Metabolic Effects of Aerobic Training and Resistance Training in Type 2 Diabetic Subjects

A randomized controlled trial (the RAED2 study)

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OBJECTIVE—To assess differences between the effects of aerobic and resistance training on HbA_{1c} (primary outcome) and several metabolic risk factors in subjects with type 2 diabetes, and to identify predictors of exercise-induced metabolic improvement.

RESEARCH DESIGN AND METHODS—Type 2 diabetic patients (n = 40) were randomly assigned to aerobic training or resistance training. Before and after 4 months of intervention, metabolic phenotypes (including HbA_{1c}, glucose clamp–measured insulin sensitivity, and oral glucose tolerance test–assessed β-cell function), body composition by dual-energy X-ray absorptiometry, visceral (VAT) and subcutaneous (SAT) adipose tissue by magnetic resonance imaging, cardiorespiratory fitness, and muscular strength were measured.

RESULTS—After training, increase in peak oxygen consumption ($V_{O_{2peak}}$) was greater in the aerobic group (time-by-group interaction $P = 0.045$), whereas increase in strength was greater in the resistance group (time-by-group interaction $P < 0.0001$). HbA_{1c} was similarly reduced in both groups (−0.40% [95% CI −0.61 to −0.18] vs. −0.35% [−0.59 to −0.10], respectively). Total and truncal fat, VAT, and SAT were also similarly reduced in both groups, whereas insulin sensitivity and lean limb mass were similarly increased. β-Cell function showed no significant changes. In multivariate analyses, improvement in HbA_{1c} after training was independently predicted by baseline HbA_{1c} and by changes in $V_{O_{2peak}}$ and truncal fat.

CONCLUSIONS—Resistance training, similarly to aerobic training, improves metabolic features and insulin sensitivity and reduces abdominal fat in type 2 diabetic patients. Changes after training in $V_{O_{2peak}}$ and truncal fat may be primary determinants of exercise-induced metabolic improvement.

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Recent data suggest that both aerobic and resistance training may exert beneficial effects on glucose control in subjects with type 2 diabetes (1,2). However, it remains unclear if the extent of improvement and the mechanisms underlying the metabolic effects of these exercise protocols are similar.

Two recent comparison studies reported similar HbA_{1c} reductions after aerobic or resistance training (3,4). However, the extent of HbA_{1c} changes in other studies using either type of exercise varied considerably (2), and therefore the results cannot be considered conclusive.

The most direct determinants of glucose control are β-cell function and insulin sensitivity. In particular, most of the benefit of regular exercise on glucose control in these subjects is attributed to attenuation of insulin resistance. However, only a few studies have accurately assessed, by the gold-standard glucose clamp technique, the effects of aerobic training on insulin sensitivity in diabetic patients (5–8), and only one small study assessed the effects of resistance training (9). In contrast, little attention has been devoted to the potential effects of physical training on insulin secretion, with controversial results (10,11).

The amelioration of insulin resistance brought about by physical training may be due to changes in a number of potential factors, including, but not limited to, body fat mass, fat distribution, lean mass, and maximal aerobic performance. The role played by these factors is still unsettled. Answering this question is of great interest and could help in programming more appropriate exercise training protocols in diabetic subjects.

We carried out the RAED2 (Resistance Versus Aerobic Exercise in Type 2 Diabetes) trial to assess what differences and similarities exist between the effects of aerobic and resistance training in diabetic subjects, and which of these are the main determinants of the exercise-induced improvement of glucose control. To answer these questions, the effects of these exercise protocols on body fat, body composition, insulin sensitivity, β-cell function, aerobic performance, and strength measures were carefully assessed.

