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The effects of aerobic, resistance, and combined exercise on metabolic control, inflammatory markers, adipocytokines, and muscle insulin signaling in patients with type 2 diabetes mellitus

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ABSTRACT

The purpose of this study was to compare the effects of 3 different modalities of exercise on metabolic control, insulin resistance, inflammatory markers, adipocytokines, and tissue expression of insulin receptor substrate (IRS)–1 after 12 weeks of training among patients with type 2 diabetes mellitus. Forty-eight patients with type 2 diabetes mellitus were randomly assigned to 4 groups of training (3 times a week, 60 minutes per session): aerobic group (n = 12), resistance group (n = 12), combined (aerobic and resistance) group (n = 12), and control group (n = 12). Fasting and postprandial blood glucose, glycated hemoglobin, lipid profile, insulin resistance index (homeostasis model assessment of insulin resistance), adipocytokines (adiponectin, visfatin, and resistin), tumor necrosis factor, interleukin, and high-sensitivity C-reactive protein (hs-CRP) were measured at baseline and at the end of the study. Patients also underwent a muscle microbiopsy before and after training to quantify IRS-1 expression. All 4 groups displayed decreases in blood pressure, fasting plasma glucose, postprandial plasma glucose, lipid profile, and hs-CRP ($P < .05$); and there was no difference across the groups. After training, the IRS-1 expression increased by 65% in the resistance group ($P < .05$) and by 90% in the combined group ($P < .01$). Exercise training favorably affects glycemic parameters, lipid profile, blood pressure, and hs-CRP. In addition, resistance and combined training can increase IRS-1 expression.

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1. Introduction

Exercise and diet are considered the cornerstones of diabetes treatment [1,2]. Indeed, several studies have demonstrated that exercise alone has clinical benefits, such as improved insulin sensitivity, reductions in glycated hemoglobin (A1c) and increased peak oxygen consumption (VO_{2peak}) [3-6].

The mechanism by which exercise improves insulin sensitivity is well documented [7]. Muscle contractions cause the translocation of glucose transporter protein–4 (GLUT-4) to the plasma membrane due to the activation of 5′-adenosine monophosphate–activated protein kinase, triggered either by increased cytoplasmic calcium concentration due to membrane depolarization [8] or by a high intracellular ratio of adenosine monophosphate to adenosine triphosphate, which reflects a compromised energy status of the cell [9]. 5′-Adenosine monophosphate–activated protein kinase activation has marked effects on the expression of a number of glycolytic and lipogenic enzymes in the liver, which likely contributes to the beneficial effects on fatty acid metabolism [9]. c-Jun N-terminal kinase and IκB kinase/IκB/nuclear factor–κB activation by stimuli such as cytokines, endoplasmic reticulum stress, and fatty acids may cause serine phosphorylation of insulin receptor substrate (IRS)–1 [10], leading to impaired phosphorylation of the Akt substrate 160, a key step in insulin signaling that regulates GLUT-4 translocation [11]. However, exercise has the potential to lower the inflammatory status by the reduction of high-sensitivity C-reactive protein (hs-CRP) and tumor necrosis factor (TNF-α) and the enhancement of adiponectin [11,12]. The effect of exercise on insulin resistance may be responsible for the decrease in blood pressure.

A single bout of exercise increases plasma membrane GLUT-4 protein by nearly 4-fold [13], which may be due to increased blood flow during exercise. However, when muscles are contracted in situ in the absence of insulin, the amount of plasma membrane GLUT-4 increases to a similar degree [14]. This finding suggests that GLUT-4 translocation is independent of the action of insulin [15]. The effects of insulin and muscle contraction on glucose transport are synergistic and are known to be of short duration. They can last up to 48 hours in the absence of further exercise [16].

Exercise training causes metabolic adaptations that result in sustained improvements in insulin sensitivity [16]. Aerobic exercise improves VO_{2peak} and glycemic control, as reflected by reductions in A1c [5]. Recent studies have demonstrated benefits from resistance exercise in type 2 diabetes mellitus. In a comparative study, strength training was more effective than aerobic training in improving the glycemic control and the lipid profile [17]. Furthermore, a recent meta-analysis demonstrated that resistance training reduced A1c, fat mass, and systolic blood pressure [18]. Other studies, however, have reported that combined exercise (aerobic plus resistance) can be even more effective in reducing A1c and improving insulin sensitivity [3,19]. Regarding intensity, one study has shown that low- to moderate-intensity exercise training is as effective as moderate- to high-intensity exercise training [20], whereas another study reported that high-intensity training was more effective in improving glycemic control [4].

