Effects of Different Modes of Exercise Training on Glucose Control and Risk Factors for Complications in Type 2 Diabetic Patients

A meta-analysis

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OBJECTIVE — We sought to meta-analyze the effects of different modes of exercise training on measures of glucose control and other risk factors for complications of diabetes.

RESEARCH DESIGN AND METHODS — The 27 qualifying studies were controlled trials providing, for each measure, 4–18 estimates for the effect of aerobic training, 2–7 for resistance training, and 1–5 for combined training, with 1,003 type 2 diabetic patients (age 55 ± 7 years [mean ± between-study SD]) over 5–104 weeks. The meta-analytic mixed model included main-effect covariates to control for between-study differences in disease severity, sex, total training time, training intensity, and dietary cointervention (13 studies). To interpret magnitudes, effects were standardized after meta-analysis using composite baseline between-subject SD.

RESULTS — Differences among the effects of aerobic, resistance, and combined training on HbA_{1c} (A1C) were trivial; for training lasting ≥12 weeks, the overall effect was a small beneficial reduction (A1C 0.8 ± 0.3% [mean ± 90% confidence limit]). There were generally small to moderate benefits for other measures of glucose control. For other risk factors, there were either small benefits or effects were trivial or unclear, although combined training was generally superior to aerobic and resistance training. Effects of covariates were generally trivial or unclear, but there were small additional benefits of exercise on glucose control with increased disease severity.

CONCLUSIONS — All forms of exercise training produce small benefits in the main measure of glucose control: A1C. The effects are similar to those of dietary, drug, and insulin treatments. The clinical importance of combining these treatments needs further research.

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Diabetes is a group of metabolic disorders characterized by hyperglycemia resulting from defects in insulin secretion, insulin action (hepatic and peripheral glucose uptake), or both. The type 2 form of the disease is associated with obesity (1) and physical inactivity (2), and the prevalence of this form is increasing in Westernized countries, owing to the increasing prevalence of obesity and sedentary lifestyles.

Physical activity or structured exercise training used alone or in combination with diet, insulin injections, or oral hypoglycemic drugs are the foundations of therapy for type 2 diabetes (3,4). Evidence for the benefit of physical activity comes from studies showing that individuals who maintain a physically active lifestyle are less likely to develop insulin resistance, impaired glucose tolerance, or type 2 diabetes (2,5). The effects of exercise training on glucose control and related physiological parameters have also been extensively studied in patients with type 2 diabetes. In 2001, Boulé et al. (6) published a meta-analysis showing beneficial effects of exercise training on one aspect of glucose control in diabetic patients, the percent of HbA_{1c} (A1C) in blood. They also found reductions in two measures of abdominal obesity and little effect on the only other parameter they meta-analyzed: body mass.

Of the 14 studies in the meta-analysis of Boulé et al. (6), 12 used aerobic training and 2 used resistance training. Some physiological adaptations to resistance training differ from those of aerobic training, so their effects on glucose control may differ (7). Boulé et al. (6) found little difference between effects of aerobic and resistance training, but there were insufficient studies of resistance training for this finding to be anything more than tentative. Since then, there have been numerous new studies of aerobic, resistance, and combined training. We have therefore meta-analyzed the effects of these three modes of training on A1C and other measures of glucose control in type 2 diabetic patients. We have included physiological parameters related to complications of diabetes, and we have dealt with study characteristics and magnitude of effects in more detail than in the previous meta-analyses.

RESEARCH DESIGN AND METHODS

— Searches of PubMed and SportDiscus databases were performed for studies published in English up to and including May 2006. Reference lists of review articles and all included articles identified by the search were examined for other eligible studies. Only controlled trials of supervised exercise

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training programs on type 2 diabetic patients were eligible. We included studies that had at least one measure of glucose control (A1C, fasting glucose, postprandial glucose, fasting insulin, and insulin sensitivity). For these studies we extracted any measures of body mass (including BMI), fat mass (including fat mass as percent body mass, visceral fat mass, and skinfold sums), blood lipids (LDL cholesterol, HDL cholesterol, total cholesterol, and triglycerides), and blood pressure (systolic and diastolic).

