Supervised Exercise Training Counterbalances the Adverse Effects of Insulin Therapy in Overweight/Obese Subjects With Type 2 Diabetes

Stefano Balducci, md[1,2,3]
Silvano Zanuso, phd[4]
Patrizia Cardelli, phd[1,5]
Gerardo Salerno, bs[1,5]
Sara Fallucca, phd[1,5]

Antonio Nicolucci, md, phd[6]
Giuseppe Pugliese, md, phd[1,2]
for the Italian Diabetes Exercise Study (IDES) Investigators*

OBJECTIVE—To examine the effect of supervised exercise on traditional and nontraditional cardiovascular risk factors in sedentary, overweight/obese insulin-treated subjects with type 2 diabetes from the Italian Diabetes Exercise Study (IDES).

RESEARCH DESIGN AND METHODS—The study randomized 73 insulin-treated patients to twice weekly supervised aerobic and resistance training plus structured exercise counseling (EXE) or to counseling alone (CON) for 12 months. Clinical and laboratory parameters were assessed at baseline and at the end of the study.

RESULTS—The volume of physical activity was significantly higher in the EXE versus the CON group. Values for hemoglobin A_{1c}, BMI, waist circumference, high-sensitivity C-reactive protein, blood pressure, LDL cholesterol, and the coronary heart disease risk score were significantly reduced only in the EXE group. No major adverse events were observed.

CONCLUSIONS—In insulin-treated subjects with type 2 diabetes, supervised exercise is safe and effective in improving glycemic control and markers of adiposity and inflammation, thus counterbalancing the adverse effects of insulin on these parameters.

Diabetes Care 35:39–41, 2012

A therosclerosis has been increasingly recognized as an inflammatory disease characterized by systemic, central fat-driven and local low-grade inflammation, which is involved in all stages of its natural history (1). Several proinflammatory mediators have been associated with cardiovascular disease (CVD), independent of traditional CVD risk factors (2). In particular, high-sensitivity C-reactive protein (hs-CRP) has been shown to be a strong independent predictor of CVD in patients with type 2 diabetes (3). More recently,

clinical trial data have demonstrated that reduction of hs-CRP is associated with marked improvements in CVD outcomes (4) and that high-intensity, preferably mixed (aerobic and resistance) exercise training, in addition to daytime physical activity (PA), is required for achieving a significant anti-inflammatory effect in subjects with type 2 diabetes (5).

When patients with type 2 diabetes in secondary failure to oral hypoglycemic agents (OHAs) are shifted to insulin treatment, alone or combined with OHAs,

glycemic control improves, but there is generally an undesirable adverse effect of increased body weight (6,7) accompanied by lower or no improvement or even worsening of the chronic inflammatory state (7–9). This adverse effect, which might counteract the positive effect of the insulin-mediated decrease in plasma glucose levels on CVD risk, could be minimized by exercise training, although there is no evidence in the literature supporting this concept.

As a subanalysis of the Italian Diabetes Exercise Study (IDES), we examined the effect of supervised exercise training in addition to structured exercise counseling, compared with counseling alone, on traditional and nontraditional CVD risk factors in sedentary, insulin-treated, overweight/obese subjects with type 2 diabetes.

RESEARCH DESIGN AND METHODS—Detailed methodology has been published previously (10,11). Briefly, sedentary patients with type 2 diabetes and the metabolic syndrome (606 of 691 eligible) were enrolled in 22 outpatient Diabetes Clinics throughout Italy between 1 October 2005 and 31 March 2006. Subjects were randomized by center, age, and diabetes treatment to twice-a-week supervised mixed (aerobic and resistance) training plus exercise counseling (exercise [EXE] group) versus counseling alone as part of standard care (control [CON] group) for 12 months. Here, we present a subanalysis of data from 73 patients treated with insulin, alone or combined with OHAs, throughout the study.

Each supervised session lasted 75 min and included aerobic exercise plus four resistance exercises. All participants received structured exercise counseling, encouraging any type of leisure-time PA. At baseline and at the end of the study, PA, hemoglobin A_{1c} (HbA_{1c}), BMI, waist circumference, hs-CRP, systolic and diastolic blood pressure (BP), triglycerides, total and HDL cholesterol, and coronary heart disease (CHD), along with 10-year UK Prospective Diabetes Study (UKPDS) risk scores were measured, as previously reported (10,11).