With regard to the effect of exercise on the intermediates of insulin signaling, the data are mixed. One study found an increase in IRS-1 expression after 1 day of training and a decrease after 5 days of training [21], whereas O'Gorman et al [22] reported that IRS-1 expression is unaffected by short-term (7 days) exercise training.

The purpose of this study was to compare the effects of 3 different modalities of exercise (aerobic, resistance, and combined) on metabolic control, insulin resistance, inflammatory markers, adipocytokines, and tissue expression of intermediates of the insulin signaling pathway after 12 weeks of training in patients with type 2 diabetes mellitus.

2. Materials and methods

2.1. Subjects

Of the 48 participants, 62.5% were female; they were 53.9 ± 9.9 years old, and the mean time since their diabetes diagnosis was 5.9 ± 4.3 years. All participants were overweight or obese. After a clinical evaluation, the participants were subjected to a laboratory protocol ("Laboratory examinations") and to a cardiovascular screening procedure consisting of ergometric testing and an echocardiogram to rule out chronic complications and any disorders that might contraindicate exercise.

2.2. Research design

Eighty-three patients with type 2 diabetes mellitus met the inclusion criteria: type 2 diabetes mellitus based on the American Diabetes Association criteria [23], aged between 30 and 70 years, and body mass index (BMI) between 25 and 40 kg/m² (because one purpose of the study was to evaluate the impact of exercise on insulin resistance). The exclusion criteria included previous or current insulin therapy (because exogenous insulin could affect the assay, leading to misinterpretation of the homeostasis model assessment [HOMA] index) and conditions that could preclude physical activity and corticosteroid use.

Between February 2007 and January 2009, subjects were selected from the Diabetes Outpatient Clinic of the Hospital de Clínicas at the University of Uberlandia, Brazil. After receiving laboratory tests and a cardiovascular evaluation, 35 subjects were excluded; and 48 were enrolled. All patients gave their written informed consent for participation. These 48 individuals with type 2 diabetes mellitus were randomized to 4 groups: aerobic (n = 12), resistance (n = 12), combined (n = 12), and control (n = 12). Table 1 shows the subject characteristics by assigned treatment regimens at allocation: age, BMI, time since diagnosis, and sex. Five patients dropped out of the study at the beginning of the trial: one patient dropped out because of health problems unrelated to the study, and the remaining 4 dropped out for private reasons.

The present study was approved by the ethics committee of the Federal University of Uberlandia (protocol 141/06).

2.3. Setting

The exercise intervention occurred at the Exercise Investigational Unit of our university between April 10 and July 8, 2009.

Table 1 – Characteristics of subjects by assigned treatment regimens at group allocation

Group/characteristics	Control	Aerobic	Resistance	Combined
Sex (male/female)	4/8	5/7	5/7	4/8
Age (y)	53.42 ± 9.82	52.09 ± 8.71	54.10 ± 8.94	57.90 ± 9.82
BMI (kg/m^2)	30.03 ± 4.90	29.30 ± 2.09	31.29 ± 4.08	31.24 ± 3.88
Time since diagnosis (y)	5.25 ± 3.52	5.45 ± 4.12	7.70 ± 3.90	7.30 ± 4.97
Medication				
Sulfonylurea	2	5	7	5
Metformin	7	10	8	10
Sulfonylurea + metformin	2	5	5	5
DPP-4 inhibitors	0	0	0	1
Lipid-lowering drug therapy	1	3	3	3
Antihypertensive	4	7	8	10

Values expressed as means ± SD. There were no differences among the groups (1-way ANOVA). DPP-4 indicates dipeptidyl peptidase–4.

2.4. *Blood pressure and anthropometric measures*

Systolic and diastolic blood pressures were measured using a standard aneroid sphygmomanometer. Body weights and heights were measured using an anthropometric scale, and these measurements were then used for BMI (kilograms per square meter) calculations.

The waist-to-hip ratio (WHR) was determined by measuring the waist circumference at the narrowest region between the costal margin and iliac crest and then dividing this measurement by the hip circumference measured at its greatest gluteal protuberance.