RESEARCH DESIGN AND METHODS

Subjects

Type 2 diabetic patients (n = 40) were enrolled from the Diabetic Outpatient Clinic of the City Hospital of Verona. Participants were recruited between September 2008 and February 2010 and followed up until

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June 2010. Inclusion criteria were type 2 diabetes for at least 1 year, age between 40 and 70 years, HbA_{1c} between 6.5 and 9.0%, and BMI between 24 and 36 kg/m^2. Subjects had to be untrained, with baseline physical activity <1,000 MET min per week by the International Physical Activity Questionnaire (IPAQ) (12). Allowed diabetes medications were oral hypoglycemic agents. Weight had to remain stable in the 2 months prior to the program. Exclusion criteria comprised moderate-severe somatic or autonomic neuropathy, cardiovascular disease, preproliferative or proliferative retinopathy, and chronic renal failure. Subjects on therapy with β-blockers, smokers, or those unable to perform the programs were also excluded. All subjects were screened by an electrocardiogram stress test. The study was approved by the Verona Hospital Ethical Committee and written informed consent was obtained from all individuals.

Randomization

Patients were allocated in a 1:1 ratio to the aerobic training (AER) or resistance training (RES) groups, matching for BMI and peak oxygen consumption ($V_{O_{2peak}}$). Each couple of matched subjects was assigned a sequential number and either the letter "a" or "b". Subsequently, on the basis of computer-generated random numbers, each "a" or "b" subject was assigned to either aerobic or resistance training. Matching and allocation sequences were carried out by an assistant from our department, who did not enroll the participants and was blinded to names and other features of subjects.

Intervention

Both experimental groups exercised three times per week for 60 min, for a period of 4 months, at the Fitness Centre of the Exercise and Sport Science School of Verona University. All training sessions were carried out under the supervision of exercise specialists.

The AER group exercised on cardiovascular training equipment. After a learning phase, the workload was gradually increased up to 60–65% of the reserve heart rate, as estimated by the Karvonen equation (13). Heart rate monitors were used to standardize exercise intensity (Polar S810i; Polar Electro, Kempele, Finland).

The RES group performed different exercises on weight machines and free weights. In each session, participants performed nine different exercises involving the major muscle groups, alternating lower body, upper body, and core exercises. After a learning phase, in which participants were instructed to exercise with three series of 10 repetitions on each machine at 30–50% 1-RM (one repetition maximum) test, the workload was gradually increased to 70–80% 1-RM.

Before entering the study, all subjects were encouraged to follow a healthy diet, according to standard recommendations for diabetic subjects (14). Thereafter, patients were instructed to maintain their baseline calorie intake by consuming self-selected foods.

Outcomes and measurement

The primary outcome was the change in HbA_{1c}. Secondary outcomes included changes in insulin sensitivity, β-cell function, cardiorespiratory fitness, muscle strength, body composition, and metabolic profile. Investigators of outcomes were blinded to treatment.

Insulin sensitivity and β-cell function

Insulin sensitivity was assessed by the glucose clamp technique and β-cell function by analysis of the glucose and C-peptide curves during the oral glucose tolerance test (OGTT) (75 g). These tests were carried out on separate days, in random order. On both days, patients were admitted to the Metabolic Clinic Research Center at 07:30 A.M. after an overnight fast. Patients were asked not to exercise in the previous 24 h and to take no medication in the morning of the test. All studies were carried out in a quiet, temperature-controlled (22°C) room.

In brief, in the hyperinsulinemic euglycemic clamp, baseline blood samples were collected, and a standard euglycemic insulin (intravenous prime, 4.8 nmol · min^{-1} · m^{-2} BSA; continuous infusion, 240 pmol · min^{-1} · m^{-2} BSA) clamp was performed. Arterialized plasma glucose was allowed to decline until 5.5 mmol/L, after which glucose clamping started with a glucose concentration goal of 5 mmol/L. The duration of the clamp was at least 120 min, but it was prolonged, if needed, to ensure at least 60 min of insulin infusion with plasma glucose around the target. Timed blood samples were collected and plasma glucose was immediately measured with a glucose analyzer (YSI-2300 Stat Plus; YSI Inc., Yellow Springs, OH). The glucose disposal rate was calculated during the last 60 min of the clamp, with standard equation (15).