Numerous studies were excluded on grounds of no control group (8–18). Some studies were excluded because the control group consisted of healthy subjects (19–25) or because the control group exercised (25–29). Other reasons for exclusion were as follows: subjects were a combination of diabetic patients and healthy subjects (30–32), the exercise program was interrupted (33,34), and program participation did not significantly increase physical activity (35). Only two studies were excluded because of insufficient data to calculate magnitude of the mean effect (36) and/or its SE (37) for at least one measure of glucose control. In one of these studies (36), the authors provided no values for A1C but reported a significant reduction ($P < 0.05$) using a nonparametric test to compare eight exercisers with eight nonexercisers. In the other (37), there was a 1.5% decrease in concentration of A1C in 14 exercisers relative to 10 nonexercisers ($P > 0.05$).

Of the 27 included studies, 18 were randomized, parallel-group, controlled trials; 1 was a randomized crossover trial; and 8 were controlled trials with unclear randomization. We included studies with a dietary cointervention in which the intervention and control groups were prescribed a caloric-restriction or other healthy diet and in which there was a reduction in body mass in at least the control group (38–43). Dietary compliance was assessed with diaries in all but one study (43), in which patients were hospitalized and provided with food.

Analyses

The main outcome from meta-analysis is a weighted mean of values of the outcome statistic from the various studies, where the weighting factor is the inverse of the square of the sampling SE of the statistic. The SE was derived from either the CI or *P* value of the outcome statistic or from SDs of change scores in control and exercise groups. For studies where the only inferential information reported for one or more outcome statistics was either a *P* value inequality (usually $P < 0.05$ or $P > 0.05$) or, equivalently, the presence or absence of statistical significance (42–53), the values of all outcome statistics and their SEs, irrespective of *P* value, were derived from analysis of posttest means and SDs in the two groups. This strategy was aimed at reducing bias that might arise from adopting different computational methods based on *P* values, although the standardized effects and their confidence limits showed little change ($\sim\pm0.04$) when analyses were repeated, making full use of the *P* values in all studies.

The meta-analyses were performed with a program (54) for the mixed-modeling procedure (PROC MIXED) in the SAS (version 8.2; SAS Institute, Cary, NC). Exercise modality (aerobic, resistance, or combined) was the most important effect in the fixed-effects model. Baseline mean value of the given measure was included as a covariate to control for the effect of disease severity; its effect was evaluated for two between-subject SDs (derived from the unweighted mean of the within-study variances) because the difference between the means of a normally distributed variable dichotomized into equal groups is 2.3 SDs. Sex of the subjects was included as a numeric effect (coded as proportion of male subjects in the study [range 0–1]). Exercise intensity was included as a numeric effect having an integer value of 1 (easy walking) through 5 (aerobic exercise >80% maximum oxygen uptake; resistance exercise >85% 1 repetition maximum; no studies achieved a 5); its effect was evaluated for two steps on this scale. To limit the number of covariates in the model, weekly frequency, session duration, and study duration were included in the model as a total time spent exercising during the study; this variable was approximately log normally distributed, so it was included after log transformation and its effect was evaluated for a doubling of exercise time. In an additional analysis for A1C, total exercise time was replaced in the model by study duration (two levels: <12 and ≥12 weeks) to account for the possibility that changes in A1C would require 8–12 weeks to plateau (55). Finally, dietary cointervention was included as a binary variable. Owing to the limited number of studies available, all fixed effects were included as main effects only; for this reason, we also limited the covariates to those that were included in most studies and that might be expected on physiological grounds to moderate the effect of exercise. The remaining unexplained true variation (heterogeneity) within and between studies was estimated where possible as one or more random effect. When the random-effect meta-analysis failed to produce a solution with the full fixed-effects model (either because there were insufficient estimates of the measure to include in the analysis or because disparities between estimates prevented convergence on a solution), the fixed-effects model was simplified; estimates for the effects removed from the model were provided by a traditional fixed-effects meta-analysis, but the confidence limits for these effects are less trustworthy.