2.5. *Pretraining care*

Before each session, the blood glucose, resting blood pressure, and heart rate were recorded. The trainers were instructed to follow these recommendations: subjects who had a blood glucose level less than 100 mg/dL at arrival were given a snack containing 15 g carbohydrates. If the preexercise blood glucose level was greater than 300 mg/dL, subjects began to exercise and were reassessed in 20 to 30 minutes to confirm that the blood glucose level had not increased. If the blood glucose level increased, exercise was stopped. When the subjects had symptoms of hypoglycemia, their blood glucose level was assessed; and they were given a 15-g carbohydrate snack if the hypoglycemia was confirmed.

A preexercise blood pressure less than 140/90 mm Hg was required for the subjects to begin exercise. If the subjects' preexercise blood pressure was greater than or equal to 140/90 mm Hg, they were asked to sit quietly for 10 minutes and were then reassessed. No exercise was permitted that day if a lower resting blood pressure was not achieved.

2.6. *Muscle strength and oxygen consumption plateau (VO_{2peak})*

The 1-maximum repetition method was used to determine muscle strength for all strength exercises (ie, leg press, bench press, latissimus [lat] pull-down, seated rowing, shoulder press, abdominal curls, and knee curls) before the first training session. To avoid injury, subjects warmed up by performing 2 sets of 10 repetitions of each exercise using light loads 5 minutes before the test. All participants successfully completed the test within 3 to 5 attempts. Three minutes of rest were allowed between repetitions. The Valsalva maneuver was no used.

For aerobic training, subjects underwent an effort test performed on a cycle ergometer (ERGO-FIT 167, Pirmasens, Germany) with the room temperature maintained between 24°C and 26°C. Participants engaged in stretching exercises and a brief 2-minute warm-up on the cycle ergometer with no load before the initiation of the test. The heart rate was measured continually with a cardiac monitor (Polar Electro Oy, Kempele, Finland), and blood samples (25 μL) were obtained from the earlobe at the end of each stage to determine the lactate threshold [24]. The test began with a 25-W load, which was increased by 25 W every 2 minutes until exhaustion. The training load of the aerobic and combined group was defined by the lactate threshold.

2.7. *Intervention: exercise training programs*

The subjects were enrolled in 60 minutes of supervised physical training sessions 3 days per week for 12 weeks.

The strength training (resistance group) routine was focused on the large muscle groups. It consisted of a 7-exercise circuit as follows: leg press, bench press, lat pull down, seated rowing, shoulder press, abdominal curls, and knee curls.

The aerobic training (aerobic group) consisted of cycling at the heart rate corresponding to the lactate threshold.

The combined training (aerobic plus resistance exercise) consisted of strength training interchanged with aerobic training performed at the same intensity and half the volume of the aerobic and resistance groups.

The subjects randomized to the control program were required to come to the University 3 times per week exactly like the other groups to perform light stretching exercises designed to provide participative involvement but not to elicit changes in muscle strength or cardiovascular fitness.

2.8. *Laboratory examinations*

Blood samples were collected before and after the 12 weeks of training. The serum biochemistry parameters of fasting plasma glucose, postprandial glucose, total cholesterol, high-density lipoprotein (HDL) cholesterol, plasma triglycerides, potassium, sodium, creatinine, urea, aspartate aminotransferase, alanine

aminotransferase, γ-glutamyl transferase, creatine kinase, and alkaline phosphatase were determined by colorimetric methods using commercial kits (Abbott, Abbott Park, IL) with an Architect c8000 analyzer (Abbott). Glycated hemoglobin was assessed using an immunoassay by turbidimetry on Dimension RXL Max SIEMENS equipment (Siemens, Chattanooga, TN, USA). Cortisol and thyroid-stimulating hormone levels were determined with a chemiluminescence assay (Diagnostic Products, Los Angeles, CA; minimum detectable value = 15 pg/mL). The hemograms were performed automatically on a Coulter STKS apparatus (Coulter Electronics, Luton, England).

Plasma insulin (Human Insulin ELISA Kit/catalog no. EZHI-14K; Linco Research, St. Charles, MO, USA), adiponectin (Human Adiponectin/catalog no. DY1065; R&D Systems, Minneapolis, MN, USA), CRP (human CRP/catalog no. DY1707; R&D Systems), resistin (Human Resistin/catalog no. DY1359; Ryogen, R&D Systems), visfatin (Visfatin C-Terminal Human/catalog no. EK-003-80; Phoenix Pharmaceuticals, Phoenix, AZ, USA), TNF-α (Human TNF-α Immunoassay/catalog no. DTA00C/STA00C/PDTA00C; R&D Systems), and interleukin (IL)-6 (Human IL-6/catalog no. D6050/S6050/PD6050; R&D Systems) were measured with the specified commercially available enzyme immunoassay kits.