In the OGTTs, blood samples to measure glucose, C-peptide and insulin concentrations, and urine to measure glycosuria were collected for 300 min. The analysis of the glucose and C-peptide curves was performed as previously described (16,17). Further details can be found in the Supplementary Materials and Methods.

Biochemistry

HbA_{1c} was measured by a Diabetes Control and Complications Trial (DCCT)-aligned method, with an automated high-performance liquid chromatography analyzer (Bio-Rad Diamat, Milan, Italy). Total cholesterol, HDL-cholesterol, triglycerides, and other blood measurements were determined by standard laboratory procedures (DAX-96; Bayer Diagnostics, Milan, Italy). LDL-cholesterol was calculated by the Friedewald equation (18).

Body composition and abdominal adipose tissue

Weight was recorded on an electronic scale (BWB-800; Tanita, Arlington Heights, IL), height was measured with a Harpenden stadiometer (Holtain Ltd., Crymych Pembs, U.K.), and BMI was calculated as weight (kg)/height^2 (m). Waist circumferences were measured at a level midway between the lowest rib and the iliac crest.

Total body and regional composition (fat mass and fat-free mass) were evaluated by dual-energy X-ray absorptiometry (DXA) using a total body scanner (QDR Explorer W; Hologic, Bedford, MA).

Magnetic resonance imaging (MRI) was used to measure visceral (VAT) and subcutaneous adipose tissue (SAT). MRI examinations were performed using a 1.5-T magnet (Magnetom Symphony; Siemens Medical, Erlangen, Germany). A single slice at the L4 level was used to measure adipose tissue distribution, using a gradient echo "in phase" and "out phase" sequence. The abdominal adipose tissue compartments were defined according to the classification of Shen et al. (19). The VAT compartment was bounded by the internal margin of the abdominal muscle walls and included intraperitoneal, preperitoneal, and retro-peritoneal adipose tissue. The SAT compartment included the adipose tissues outside of the VAT boundary.

Physical fitness and caloric intake

Cardiorespiratory fitness was measured during a cycle ergometer (Sport Excalibur; Lode, Groningen, the Netherlands) incremental stress test by breath-by-breath analysis of oxygen consumption and carbon dioxide production (Quark b2; Cosmed, Rome, Italy). After a warm-up load of 30 W for 3 min, 10-W increments were applied each minute up to voluntary exhaustion.

Peak oxygen consumption was calculated in the last 30 s of the test. In all tests, maximal heart ratio was >85% of age-predicted maximum and respiratory quotient >1.10. $V_{O_{2peak}}$ was expressed in $mL \cdot kg^{-1} \cdot min^{-1}$.

Strength was measured by 1-RM test using the Brzycki method (20), after two familiarization sessions. This was carried out for both upper (chest press) and lower (leg extension) extremity muscles. Weekly physical activity was estimated by the IPAQ questionnaire (12).

Caloric intake was assessed through the MetaDieta software version 3.1 (METEDA, Ascoli Piceno, Italy). All participants filled in a 3-day food recall and the questionnaires were analyzed by the same trained dietitian. The output of the software included total calorie intake and macronutrient percentages.

Medication regimens and adverse events

At baseline and at the end of the intervention, all medications were recorded. Physicians were allowed to change antidiabetic medication regimens during the study, in particular to avoid hypoglycemic events.

Any adverse events were recorded throughout the training program by both the exercise specialists and the physicians. A glucose level of ≤70 mg/dL was used to define documented hypoglycemia (21).

Statistical analysis

Data are shown as mean and SE, mean and 95% CI, or median and IQR, as appropriate. Considering available literature evidence showing that HbA_{1c} reduction ranged 0.30–1.50 and 0.0–0.30% in studies using aerobic training or resistance training, respectively (22), power and sample size were calculated on a predicted HbA_{1c} difference between groups of 0.30 HbA_{1c} units with a standard deviation of effect of 0.34 HbA_{1c} units, $\alpha = 0.05$, power = 0.80. The 0.3-unit difference was chosen with the aim of establishing whether there was a clinically meaningful difference between treatments in terms of metabolic improvement. The calculation yielded 20 participants per group. Normality of the distribution of the studied variables was assessed by the Shapiro-Wilk test.