When different scales were used in different studies for a similar measure, we expressed the effect of exercise relative to control in each study as a percent; we then meta-analyzed the log-transformed measure for estimation of standardized effects and used back transformation to estimate mean percent effects. We adopted this approach with postprandial glucose, insulin sensitivity, body mass, body fat, and waist circumference. Fasting insulin was also analyzed following log transformation, since the wide range in baseline values between studies may reflect systematic methodological differences. The baseline mean value could not be included in the fixed-effects model for these variables. Postprandial glucose was measured using either area under the glucose curve following a glucose challenge (40,41,44, 48,56) or glucose concentration at a specific time (42,50,53,57,58). Insulin sensitivity was measured using the insulin sensitivity index (57), homeostasis model assessment (39), hyperinsulinemic-euglycemic glucose clamp (43,46,59), and insulin tolerance test (49,50,52). Body mass was either the mass (weight in kilograms) (38–45,47,48,50,52,57–63) or the BMI (weight in kilograms divided by the square of height in meters) (46,51,64,65). Body fat included total fat mass and fat at specific sites determined by dual X-ray absorptiometry (39,46,60,63,65), hydrostatic weighing (57,62), estimation from skinfolds (47,50), and magnetic resonance imaging (41,50,52,59). Waist circumference was either the circumference (in centimeters) (39,41,50,60,65) or the waist-to-hip ratio (38,44,47,61).

For each outcome measure, funnel plots of the inverse of the SE of the esti-

mate of the effect versus the value of the estimate were examined qualitatively for evidence of outliers (points judged visually to be more than ~4 SDs of horizontal scatter away from the center of the plot). Six estimates were thereby excluded, as shown in Table 2: five because of unrealistically large positive or negative effects that presumably represent computational or transcriptional errors (38,41,50,62) and one because of an unrealistically small SE (60). There were too few estimates and too wide a range in the SEs for any firm conclusion about publication bias based on asymmetry in the funnel plot.

Meta-analyzed effects for each measure in each study were expressed as standardized (Cohen) effects (66) by dividing by the average baseline between-subject SD (derived as square root of unweighted mean of variances). Bias in the standardized effects was negligible and not corrected, owing to the large number of degrees of freedom in the estimate of the SD. Magnitudes of the standardized effects were interpreted using thresholds of 0.2, 0.6, and 1.2 for small, moderate, and large, respectively, a modification of Cohen's thresholds of 0.2, 0.5, and 0.8 (66); the modifications are based primarily on congruence with Cohen's thresholds for correlation coefficients (available at http://newstats.org). In keeping with recent trends in inferential statistics (e.g., 67), we made magnitude-based inferences about true (population) values of effects by expressing the uncertainty in the effects as 90% confidence limits. An effect was deemed unclear if its CI overlapped the thresholds for substantiveness (i.e., if the chances of the effect being substantially positive and negative were both >5%); otherwise, the magnitude of the effect was reported as the magnitude of its observed value (68).

RESULTS

Descriptive statistics

Six of the 27 publications included in the meta-analysis (Table 1) provided two outcomes (via multiple groups, men and women, 3- and 6-month durations of training, or aerobic and combined training), giving 4–18 estimates for the effect of aerobic training, 2–7 for resistance training, and 1–5 for combined aerobic-resistance training (Table 2; e.g., there were 4 estimates for the effect of aerobic training on systolic blood pressure and 18 for its effect on A1C). Means and between-study SDs for the study-mean characteristics of the 1,003 subjects from the 27 studies were as follows: age 55 ± 7 years, duration of diabetes 4.9 ± 1.8 years, proportion of male subjects 0.55 ± 0.34, proportion using medication for diabetes 0.71 ± 0.38, baseline A1C 8.6 ± 1.3%, and baseline fasting glucose 9.5 ± 1.7 mmol/l. Studies included in the meta-analysis had an intervention duration ranging from 5 to 104 weeks, a total training time of 58 ± 44 h, and a training intensity of 3.0 ± 0.7 on the 1- to 5-point scale.

