exercise increased substantially GLUT-4 protein and almost normalized insulin action in Zucker fatty rats. Finally ,we speculated that our combined therapeutic modality attenuated hepatic/muscle insulin resistance through the modification of adipocytokines [20]. Future studies will draw firm conclusions.

Among anti-inflammatory cytokines, IL-10 has recently emerged as a key factor in cardiovascular diseases progression. Interleukin-10 has anti-inflammatory properties including inhibition of the proinflammatory transcription factor nuclear factor–κB leading to suppressed cytokine production, reduced matrix metalloproteinase production, reduced tissue factor expression, and promotion of the phenotypic switch of lymphocytes to Th2 phenotype [41]. Up-regulation of IL-10 has been reported to be associated with good prognosis in patients with unstable coronary artery disease [42,43]. In our study population, all active groups had significantly elevated IL-10 levels at the end of the study, whereas combined treatment exerted additive results, which are of clinical relevance.

Interleukin-18 is the interferon-γ–inducing factor and a pleiotropic proinflammatory cytokine associated with poor cardiovascular outcomes [44]. Circulating levels of IL-18 have been demonstrated to increase in patients with T2DM [45]. To our knowledge, this is the second study showing a significant down-regulation in IL-18 levels after either rosiglitazone treatment or exercise training, which is of clinical importance [18,46]. Most importantly, the addition of exercise training to rosiglitazone remarkably suppressed IL-18 levels, indicating complementary anti-inflammatory effects of persistent exercise and TZDs. Unambiguously, the anti-inflammatory properties of insulin-sensitizing agents require further investigation.

Exercise capacity is well documented to be impaired in diabetic individuals compared with age-, sex-, BMI- and activity-matched nondiabetic subjects [9,47]. In our study, all active groups significantly increased Vo_2peak compared with controls. In comparison with our previously published study [20], exercise-treated groups maintained to a lesser extent the improvement of exercise capacity. Thus, the implementation of even self-controlled exercise should be consistently promoted in the therapeutic strategy of T2DM. In multiple regression analysis, the aforementioned disproportionate increment of Vo_2peak in the RSG + EX group was independently associated with the amelioration of hyperglycemia, insulin resistance, hsCRP, IL-10, and IL-18 plasma levels. As we previously reported [20], the latter findings outline an interplay between metabolic, inflammatory, and cardiovascular functional parameters, suggesting the cardioprotective role of lifestyle intervention.

The principal limitation of our study was the small number of patients in each group. To restrict patients' disparity, we recruited subjects with poor glycemic control, but on the same oral antidiabetic regimen. Another limitation of our study was the use of HOMA-IR, which reflects both peripheral and hepatic insulin sensitivity. However, it is quite difficult to perform euglycemic clamp as a monitoring test in clinical studies.

In conclusion, the combination of rosiglitazone and exercise improved the overall cardiovascular profile to a greater extent than each intervention alone in patients with T2DM. Effective therapeutic strategies in the diabetic population should incorporate intensive pharmaceutical treatment and sustained encouragement for lifestyle alterations.

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