Skewed variables (HbA_{1c}, triglycerides, VAT, SAT, and VAT/SAT ratio) were log-transformed before analysis. Repeated-measures ANOVA was used to compare changes over the intervention period, with the variables assessed in the study as the dependent variable and effects for time, study group, and time-by-group interaction. In this analysis, particular attention was given to the interaction term as its significance meant a different trend of the dependent variable in the two groups; when this was true, separate Student *t* tests for paired data were performed in both groups. The Fisher exact test was used to check for differences in the number of antidiabetic therapy changes between groups. Bivariate associations between variables of interest were assessed by Pearson correlation coefficients or Sperman rank correlations.

Multiple regression analyses were performed, using changes in either HbA_{1c} or insulin sensitivity as the dependent variable. In these analyses, independent variables were chosen on the basis of associations in bivariate analyses with the dependent variable and/or of biological plausibility. Therefore, in these analyses, baseline values of the dependent variable, changes in $V_{O_{2peak}}$, strength, insulin sensitivity and anthropometric features, type of intervention, compliance to intervention, sex, and age were tested in the models as independent variables. The final models chosen were those with the highest explained variance, considering that the number of independent variables must take into account the sample size.

Tests with $P < 0.05$ were considered statistically significant. Analyses were carried out using STATA version 10.1 (StataCorp, College Station, TX).

RESULTS—Of the 40 subjects enrolled in the study, 38 completed the protocol and were included in the analyses. One subject, in the RES group, abandoned the study just before starting the exercise program, and one subject, in the AER group, dropped out early during the intervention period due to repeated infections of the upper respiratory tract precluding participation in the exercise sessions. Median attendance to supervised training sessions was similar in the two groups: 93% (IQR 81–98%) and 89% (IQR 82–98%) in the AER and the RES groups, respectively (P = 0.97). The two groups had similar baseline characteristics (Table 1).

Physical fitness and dietary intake

Table 2 shows the changes after training in the two groups. $V_{O_{2peak}}$ and workload significantly increased in both groups. However, for both parameters, the increases were twice as high in the AER as compared with the RES group (time-by-group interaction P = 0.04). Conversely, increases in both lower and upper limb strength were found in the RES, but not in the AER group (time-by-group interaction $P < 0.0001$). The amount of overall physical activity, as measured by the IPAQ questionnaire, increased significantly to a similar extent in both groups. At the end of the study, a similar slight decrease in mean total calorie intake was observed in both groups. No significant changes in diet composition were observed.

Body fat and body composition

In both groups there were similar slight reductions of body weight and waist circumference (Table 2). Consistently, DXA measures of total body and truncal fat showed similar reductions in the two groups. Lean limb mass increased by ~0.4 kg in the AER group and by ~0.8 kg in the RES group, with no statistically significant difference between groups.

MRI-assessed VAT and SAT were similarly reduced in the two groups. Reduction of VAT was higher than reduction of SAT with both protocols, resulting in significant declines in VAT/SAT ratios in both groups, without differences between groups (P = 0.12).

Metabolic control, insulin sensitivity, and β-cell function

HbA_{1c} showed similar improvements in the two groups. The mean change was −0.40% (95% CI −0.61 to −0.18) versus −0.35% (−0.59 to −0.10) in the AER and RES groups, respectively (P = 0.759). HDL cholesterol, triglycerides, and blood pressure also improved significantly, to a similar extent, in both groups (Table 2).

Insulin sensitivity, as assessed by the euglycemic clamp, significantly increased by ~30% and by ~15% in the AER and RES groups, respectively, with no statistically significant differences between groups. Neither intervention was associated with significant improvements in β-cell function (Supplementary Fig. 1).

After 4 months of training, only minor changes in antidiabetic medication regimens were recorded. These drugs were reduced in four subjects in the AER group and in two subjects in the RES group (P = 0.66).