Eight studies with a total of eight outcomes had no dropouts. Sixteen studies with 19 outcomes had dropouts explained as being unrelated to the intervention. Two studies with a total of four outcomes did not adequately explain dropouts, although the rate was low: 2 of 12 and 1 of 13 in exercise and control groups, respectively (42); 2 of 15 and 0 of 15 in exercise and control groups, respectively (42); and 4 of 85 in all groups combined (64). One study with two outcomes did not mention dropouts (59). For studies in which attendance at exercise sessions was stated (39–42,47,48,50,51,53,57,59,60), attendance rate was high (mean 86%); in two studies it was "good" (58,61); in one it was "very good" (49); and in one "met the requirement" was indicated (69). Twelve studies had no comment on exercise attendance. All studies appear to have been analyzed on an intention-to-treat basis (i.e., without excluding noncompliant subjects) in relation to exercise adherence.

Effects of exercise

The effects of exercise on the various outcome measures expressed as changes in absolute or percent units in each study are shown in Table 2, along with the meta-analyzed mean effects. Table 3 shows the meta-analyzed means and the effects of study characteristics, all expressed in standardized units with an interpretation of magnitudes.

There were clear but small reductions in A1C with all three exercise modes. For all other measures of glucose control (fasting glucose, postprandial glucose, insulin sensitivity, and fasting insulin), most of the effects were clearly beneficial and of small to moderate magnitude. The effect of combined exercise on insulin sensitivity was large, but the large degree of uncertainty (only one study contributed) allows for the true effect to be small to moderate. For the anthropometric measures, only one effect of exercise was unclear and the remainder were either trivial or of small benefit. Aerobic and combined exercise had clear small or moderate effects on blood pressure, while the effects of resistance exercise were unclear. With the exception of a small benefit of combined exercise on HDL cholesterol and aerobic exercise on triglycerides, all three modes of exercise produced trivial or unclear effects on blood lipids.

In comparison with resistance exercise, aerobic exercise had a clear but small benefit for total cholesterol, and in comparison with aerobic exercise, combined exercise had a clear but small benefit for fasting glucose, body mass, HDL cholesterol, and diastolic blood pressure (Table 3). For all other outcomes, these pairwise differences between the exercise modes were trivial or unclear.

Moderating effects of study characteristics

The effects of initial mean value of A1C and fasting glucose show that there was a small additional benefit of exercise for patients with increased disease severity, whereas the effects on blood lipids were either trivial or unclear. The effect of disease severity on the other measures of glucose control and on anthropometry and blood pressure could not be estimated. There was a large benefit for male relative to female subjects for insulin sensitivity, but the uncertainty allows for this effect to be trivial through moderate; the other effects of sex were mainly unclear, and all are consistent with trivial or small differences. Longer total duration of exercise was generally associated with unclear or trivial effects, and the one small harmful effect had confidence limits consistent with a trivial effect. A further doubling of exercise time would have little further effect on any measures. Higher exercise intensity had a moderately harmful effect on one measure of glucose control; otherwise, the effects were unclear, trivial, or small and beneficial. Diet cointervention conferred several small beneficial and harmful effects to the effect of exercise, and its other effects were unclear or trivial. The unexplained differences between studies represented by the random effect were generally negligible or small, showing that the meta-analytic model adequately accounted for the between-study variation in effects of exercise.

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Table 1—*Descriptive statistics of studies included in the meta-analysis*