Table 1—Demographics and outcomes of the CON and EXE groups

Variable	CON			EXE			Mean difference (95% CI)	P† EXE vs. CON
	Baseline	12 months	P* 0–12 months	Baseline	12 months	P* 0–12 months		
n	36	34	NA	37	36	NA	NA	NA
Male	19 (53)	19 (56)	NA	21 (57)	21 (58)	NA	NA	NA
Age (years)	61.6 ± 7.8	NA	NA	59.6 ± 8.7	NA	NA	NA	NA
Diabetes duration (years)	10.6 ± 6.5	NA	NA	10.8 ± 7.8	NA	NA	NA	NA
Smoking	6 (16.7)	NA	NA	6 (16.2)	NA	NA	NA	NA
Insulin only	13 (36.1)	14 (38.9)	0.99	18 (48.6)	17 (45.9)	0.99	NA	0.50
Insulin plus OHA	23 (63.9)	24 (66.7)	0.99	19 (51.3)	15 (40.5)	0.12	NA	0.40
Daily insulin dose (IU)	43.9 ± 31.0	51.9 ± 38.5	0.02	43.6 ± 33.4	37.0 ± 24.4	0.012	−14.5 (−25.7 to −3.3)	<0.001
Lipid-lowering agents	17 (47.2)	18 (48.6)	0.99	17 (45.9)	18 (48.6)	0.99	NA	0.66
Antihypertensive agents	21 (58.3)	22 (61.1)	0.99	25 (67.6)	24 (64.9)	0.99	NA	0.61
Antiplatelet agents	15 (41.7)	16 (44.4)	0.99	12 (32.4)	12 (32.4)	NA	NA	0.98
PA (METs h^{-1}·week^{-1})								
Unsupervised	0.6 ± 1.3	6.9 ± 4.4	<0.001	0.6 ± 1.8	8.2 ± 4.8	<0.001	1.3 (0.9–2.7)	<0.001
Supervised	NA	NA	NA	NA	7.2 ± 2.2	NA	NA	NA
Total	0.6 ± 1.3	6.9 ± 4.4	<0.001	0.6 ± 1.8	15.4 ± 6.9	<0.001	8.5 (5.6–11.4)	<0.001
BMI (kg/m^2)	30.7 ± 4.1	31.0 ± 4.0	0.24	31.8 ± 5.3	30.7 ± 4.9	<0.001	−1.3 (−2.0 to −0.8)	<0.001
Waist circumference (cm)	100.5 ± 10.1	101.9 ± 10.0	0.13	107.4 ± 13.6	103.6 ± 11.9	<0.001	−0.07 (−0.18 to 0.02)	<0.001
BP (mmHg)								
Systolic	145 ± 19	142 ± 14	0.27	143 ± 20	136 ± 14	0.001	−4.2 (−10.9 to 2.5)	0.20
Diastolic	86 ± 11	84 ± 7	0.27	82 ± 11	79 ± 8	0.012	−4.7 (−3.8 to 13.2)	0.70
HbA$_{1c}$ (%)	8.11 ± 1.41	7.82 ± 1.39	0.16	8.11 ± 1.82	7.08 ± 1.14	<0.001	−0.74 (−1.44 to −0.04)	0.03
Triglycerides (mmol/L)	1.51 ± 0.89	1.92 ± 1.37	0.08	1.47 ± 1.53	1.54 ± 0.82	0.80	−0.33 (−0.99 to 0.33)	0.32
Cholesterol (mmol/L)								
Total	5.34 ± 0.88	4.79 ± 1.30	0.035	4.92 ± 0.85	4.64 ± 1.19	0.20	0.01 (−0.63 to 0.65)	0.70
HDL	1.27 ± 0.32	1.25 ± 0.10	0.74	1.13 ± 0.28	1.20 ± 0.33	0.25	0.10 (−0.06 to 0.25)	0.20
LDL	3.34 ± 0.85	3.10 ± 0.98	0.18	3.26 ± 0.99	2.85 ± 0.84	0.04	0.18 (−0.70 to 0.35)	0.51
hs-CRP (mg/L)	3.37 ± 2.3	3.12 ± 2.1	0.75	3.53 ± 2.2	2.40 ± 1.9	0.001	−0.9 (−1.9 to 0.1)	0.04
CHD UKPDS 10-year risk score	19.3 ± 11.8	18.9 ± 13.5	0.42	19.4 ± 11.7	15.8 ± 8.8	0.004	−3.2 (−6.3 to 0.05)	0.03

Categorical data are presented as n (%) and continuous data as mean ± SD. NA, not applicable. *Wilcoxon signed rank test for continuous variables and the McNemar test for categorical variables. †Unpaired t test or Mann-Whitney U test for continuous variables and comparison of proportions for categorical variables.

Statistical analysis

Data are expressed as mean ± SD, unless otherwise specified. The χ^2 test for categorical variables and the Student t test or the corresponding nonparametric Mann-Whitney test for continuous variables were used to compare patients' characteristics at baseline. Wilcoxon signed rank test for continuous variables and the McNemar test for categorical variables were applied to analyze baseline to end-of-study change within each group. The unpaired t test or Mann-Whitney U test for continuous variables and comparison of proportions for categorical variables were used to compare changes from baseline between the two groups. Statistical analysis was performed using Graph Pad Prism 5.0 (GraphPad Software Inc., San Diego, CA) and SigmaPlot 11 (Systat Software, Inc., Chicago, IL) software. A P value < 0.05 was considered statistically significant.

RESULTS—At baseline, there were no statistically significant differences in all parameters between the two groups (data not shown). During the 12-month period, two patients in the CON and one in the EXE group abandoned the study for various reasons. No major adverse events were observed, including severe hypoglycemia. Mild hypoglycemia, not requiring assistance, was reported in 7 of 37 patients in the EXE group. The daily insulin dose increased significantly in the CON group, whereas it decreased in the EXE group (Table 1).