Predictors of changes in metabolic control and insulin sensitivity

In the entire cohort of subjects, HbA_{1c} reduction after training was positively associated with changes in DXA measures of total body fat (r = 0.45, P = 0.005) and truncal fat (r = 0.36, P = 0.030). Furthermore, change in HbA_{1c} was negatively associated with the increases in insulin sensitivity (r = −0.43, P = 0.007), $V_{O_{2peak}}$ (r = −0.46, P = 0.005),

Table 1—*Main baseline characteristics of the subjects enrolled in the study*

	Aerobic group (n = 20)	Resistance group (n = 20)
Age, years	57.2 (1.6)	55.6 (1.7)
Men/women, *n/n*	14/6	14/6
Diabetes features		
HbA_{1c}, %	7.29 (0.15)	7.30 (0.16)
Fasting glucose, mg/dL	153 (6.0)	164 (7.7)
Duration of diabetes, years	10.7 (1.4)	9.7 (1.7)
Antidiabetic therapy, *n* (%)		
Diet alone	1 (5)	2 (10)
Metformin	17 (85)	16 (80)
Thiazolidinediones	3 (5)	0 (0)
Sulfonylureas	6 (30)	5 (25)
Incretins	0 (0)	0 (0)
Meglitinides	1 (5)	4 (20)
Anthropometric parameters		
BMI, kg/m^2	29.5 (1.1)	29.2 (1.0)
Waist circumference, cm	99.0 (2.6)	99.2 (2.7)
Fat mass, %	31.2 (1.4)	30.3 (1.8)
Blood pressure		
Systolic, mmHg	136 (3.7)	128 (3.5)
Diastolic, mmHg	82 (1.8)	78 (2.0)
Exercise testing		
$V_{O_{2peak}}$, $mL \cdot kg^{-1} \cdot min^{-1}$	25.90 (1.0)	25.94 (1.1)
Leg extension 1-RM test, kg	64.6 (4.6)	64.5 (3.7)
Energy expenditure and caloric intake		
Overall physical activity, MET min per week	277 (48)	267 (54)
Caloric intake, kcal per day	1,607 (81)	1,501 (59)
Carbohydrates, %	49.0 (1.6)	50.9 (1.9)
Lipids, %	32.7 (1.4)	31.0 (1.2)
Protein, %	18.1 (0.5)	17.9 (0.4)

Values are mean (SE) unless otherwise specified.

and maximal workload ($r = -0.42$, $P < 0.01$). Improvement after training of insulin sensitivity was significantly associated with changes in $V_{O_{2peak}}$ ($r = 0.33$, $P = 0.05$).

In multivariate models, change after intervention in HbA_{1c} was independently predicted by HbA_{1c} at baseline, and by changes in $V_{O_{2peak}}$ and truncal fat ($R^2 = 0.55$) (Table 3). The introduction of type of intervention, sex, age, or changes in insulin sensitivity as additional independent variables did not affect the results.

Change in insulin sensitivity after training was predicted by baseline insulin sensitivity and change in $V_{O_{2peak}}$ (Table 3). When considering a model not including baseline insulin sensitivity, reduction in VAT was also independently associated with the outcome ($P = 0.045$).

Adverse events

One subject in the AER group and three in the RES group complained of back pain, and one subject in the RES group had elbow tendonitis. These complaints were mild and resolved in 2 weeks. No patients had musculoskeletal accidents while exercising. Mild asymptomatic hypoglycemias were recorded after the training sessions in nine subjects in the AER group and in eight subjects in the RES group (range of one to five episodes per patient in both groups, $P = 0.75$).

CONCLUSIONS—In this randomized controlled trial involving subjects with type 2 diabetes, aerobic and resistance training lowered HbA_{1c} levels to a similar extent, by 0.40 and 0.35% respectively, in the absence of significant changes in antidiabetic medications. Amelioration in glucose control was attributable primarily to an improvement in insulin sensitivity, with no significant changes in β-cell function. Although dietary changes were minimal during the intervention period, both groups had significant reductions in abdominal, particularly visceral, fat, with a fall in the VAT/SAT ratio. Interestingly, changes in metabolic features and body composition were similar after aerobic or resistance training, despite the expected differences in the effects of these protocols on cardiorespiratory fitness and strength measures.