Study (ref.)	Ethnicity	Age (years)	Sample size (*n*)		Dietary cointervention*	Exercise intervention					
			Exercise	Control		Frequency (weeks^{-1})	Duration (weeks)	Session time (min)	Total time (h)	Intensity rating	Intensity description
Aerobic training											
Agurs-Collins et al. (38)	African American	62	31	27	Yes	3	13	30	19.5	3	Low impact aerobic
Agurs-Collins et al. (38)	African American	62	30	25	Yes	3	26	30	39	3	Low impact aerobic
Boudou et al. (52)	European	45	8 M, 0 F	8 M, 0 F	No	3	8	45	18	4	75% Vo_{2max} 2 days/week + 85% Vo_{2max} 1 day/week
Cuff et al. (59)	European	61	0 M, 9 F	0 M, 9 F	No	3	16	75	60	2	Low impact aerobic
Dunstan et al. (40)	European	53	8 M, 3 F	9 M, 3 F	Yes	3	8	40	16	3	50–65% Vo_{2max}
Dunstan et al. (40)	European	53	10 M, 4 F	10 M, 2 F	Yes†	3	8	40	16	3	50–65% Vo_{2max}
Fujii et al. (56)	Japanese	40	6 M, 4 F	9 M, 6 F	No	5	26	30	65	2	40% Vo_{2max}
Giannopoulou et al. (41)	European	57	0 M, 11 F	0 M, 11 F	Yes	3	14	50	35	3	65–70% Vo_{2max}
Khan and Rupp (63)	European	50	21	18	No	5	15	50	63	2	40–60% Vo_{2max}
Lehmann et al. (61)	European	56	6 M, 8 F	7 M, 6 F	No	3	13	90	58.5	3	50–70% Vo_{2max}
Ligtenberg et al. (49)	European	62	25	26	No	3	6	50	15	4	60–80% Vo_{2max}
Mourier et al. (50)	European	46	10	11	No	3	10	55	27.5	4	75% Vo_{2max}
Raz et al. (51)	European	57	7 M, 12 F	7 M, 12 F	No	3	12	55	33	3	65% Vo_{2max}
Ronnemaa et al. (58)	European	53	13	12	No	6	17.5	45	78.75	3	70% Vo_{2max}
Skarfors et al. (53)	European	59	8 M, 0 F	8 M, 0 F	No	2	104	45	156	4	75% Vo_{2max}
Vanninen et al. (64)	European	53	21 M, 0 F	24 M, 0 F	No	3.5	52	45	135.2	3	Heart rate 110–140 bpm
Vanninen et al. (64)	European	54	0 M, 17 F	0 M, 16 F	No	3.5	52	45	135.2	3	Heart rate 110–140 bpm
Yamnouchi et al. (43)	Japanese	42	8 M, 2 F	11 M, 3 F	Yes	7	7	120‡	14	1	Exercise group 19,200 steps/day, control group 4,500 steps/day
Wing et al. (42)	European	54	10	12	Yes	3	10	60	30	3	4.8 km/h
Wing et al. (42)	European	56	13	15	Yes	4	10	60	40	3	4.8 km/h
Verity and Ismail (62)	European	59	0 M, 5 F	0 M, 5 F	No	3	17	75	63.75	4	65–80% heart-rate reserve
Resistance training											
Baldi and Snowling (57)	Polynesian, European	48	9 M, 0 F	9 M, 0 F	No	3	10	60	30	3	2 sets, 12–15 reps, 10 exercises
Castaneda et al. (60)	Hispanic	66	9 M, 20 F	12 M, 19 F	No	3	16	45	36	4	3 sets, 8 reps, 5 exercises
Dunstan et al. (44)	European	51	8 M, 3 F	5 M, 5 F	No	3	8	60	24	2	2–3 sets, 10–15 reps, 10 exercises, 50–55% 1 RM
Dunstan et al. (39)	European	67	10 M, 6 F	6 M, 7 F	Yes	3	13	45	29.25	4	3 sets, 10 reps, 9 exercises, 50–85% 1 RM
Dunstan et al. (39)	European	67	10 M, 6 F	6 M, 7 F	Yes	3	26	45	58.50	4	3 sets, 10 reps, 9 exercises, 50–85% 1 RM
Honkola et al. (45)	European	65	12 M, 6 F	5 M, 15 F	No	3	22	45	49.50	3	2 sets, 12–15 reps, 8–10 exercises
Ishii et al. (46)	Japanese	49	9	8	No	5	5	60	25	2	2 sets, 10–20 reps, 10 exercises, 40–50% 1 RM
Combined training											
Balducci et al. (65)	European	61	28 M, 29 F	28 M, 27 F	No	3	52	60	156	3	40–80% heart-rate reserve, 40–60% 1 RM, 1 set, 12 reps, 6 exercises
Cuff et al. (59)	European	61	0 M, 10 F	0 M, 9 F	No	3	16	75	60	3	60–70% heart-rate reserve on 5 machines, 2 sets, 12 reps, 5 exercises
Loimaala et al. (69)	European	54	24 M, 0 F	25 M, 0 F	No	4	52	45	156	3	65–75% Vo_{2max}; 3 sets, 10–12 reps, 8 exercises
Maiorana et al. (47)	European	52	14 M, 2 F	14 M, 2 F	No	3	8	60	24	3	Circuit training: 8 aerobic + 7 resistance exercises, 45 s each with 15 s rest
Tessier et al. (48)	European	69	12 M, 7 F	11 M, 9 F	No	3	16	60	48	3	60–79% Vo_{2max}; 2 sets, 20 reps, 9 exercises