The HOMA insulin resistance index (HOMA-IR) was calculated using the following equation: [fasting serum insulin (microunits per milliliter) × fasting plasma glucose (millimoles per liter)]/22.5.

2.9. *Skeletal muscle microbiopsy*

Fine-needle muscle biopsy, also termed *microbiopsy*, was performed using an automatic instrument (Pro-Mag Ultra, Ecomed, Rio de Janeiro, RJ, Brazil). The biopsy was performed under ultrasonographic visualization. Disposable 10-cm 14-gauge needles were used. The ultrasonographic equipment used was a Medison Sonoace 8000 (Medison, CA, USA) with a 10-MHz broadband linear transducer. The patient received a topical anesthetic (2% Xylocaine - Instituto Vital Brazil, Niteroi, RJ, Brazil) without a vasoconstrictor administered with an 8-cm 22-gauge needle. Anesthesia was applied to the skin, subcutaneous tissue, and muscle. A 15-mm fragment of the vastus lateralis muscle was obtained, placed in a minitube, and immediately frozen with liquid nitrogen before being stored at –80°C for subsequent molecular analyses.

2.10. *Western blot analysis*

Skeletal muscle samples obtained before and after each exercise protocol were homogenized in an extraction buffer containing (in millimoles per liter): Tris 100 (pH 7.4), sodium pyrophosphate 100, sodium fluoride 100, EDTA 10, sodium vanadate 10, phenylmethylsulfonyl fluoride 2, 0.1 mg/mL aprotinin, and 1% Triton-X100 at 4°C with a Polytron PTA 20S generator (model PT 10/35; Brinkmann Instruments, Westbury, NY, USA) operated at maximum speed for 30 seconds. The extracts were centrifuged at 15 000 rpm (9000*g*) and 4°C in a Beckman 70.1-Ti rotor (Palo Alto, CA) for 40 minutes to remove insoluble material, and the supernatants of these samples were used for protein quantification using the Bradford method. Proteins were denatured by boiling in a Laemmli buffer containing 100 mmol/L dithiothreitol, run on sodium dodecyl sulfate polyacrylamide gel electrophoresis, and transferred to nitrocellulose membranes that were blocked, probed, and developed. The antibody used for the immunoblotting was anti–IRS-1 (ab64954) from Abcam (Cambridge, UK). Immunoreactive bands were detected using the enhanced chemiluminescence method (RPN 2108; Amersham Biosciences, Uppsala, Sweden) and quantified by optical densitometry (Scion Image software, ScionCorp, Frederick, MD) of the developed autoradiographs.

2.11. *Statistical analysis*

Data were analyzed with SPSS for Windows version 17.0 (SPSS, Chicago, IL). All parameters are described as mean values ± SD. We used the analysis of variance (ANOVA) split plot in time design to assess significant differences between the groups before and after the training. For the variables that were not normally distributed, a logarithm was applied to transform the data. All tests were 2-tailed, and a P value < .05 was considered statistically significant.

3. Results

At study entry, each of the groups (control, aerobic, resistance, and combined) had a similar profile for all parameters, as demonstrated in Table 2.

From baseline to 12 weeks, the median exercise training attendance was 96% in the combined exercise training group, 97% in the aerobic training group, 99% in the resistance training group, and 97% in the control group.

As shown in Table 3, the BMI and WHR did not differ between the groups after training ($P > .05$).

As expected, aerobic training increased the VO_{2peak} (milliliters per kilogram per minute) (19.81 [SD 4.64] vs 23.04 [SD 4.61]; $P < .05$ in 16.3% after training) (Table 3).

All 4 groups displayed a decrease in blood pressure (both systolic and diastolic), fasting plasma glucose, postprandial plasma glucose, and lipid levels ($P < .05$). However, there was no difference across the groups in these parameters (Table 3).

The plasma insulin level, HOMA-IR, adiponectin, and resistin did not differ between the groups after training ($P > .05$). Visfatin increased in all groups after training ($P < .05$), but no difference was found across the groups (Table 3).

High-sensitivity C-reactive protein decreased in all groups ($P < .05$), including the control group. Tumor necrosis factor–α and IL-6 increased in the resistance group, but these increases were not statistically significant (Table 3).