Our finding of a similar efficacy of resistance training versus aerobic training on metabolic control of type 2 diabetic subjects is consistent with the results of two previous trials comparing head-to-head the metabolic effects of these training protocols in diabetic patients. Sigal et al. (3) reported a similar mean HbA_{1c} reduction after aerobic or resistance training, by 0.51 and 0.38%, respectively. On the other hand, Church et al. (4) reported negligible HbA_{1c} changes after 1 year of either aerobic or resistance training. Nevertheless, reductions were greater, 0.50 and 0.33%, respectively, in the two groups in patients with baseline HbA_{1c} of 7.0% or more. Interestingly, in both studies, the combination of aerobic and resistance exercise was better than each type of training alone, suggesting that combination may have synergistic effects. However, exercise volume was higher in the combined groups.

One strength of our study is the assessment with state-of-art methods of both insulin sensitivity and β-cell function. It is widely accepted that aerobic exercise improves insulin action, whereas putative effects on β-cell function are controversial (10,11). However, only a few small-size studies have previously measured the effects of the aerobic training alone on insulin sensitivity in diabetic subjects by using the clamp technique, the gold standard for measuring in vivo insulin action (15). These studies reported an increase in insulin-induced glucose utilization, ranging between 12 and 52% after 2–16 weeks of training (5–8). On the other hand, until now, only one small study has assessed the effects of the resistance training alone on insulin sensitivity in diabetic patients, reporting a significant increase in insulin action, by 48%, in nine nonobese patients trained five times a week for 6 weeks (9).

To the best of our knowledge, our study is the first to compare the two training regimens in terms of effects on insulin-induced glucose disposal and β-cell function. We found that, after 4 months of training, insulin sensitivity increased in both groups, by 30% in the aerobic group and 15% in the resistance group. On the other hand, we observed nonsignificant differences in changes of β-cell function according to exercise type. The latter issue, therefore, needs further studies.

Table 2—*Changes observed after 4 months of training in the aerobic and resistance groups*