*Applies to experimental and control groups; †including a diet high in fish; ‡estimated. RM, repetition maximum.

Table 2—*Changes in measures of blood glucose control and related physiological parameters for the individual studies included in the meta-analysis and for the meta-analyzed means after controlling for moderating effects of study characteristics*

Study (ref.)	A1C (%)	Blood glucose		Insulin sensitivity (%)	Fasting insulin (%)	Body mass (%)
		Fasting (mmol/l)	Postprandial (%)			
Aerobic training						
Agurs-Collins et al. (38)						
3 months	−1.6 ± 0.7	—	—	—	—	−2.1 ± 1.3
6 months	−2.4 ± 1.5	—	—	—	—	−2.6 ± 1.7
Boudou et al. (52)	−3.1 ± 1.0	0.3 ± 1.6	—	61 ± 38	−8 ± 48	−0.3 ± 12.5
Cuff et al. (59)	−0.1 ± 0.4	—	—	19 ± 32	—	−3.6 ± 2.8
Dunstan et al. (40)	−0.2 ± 0.4	−0.9 ± 0.9	−8 ± 8	—	—	−1.7 ± 1.4
Dunstan et al. (40) (diet)	−0.5 ± 0.5	−1.5 ± 1.1	−9 ± 10	—	—	−1.1 ± 1.6
Fujii et al. (56)	—	—	−23 ± 16	—	—	—
Giannopoulou et al. (41)	−1.0 ± 1.1	−1.1 ± 0.9	−8 ± 17	—	−66 ± 71	−0.9 ± 2.2
Khan and Rupp (63)	−0.2 ± 1.2	1.2 ± 4.5	—	—	—	−0.3 ± 1.3
Lehmann et al. (61)	−0.6 ± 1.0	0.0 ± 1.4	—	—	−67 ± 42	−1 ± 12
Ligtenberg et al. (49)	−0.3 ± 0.8	—	—	−6 ± 36	—	—
Mourier et al. (50)	**−2.6 ± 0.8**	0.1 ± 1.2	2 ± 16	54 ± 34	2 ± 40	−2 ± 12
Raz et al. (51)	−1.3 ± 1.9	−1.7 ± 2.1	—	—	—	−2.3 ± 7.5
Ronnemaa et al. (58)	−0.9 ± 1.2	−1.1 ± 2.4	−17 ± 20	—	−7 ± 39	−3 ± 13
Skarfors et al. (53)	—	0.3 ± 2.5	8 ± 29	—	13 ± 45	—
Vanninen et al. (64)						
Men	−0.2 ± 0.9	−0.5 ± 1.1	—	—	—	−4.6 ± 5.7
Women	0.0 ± 0.8	0.7 ± 1.0	—	—	—	−2 ± 11
Yamnouchi et al. (43)	—	−0.1 ± 0.7	—	45 ± 10 G, 64 ± 12 M	−18 ± 30	−4 ± 16
Wing et al. (42)						
A	−0.2 ± 1.1	−0.5 ± 2.1	−1 ± 17	—	−16 ± 20	−1 ± 11
B	−0.5 ± 0.7	0.2 ± 1.5	−1 ± 21	—	−28 ± 44	−4 ± 13
Verity and Ismail (62)	0.5 ± 1.2	0.5 ± 2.4	—	—	—	1.0 ± 4.9
Meta-analyzed mean (upper, lower 90% confidence limit)	−0.7 (−1.0, −0.4)	−0.5 (−1.0, −0.1)	−9 (−13, −5)	28 (9, 49)	−20 (−41, 8)	−1.5 (−2.1, −1.0)
Resistance training						
Baldi and Snowling (57)	−0.4 ± 0.5	−0.5 ± 0.5	−9 ± 10	22 ± 32	−63 ± 52	1.0 ± 1.6
Castaneda et al. (60)	−1.0 ± 0.6	**−0.1 ± 0.2**	—	—	—	−0.8 ± 9.1
Dunstan et al. (44)	−0.4 ± 1.5	−0.1 ± 2.7	−11 ± 6	—	−17 ± 42	−2 ± 11
Dunstan et al. (39)						
3 months	−0.5 ± 0.5	−0.6 ± 1.5	—	−5 ± 18	−8 ± 29	0.2 ± 1.2
6 months	−0.8 ± 0.6	−0.8 ± 1.6	—	−4 ± 20	13 ± 20	0.7 ± 1.8
Honkola et al. (45)	−0.5 ± 0.6	—	—	—	—	−3 ± 12
Ishii et al. (46)	−0.8 ± 1.4	—	—	45 ± 33	—	0.0 ± 10.5
Meta-analyzed mean (upper, lower 90% confidence limit)	−0.5 (−1.0, −0.1)	−0.3 (−1.1, 0.6)	−2 (−13, 10)	12 (−6, 33)	−31 (−57, 10)	0.5 (−0.3, 1.4)
Aerobic plus resistance training						
Balducci et al. (65)	−1.2 ± 0.4	−1.9 ± 1.4	—	—	—	−7.0 ± 5.7
Cuff et al. (59)	−0.1 ± 0.5	—	—	75 ± 45	—	−5.3 ± 3.4
Loimaala et al. (69)	−1.0 ± 0.6	—	—	—	—	—
Maiorana et al. (47)	−0.6 ± 0.9	−2.2 ± 1.2	—	—	—	0 ± 12
Tessier et al. (48)	−0.4 ± 0.7	0.4 ± 1.3	−7 ± 10	—	−28 ± 33	−0.2 ± 10.8
Meta-analyzed mean (upper, lower 90% confidence limit)	−0.8 (−1.3, −0.2)	−1.5 (−2.3, −0.6)	−6 (−15, 4)	106 (12, 280)	−7 (−63, 132)	−5.1 (−7.6, −2.5)