After training, the IRS-1 expression (Fig. 1) increased by 65% in the resistance group ($P < .05$) and by 90% in the combined group ($P < .01$).

During the exercise training, 4 patients had their antihypertensive medications decreased: 2 in the aerobic group (18.1% reduction) and 2 in the combined group (20% reduction). With respect to oral antidiabetic medications, 2 patients had their sulfonylurea dosage decreased: 1 in the resistance group (10% reduction) and 1 in the combined group (10% reduction). The reasons for these changes were always

Table 2 – Subject characteristics at baseline

Group/characteristics	Control	Aerobic	Resistance	Combined	P value
Sex (male/female)	4/8	5/7	5/7	4/8	
Age (y)	53.41 ± 9.82	52.09 ± 8.71	54.1 ± 8.93	57.90 ± 8.06	.50
BMI (kg/m^2)	29.59 ± 4.90	29.29 ± 2.19	30.89 ± 4.09	31.23 ± 3.88	.66
Waist circumference	97.96 ± 11.35	101.63 ± 8.77	101.88 ± 7.18	104.11 ± 5.76	.42
WHR	0.97 ± 0.07	0.99 ± 0.06	1.01 ± 0.05	1.02 ± 0.08	.41
Time since diagnosis (y)	5.25 ± 3.51	5.45 ± 4.32	7.7 ± 4.11	7.30 ± 4.96	.43
Glycemic parameters					
FPG (mg/dL)	156.91 ± 49.79	148.90 ± 40.16	185.9 ± 79.46	158.80 ± 50.47	.48
PPG (mg/dL)	149 ± 41.31	162.5 ± 63.25	195.3 ± 111.69	175.44 ± 104.68	.50
A1c (%)	6.99 ± 0.72	7.69 ± 1.62	8.27 ± 2.43	7.55 ± 1.42	.35
Lipid profile					
Chl (mg/dL)	179.25 ± 32.19	177.18 ± 23.04	164.7 ± 29.65	179.60 ± 28.82	.61
HDLChl (mg/dL)	45.12 ± 8.53	45.65 ± 8.89	39.00 ± 7.00	44.40 ± 8.00	.24
LDLChl (mg/dL)	93.58 ± 36.88	103.2 ± 22.16	88.5 ± 28.85	99.11 ± 21.03	.24
TG (mg/dL)	201.91 ± 76.40	141.27 ± 48.32	242.50 ± 28.85	210.10 ± 160.14	.41
Kidney function markers					
Urea (mg/dL)	34.72 ± 22.30	29.27 ± 5.93	31.00 ± 10.55	34.40 ± 9.91	.78
Cr (mg/dL)	0.91 ± 0.36	0.84 ± 0.22	0,85 ± 0,17	0.88 ± 0.16	.41
Cardiorespiratory fitness					
VO_{2peak} (L/min)	1.63 ± 0.28	1.60 ± 0.57	1.34 ± 0.46	1.52 ± 0.47	.69
VO_{2peak} (mL/[kg min])	22.37 ± 3.64	21.28 ± 6.20	18.14 ± 4.65	19.58 ± 4.03	.76
Blood pressure					
SBP (mm Hg)	135.83 ± 16.21	139.09 ± 13.00	137.00 ± 18.28	135.00 ± 15.09	.94
DBP (mm Hg)	85.00 ± 6.74	87.27 ± 11.90	86.00 ± 15.05	86.00 ± 8.43	.97

Data are means ± SD. No significant differences were observed between groups ($P > .05$). FPG indicates fasting plasma glucose; PPG, postprandial glucose; CHl, total cholesterol; HDLChl, high-density lipoprotein cholesterol; LDLChl, low-density lipoprotein cholesterol; TG, triglycerides; Cr, creatinine; SBP, systolic blood pressure; DBP, diastolic blood pressure.

hypoglycemia as documented by the capillary glucose levels and hypotension that were measured during the exercise training. The hypoglycemia episodes occurred only in the resistance and combined groups, and they were similar in frequency between these groups. The dosage of the reported medications was not decreased for any patient in the control group.

4. Discussion

All 4 groups displayed decreases in blood pressure, fasting plasma glucose, postprandial plasma glucose, lipid profile, and hs-CRP; but only the resistance and combined groups demonstrated increased IRS-1 expression after training. The improvement in these parameters in the training and no-training groups may reflect differences in uncontrolled variables, such as diet, medication adherence, or the reduction of antidiabetic drugs in the training groups (resistance and combined); but the molecular findings confirmed the beneficial effects of exercise training.