	Aerobic group (n = 19)	Resistance group (n = 19)	P value, time	P value, time-by-group interaction
HbA_{1c}, %	−0.40 (−0.61 to −0.18)	−0.35 (−0.59 to −0.10)	**<0.0001**	0.759
Fasting glycemia, mg/dL	−15.2 (−29.8 to −0.57)	−12.0 (−23.4 to −0.5)	**0.004**	0.718
Total cholesterol, mg/dL	−0.8 (−15.8 to 14.1)	−0.7 (−8.5 to 7.1)	0.845	0.989
LDL cholesterol, mg/dL	1.8 (−9.9 to 13.5)	2.3 (−4.5 to 9.2)	0.537	0.933
HDL cholesterol, mg/dL	2.9 (−0.28 to 6.1)	1.3 (−1.1 to 3.8)	**0.034**	0.413
Triglycerides, mg/dL	−27.8 (−57.5 to 1.7)	−23.9 (−49.5 to 1.6)	**0.001**	0.926
Glucose disposal rate, $mg \cdot kg\ FFM^{-1} \cdot min^{-1}$	1.15 (0.22–2.07)	0.52 (0.01–1.05)	**0.006**	0.271
Systolic, mmHg	−6.8 (−15.5 to 1.8)	−5.1 (−12.4 to 2.3)	**0.034**	0.750
Diastolic, mmHg	−4.6 (−9.3 to 0.06)	−2.0 (−6.6 to 2.6)	**0.041**	0.407
$V_{O_{2peak}}$, $mL \cdot kg^{-1} \cdot min^{-1}$	4.0 (2.7–5.3)†	2.1 (0.6–3.5)*	—	**0.045**
Watt	20 (10.1–29.9)†	9 (4.2–14.6)*	—	**0.044**
HR_{peak}, bpm	−0.91 (−6.0 to 4.1)	0.84 (−2.7 to 4.4)	0.979	0.546
Chest press, kg	1.3 (−1.1 to 3.7)	10.3 (7.2–13.2)†	—	**<0.0001**
Leg extension, kg	3.0 (−0.3 to 6.3)	12.3 (9.0–15.5)†	—	**<0.0001**
Overall physical activity, MET min per week	710 (575–843)	808 (675–941)	**<0.0001**	0.278
Caloric intake, kcal per day	−96 (−240 to 48)	−76 (−177 to 23)	**0.040**	0.814
BMI, kg/m^2	−0.76 (−1.1 to −0.4)	−0.54 (−0.85 to −0.22)	**<0.0001**	0.330
Waist circumference, cm	−3.2 (−4.5 to −1.9)	−2.4 (−3.8 to −0.9)	**<0.0001**	0.373
Lean total, kg	−0.12 (−0.60 to 0.34)	0.32 (−0.27 to 0.91)	0.592	0.225
Lean mass of limbs, kg	0.43 (0.11–0.76)	0.72 (0.34–1.1)	**<0.0001**	0.239
Fat total, kg	−1.96 (−2.7 to −1.2)	−1.71 (−2.4 to −1.0)	**<0.0001**	0.605
Fat trunk, kg	−1.66 (−2.2 to −1.1)	−1.41 (−1.9 to −0.89)	**<0.0001**	0.506
VAT, cm^2	−61.4 (−98.4 to −24.4)	−33.5 (−52.9 to −14.0)	**<0.0001**	0.360
SAT, cm^2	−13.8 (−23.9 to −3.7)	−19.5 (−35.4 to −3.6)	**0.001**	0.627
VAT/SAT ratio	−0.40 (−0.69 to −0.11)	−0.14 (−0.25 to −0.03)	**<0.0001**	0.121

Data are mean change (95% CI). P values refer to comparisons between groups by repeated-measures ANOVA. Statistically significant figures are in boldface type. When a significant time-by-group interaction was found, differences within each group versus the corresponding baseline values were assessed, and statistically significant figures are indicated by symbols. *$0.001 \leq P < 0.01$. †$P \leq 0.001$ vs. baseline.

Our study is also unique in that we have carefully assessed several intermediate factors that may potentially contribute to explaining the metabolic effects of training, such as changes in body fat mass, fat distribution, lean mass, and aerobic performance. In multivariate analyses, improvement of HbA_{1c} was best predicted by baseline HbA_{1c} and changes in DXA measure of truncal fat and $V_{O_{2peak}}$. The relationship between baseline HbA_{1c} levels and its change after intervention is an expected finding in diabetic subjects, because the closer HbA_{1c} is to normal values, the less room there is for improvement. However, our data showing independent associations of the metabolic improvement with changes in both cardiorespiratory fitness and truncal fat are intriguing.

Until now, only one study (23) has investigated the relationships between improvement in HbA_{1c} and changes of $V_{O_{2peak}}$ and muscle strength in these patients. In univariate analyses, this study found that HbA_{1c} change was associated with the increase of $V_{O_{2peak}}$, in the aerobic and the combined training groups, and of muscular strength, in the resistance training group. In this study, multivariate analyses were not carried out.

With regard to body composition, a recent systematic review (24) concluded that in obese/overweight individuals, there is limited evidence suggesting a beneficial influence of exercise on reductions in abdominal and/or visceral fat. This review, however, included only two studies assessing these features in diabetic patients, by MRI (25,26). These studies reported that both VAT and SAT were reduced after 8–10 weeks of exercise, carried out with aerobic and interval training protocols. More recently, Sigal et al. (3) compared the effects of different types of training on VAT and SAT, assessed by CT imaging. These authors found similar reductions of abdominal fat in the aerobic and resistance groups, without additional effects from the combined training. Moreover, in this study, SAT but not VAT was significantly reduced by the training protocols. The reasons for these discrepancies are not easily explained.