As in the whole cohort (11), total PA volume was significantly higher in EXE versus CON group. HbA$_{1c}$, waist circumference, systolic and diastolic BP, LDL, hs-CRP, and CHD risk score were significantly reduced in the EXE group, whereas only total cholesterol decreased significantly in the CON group. As a result, compared with CON subjects, EXE participants showed significantly higher improvements in HbA$_{1c}$, BMI, waist circumference, hs-CRP, and CHD risk score (Table 1).

CONCLUSIONS—Despite the limited number of participants, this is the first study, to the best of our knowledge, that assesses the effect of long-term supervised exercise training in insulin-treated subjects with type 2 diabetes. This analysis indicates that for this subgroup, like the other IDES subjects, supervised exercise training is safe and effective in improving CVD risk factors and CHD risk score and in achieving a considerable amount of PA. However, the volume of unsupervised PA was somewhat lower than in the EXE participants from the whole cohort (11), likely because insulin-treated patients are less confident to perform PA than those treated with OHAs for fear of hypoglycemia.

More importantly, our findings indicate that improvements in HbA$_{1c}$, which were higher than in the whole cohort, consistent with the higher baseline values (11), were associated with a reduction of those parameters (i.e., waist, BMI, and hs-CRP) that were shown to be negatively affected by insulin treatment (6–8). This is consistent with a small-sized study from Aas et al. (8) showing that lifestyle intervention is more effective than insulin treatment on adipokine levels in subjects with type 2 diabetes. This supports the concept that exercise may counterbalance the adverse effects of insulin therapy on adiposity and inflammation, directly or via reduction of daily insulin dose, and suggests that lifestyle interventions, including supervised exercise training, should be encouraged in these individuals.

Supervised mixed (aerobic and resistance) exercise training is safe and effective in promoting PA and improving HbA$_{1c}$ and the CVD risk profile in insulin-treated, overweight/obese subjects with type 2 diabetes. This intervention strategy appears to counterbalance the adverse effects of insulin therapy on adiposity and inflammation.

References

1. Hansson GK, Robertson AK, Söderberg-Nauclér C. Inflammation and atherosclerosis. Annu Rev Pathol 2006;1:297–329
2. Hayden JM, Reaven PD. Cardiovascular disease in diabetes mellitus type 2: a potential role for novel cardiovascular risk factors. Curr Opin Lipidol 2000;11:519–528
3. Ridker PM, Rifai N, Rose L, Buring JE, Cook NR. Comparison of C-reactive protein and low-density lipoprotein cholesterol levels in the prediction of first cardiovascular events. N Engl J Med 2002;347:1557–1565
4. Ridker PM, Danielson E, Fonseca FA, et al.; JUPITER Trial Study Group. Reduction in C-reactive protein and LDL cholesterol and cardiovascular event rates after initiation of rosuvastatin: a prospective study of the JUPITER trial. Lancet 2009;373:1175–1182
5. Balducci S, Zanuso S, Nicolucci A, et al. Anti-inflammatory effect of exercise training in subjects with type 2 diabetes and the metabolic syndrome is dependent on exercise modalities and independent of weight loss. Nutr Metab Cardiovasc Dis 2010;20:608–617
6. Esposito K, Ciotola M, Maiorino MI, et al. Addition of neutral protamine lispro insulin or insulin glargine to oral type 2 diabetes regimens for patients with suboptimal glycemic control: a randomized trial. Ann Intern Med 2008;149:531–539
7. Pradhan AD, Everett BM, Cook NR, Rifai N, Ridker PM. Effects of initiating insulin and metformin on glycemic control and inflammatory biomarkers among patients with type 2 diabetes: the LANCET randomized trial. JAMA 2009;302:1186–1194
8. Aas AM, Seljeflot I, Torjesen PA, Diep LM, Thorsby PM, Birkeland KI. Blood glucose lowering by means of lifestyle intervention has different effects on adipokines as compared with insulin treatment in subjects with type 2 diabetes. Diabetologia 2006;49:872–880
9. Mavridis G, Souliou E, Diza E, et al. Inflammatory cytokines in insulin-treated patients with type 2 diabetes. Nutr Metab Cardiovasc Dis 2008;18:471–476
10. Balducci S, Zanuso S, Massarini M, et al.; Italian Diabetes Exercise Study (IDES) Group. The Italian Diabetes and Exercise Study (IDES): design and methods for a prospective Italian multicentre trial of intensive lifestyle intervention in people with type 2 diabetes and the metabolic syndrome. Nutr Metab Cardiovasc Dis 2008;18:585–595
11. Balducci S, Zanuso S, Nicolucci A, et al.; Italian Diabetes Exercise Study (IDES) Investigators. Effect of an intensive exercise intervention strategy on modifiable cardiovascular risk factors in type 2 diabetes mellitus: a randomized controlled trial: the Italian Diabetes and Exercise Study (IDES). Arch Intern Med 2010;170:1794–1803