Improvements in aerobic capacity were demonstrated by the significant 16.3% increase in VO_{2peak}.

The effects of exercise training on blood pressure, lipid profile, and glycemic control were heterogeneous. We found decreases in blood pressure in all groups; and this phenomenon was also described by Gordon et al [25], who showed a significant reduction in systolic blood pressure after resistance training in patients with type 2 diabetes mellitus. However, another study did not find any blood pressure reductions after exercise training [4]. In our study, the blood pressure in the control group also decreased after 12 weeks; and thus, this decrease cannot be attributed to exercise.

The impact of exercise training on the lipid profile is variable. The possible mechanisms that explain the improvement in the lipid profile include increased muscle and adipose tissue PPARγ and PGC-1α messenger RNA expression after physical training, as demonstrated by Ruschke et al [26]. Some studies [20,25] have reported low-density lipoprotein cholesterol reductions after aerobic and resistance training. Another study demonstrated a trend toward triglyceride level reductions after resistance training only [27], whereas others did not find any change after aerobic, resistance, and combined training [5]. Our finding regarding the decrease in HDL cholesterol in the aerobic, resistance, and control groups was somewhat unexpected because most studies have reported either no change or improvement [17].

The surprising decrease in blood pressure, glycemic control, and lipid profile in the control group may reflect better compliance with diet and medication in this group. The lack of demonstrable differences in blood pressure, glycemic control, and lipid profile across the groups in our study was likely influenced by the absence of weight loss, as hypothesized by other authors [4,28].

The effect of exercise training on A1c reduction has been observed by many researchers who used aerobic, resistance, and combined protocols to assess the effect of exercise on A1c [17,20,29]. The lack of a significant decrease in A1c levels may be due to the limited number of participants, the duration of training, the good overall baseline metabolic control in our sample (as reflected by a mean baseline A1c <7.6% in all groups except the resistance group, which had a baseline A1c

Table 3 – Anthropometric parameters, cardiorespiratory fitness, blood pressure, metabolic control, lipid profile, insulin resistance, and inflammatory markers before and after 12 weeks of training