Interestingly, we found that the increase in insulin sensitivity did not contribute to explaining the changes in HbA_{1c} over and above the effects of changes in $V_{O_{2peak}}$ and truncal fat. Anyhow, our data suggest that the increase in cardiorespiratory fitness may account for a relevant part of the exercise-induced improvement in insulin sensitivity. In our analyses, the reduction of VAT was also associated with improvement in insulin resistance when excluding baseline insulin sensitivity from the model. Consistently, previous studies (25,26) reported an association between changes after training in VAT and changes in insulin sensitivity, measured by the insulin tolerance test.

The strengths of our study are the well-matched characteristics of subjects included in the two groups, the tightly

Table 3—*Predictors of changes in HbA_{1c} and insulin sensitivity by multiple regression analyses in the whole group of subjects* (n = 38)

Variables in the model	Coefficient	Standard coefficient	*P* value
Logarithm of change in HbA_{1c} ($R^2 = 0.55$, $P < 0.0001$)			
Intercept	−1.392	−1.392	0.008
Change in $V_{O_{2peak}}$, $mL \cdot kg^{-1} \cdot min^{-1}$	−0.049	−0.422	**0.002**
Change in truncal fat, kg	0.110	0.372	**0.006**
HbA_{1c} at baseline, %	0.175	0.337	**0.017**
Change in leg extension performance, kg	−0.006	−0.152	0.250
Change in insulin sensitivity ($R^2 = 0.50$, $P = 0.004$)			
Intercept	1.014	1.014	0.151
Glucose disposal rate at baseline, $mg \cdot kg\ FFM^{-1} \cdot min^{-1}$	−0.314	−0.430	**0.009**
Change in $V_{O_{2peak}}$, $mL \cdot kg^{-1} \cdot min^{-1}$	0.251	0.419	**0.012**
Change in VAT, cm^2	−0.008	−0.280	0.092
Change in SAT, cm^2	−0.017	−0.257	0.109
Change in limb lean mass, kg	−0.62	−0.245	0.132

Statistically significant figures are in boldface type.

supervised and monitored exercise regimens, the good compliance to exercise programs, the assessment by state-of-the-art techniques of several features, the absence of significant changes in medications during the protocol, and the diet monitoring.

The main limitations are lack of a pure control group and a somewhat small sample size. Although inclusion of a nonexercise control group would have added value to the study, the care adopted in designing the experimental protocol, controlling for the main potential bias through assessment of changes in caloric intake and antidiabetic medications, and weight stability in the 2 months preceding the intervention period, when patients were following diet recommendations, make it unlikely that our findings can be attributed to factors other than the exercise training itself. On the other hand, the small sample size could have reduced our ability to detect significant differences between groups in some features showing a tendency toward greater changes in the aerobic group.

Moreover, owing to the tight inclusion/exclusion criteria, extrapolation of the present findings to other classes of diabetic patients, such as those with advanced chronic complications or those on insulin therapy, should be undertaken with caution.

In conclusion, aerobic and resistance training similarly improve glucose control and insulin sensitivity in type 2 diabetic patients, reducing both visceral and subcutaneous abdominal fat. The increase in oxygen consumption capacity and the reduction in truncal fat may be primary predictors of the exercise-induced metabolic improvement in these subjects. Future research should address whether interventions focused on specifically ameliorating these intermediate factors may have a selective impact on HbA_{1c} levels in subjects with type 2 diabetes.

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E.B. designed the study, researched data, performed statistical analyses, and wrote, reviewed, and edited the manuscript. C.N. and A.C. researched data and reviewed and edited the manuscript. M.E.Z. performed statistical analyses, contributed to discussion, and reviewed the manuscript. C.M., N.F., and M.T. researched data and contributed to discussion. G.Z., F.S., and E.B. contributed to discussion and reviewed and edited the manuscript. R.C.B. researched data, contributed to discussion, and reviewed and edited the manuscript. M.L. conceived and designed the study, researched data, and reviewed the manuscript. P.M. conceived and designed the study and wrote, reviewed, and edited the manuscript. P.M. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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