Group/characteristics	Control		Aerobic		Resistance		Combined	
	Baseline	After training	Baseline	After training	Baseline	After training	Baseline	After training
Anthropometric parameters								
BMI	30.03 ± 4.90	30.12 ± 4.75	29.30 ± 2.20	29.08 ± 2.42	32.07 ± 3.79	30.76 ± 5.03	31.23 ± 3.88	31.10 ± 3.53
WHR	0.98 ± 0.07	0.98 ± 0.10	1.00 ± 0.06	0.99 ± 0.06	1.02 ± 0.06	0.99 ± 0.06	1.02 ± 0.09	1.02 ± 0.08
Cardiorespiratory fitness								
VO_{2peak} (mL/[kg min])	22.38 ± 3.64	22.83 ± 4.65	19.81 ± 4.64	23.04 ± 4.61 *	17.03 ± 3.95	18.85 ± 2.74	19.59 ± 4.04	20.50 ± 2.77
Blood pressure								
SBP (mm Hg)	135.83 ± 16.21	124.17 ± 17.30 *	141.11 ± 13.64	131.11 ± 16.16 *	135.00 ± 20.00	125.00 ± 14.14 *	132.50 ± 15.81	128.75 ± 12.46 *
DBP (mm Hg)	85 ± 6.74	78.33 ± 10.30 *	88.89 ± 12.69	80.00 ± 10.00 *	83.75 ± 14.08	81.25 ± 9.91 *	86.25 ± 9.16	78.75 ± 3.54 *
Glycemic parameters								
FPG (mg/dL)	148.82 ± 43.14	125.00 ± 20.58 *	146.6 ± 41.56	126.8 ± 35.94 *	194.22 ± 79.53	166.11 ± 60. 59 *	154.57 ± 42.26	142 ± 36.70 *
PPG (mg/dL)	147.35 ± 43.35	131.00 ± 38.72 *	162.89 ± 67.08	122.22 ± 36.03 *	202.22 ± 116.17	191.11 ± 93.37 *	171.50 ± 85.89	151.29 ± 45.73 *
A1C (%)	6.94 ± 0.74	7.07 ± 0.70	7.63 ± 1.70	7.42 ± 1.48	8.51 ± 2.45	8.24 ± 2.13	7.6 ± 1.12	7.53 ± 1.05
Lipid profile								
Chl (mg/dL)	179.45 ± 33.76	167.91 ± 35.76 *	183.13 ± 23.09	165.75 ± 31.38 *	164.38 ± 30.10	153.00 ± 25.56 *	181.13 ± 29.23	178.75 ± 30.27 *
HDLChl (mg/dL)	44 ± 8.20	41.89 ± 7.65 *	47.15 ± 9.54	44.11 ± 7.74 *	39.38 ± 7.78	34.75 ± 3.62 *	46.13 ± 7.97	46.50 ± 7.58
TGL (mg/dL)	208.36 ± 76.63	157.09 ± 64.46 *	141.88 ± 47.63	127.63 ± 55.22 *	236.38 ± 231.37	154.63 ± 76.44 *	157.88 ± 86.62	131.75 ± 68.72 *
Insulin resistance markers								
HOMA-IR	3.91 ± 4.42	4.28 ± 5.74	2.45 ± 1.31	2.24 ± 1.52	4.54 ± 3.94	4.07 ± 2.90	3.14 ± 2.12	2.59 ± 1.31
Adiponectin (μg/mL)	5.07 ± 5.50	3.75 ± 2.93	5.58 ± 5.73	3.38 ± 2.22	4.45 ± 4.12	5.13 ± 4.30	5.98 ± 3.43	6.58 ± 5.44
Visfatin (ng/mL)	103.57 ± 55.06	134.12 ± 72.06 *	112.24 ± 45.83	131.54 ± 58.38 *	112.11 ± 42.85	142.25 ± 51.04 *	116.19 ± 75.41	127.46 ± 45.22 *
Resistin (ng/mL)	8.24 ± 1.66	8.02 ± 1.43	7.34 ± 1.36	7.19 ± 1.08	8.54 ± 1.46	7.62 ± 1.68	8.21 ± 3.13	7.57 ± 2.89
Inflammatory markers								
hs-CRP (mg/mL)	15.05 ± 4.22	12.24 ± 4.31 *	14.35 ± 4.51	12.95 ± 3.41 *	16.55 ± 2.55	14.39 ± 1.80 *	15.64 ± 3.86	14.14 ± 2.56 *
TNF-α (pg/mL)	2.29 ± 0.46	2.74 ± 1.10	2.38 ± 1.31	2.46 ± 1.26	2.91 ± 2.44	4.76 ± 5.18	3.47 ± 1.40	3.10 ± 1.08
IL-6 (pg/mL)	23.69 ± 9.81	21.29 ± 0.91	21.15 ± 1.44	21.06 ± 1.36	21.39 ± 2.60	26.11 ± 18.43	20.93 ± 0.86	20.23 ± 0.83

Data are means ± SD.

* $P < .05$ for baseline and after training (ANOVA split plot in time design).

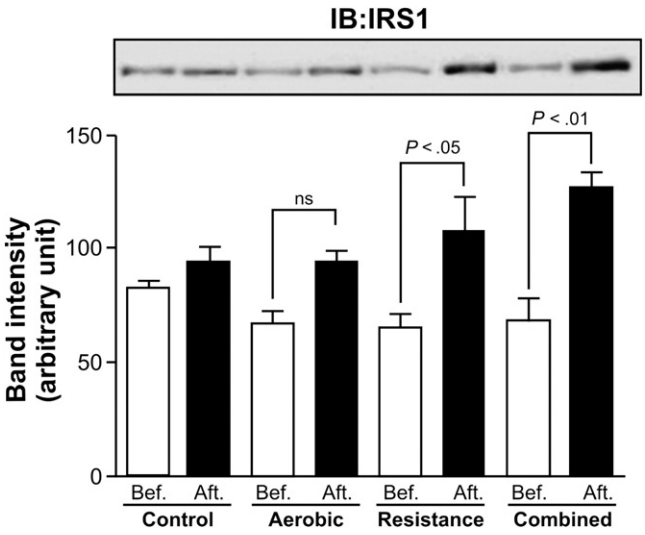

Fig. 1 – Immunoblots: IRS-1 expression in the control, aerobic, resistance, and combined groups before and after training.

of <8.5%), and the slight reduction in antidiabetic medication dosage seen in 2 of the groups, which reinforced the notion that exercise confers benefits.

With regard to insulin resistance markers, in our study, the HOMA-IR did not change after training, which is in accordance with the findings of other studies that were also unable to detect a change in the HOMA index despite a decrease in A1c [4,20]. In contrast to these data, increased insulin sensitivity was demonstrated after training, without a change in A1c [19]. These discrepant findings may reflect the different methods used to evaluate insulin sensitivity. For instance, the euglycemic-hyperinsulinemic clamp is more sensitive in estimating insulin action [30,31].

Levels of adiponectin, a cytokine produced by adipose tissue, correlate with insulin resistance. The adiponectin levels in our patients did not change after training, and these data are in accordance with other work demonstrating that adiponectin levels are not affected by exercise training despite enhanced insulin action [32,33]. However, they only changed in patients with weight loss, as demonstrated by researchers in different protocols [12,33,34].

The physiological role of visfatin is not completely understood, but it is hypothesized to be a beneficial adipokine with an insulin-sensitizing effect. Our finding of increased levels of visfatin in all groups after training, including the control group, disagrees with those of other studies demonstrating no changes in the control group and reduced levels of visfatin after training [35,36]. A recent publication found that weight reduction is associated with increased levels of visfatin and improved insulin sensitivity in obese nondiabetic women [37].

The anti-inflammatory effect of exercise training has been discussed recently, and the data are conflicting [38-40]. Data from different longitudinal studies show a reduction in CRP levels, suggesting that physical activity may suppress systemic low-grade inflammation [11]. We found a decrease in hs-CRP levels in all groups and a trend toward increased TNF-α and IL-6 in the resistance group. Highly-sensitive CRP is a nonspecific marker of inflammation, and many factors (eg, diet and drugs [41]) could be responsible for the reduction in the control group. One study [39] demonstrated that the anti-inflammatory effect of exercise training depends on the exercise modality (high intensity of long duration and preferably combined), independently of weight loss. In contrast, another study [40] found a tendency of the TNF-α to rise after combined exercise training in premenopausal and postmenopausal women, which was also found in our data. With regard to IL-6, a number of studies have demonstrated that working muscle produces IL-6. The data suggest that IL-6 exerts inhibitory effects on TNF-α; and it leads to increased levels of well-known anti-inflammatory cytokines, such as IL-10 and IL-1ra. It seems that IL-6 has an important role in hepatic glucose production during muscle contraction and that it exerts this role by preventing hypoglycemia in the presence of increased insulin sensitivity [30].

Defects in insulin signal transduction in the skeletal muscle of subjects with type 2 diabetes mellitus have been demonstrated [42,43]. The effects of exercise training on the insulin receptor substrates IRS-1 and IRS-2 are highly variable [16]. To our knowledge, this is the first study in which 3 different modalities of exercise have been compared before and after training with a control group, with respect to the expression of intermediates of the insulin signaling pathway in patients with type 2 diabetes mellitus.

We found an important increase in the IRS-1 expression after training in the resistance and combined groups. This finding conflicts with the report of decreased IRS-1 expression in humans who are habitual runners (compared with sedentary controls) [44] and the finding of increased IRS-1 expression after 1 day of training, with subsequent reductions after 5 days of training in rodents subjected to exhaustive swimming [21]. There is a report of increased whole-body insulin-mediated glucose disposal in patients with type 2 diabetes mellitus, which occurs without changes in insulin signaling intermediates (ie, IRS-1, IRS-2, phosphatidylinositol-3-kinase, and atypical protein kinase C) but results in increased GLUT-4 protein content [22]. Biopsies were performed 16 hours after a single bout of exercise and a 7-day course of exercise training [22]. These conflicting results likely reflect the influence of differences in training, timing of the biopsy, and the heterogeneity of the sample analyzed. Furthermore, we were careful to perform the biopsy between 60 and 96 hours after the last exercise session to rule out the effect of acute exercise. Our finding of an increased expression of IRS-1 may be the result of increased gene expression related to exercise training.

The principal limitation of our study was the small sample size, which may have limited the power of our study to uncover differences between the groups. Another problem may be the fact that most of the patients had good metabolic control (except the resistance group, which had a mean hemoglobin A1c value of 8.5%) before the intervention. Thus, the impact of exercise may be less clear. The choice of the HOMA index to measure insulin sensitivity may also have limited our ability to detect the sensitizing effect from exercise.

In conclusion, we demonstrated that exercise training can favorably affect glycemic parameters, the lipid profile, blood

pressure, and hs-CRP. The established effect of resistance training and combined exercise on insulin sensitivity can be attributed, at least in part, to increased IRS-1 expression.

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