Data are mean ± 90% confidence limit, unless otherwise indicated. Data in bold are outliers excluded from the meta-analysis. G, glucose infusion rate; M, metabolic clearance rate; S, subcutaneous adipose tissue; V, visceral adipose tissue.

of study duration on A1C, the mean effect of all three modes of exercise in studies lasting ≥12 weeks was a reduction in A1C of 0.8 ± 0.3% (mean ± 90% confidence limit), whereas the A1C reduction in studies lasting <12 weeks was only 0.4 ± 0.4%. In standardized units, the reductions were small (0.42 ± 0.16 and 0.23 ± 0.22, respectively), and the difference between the effects of long and short studies was possibly trivial or small (−0.19 ± 0.26).

CONCLUSIONS — There are sufficient studies to allow us to conclude that aerobic, resistance, and combined exercise have small to moderate beneficial effects on glucose control in type 2 diabetic patients and small beneficial effects on some related risk factors for complications of diabetes. Furthermore, there is some evidence of small additional benefits resulting from combining aerobic and resistance exercise.

Table 2—*Continued*

Body fat (%)		Waist circumference (%)	Total cholesterol (mmol/l)	LDL cholesterol (mmol/l)	HDL cholesterol (mmol/l)	Triglycerides (mmol/l)	Blood pressure (mmHg)	
Fat mass	Abdominal fat						Systolic	Diastolic
—	—	−0.0 ± 1.8	−0.2 ± 0.5	0.1 ± 0.3	−0.00 ± 0.08	−0.1 ± 0.5	−8.4 ± 7.3	−3.3 ± 3.2
—	—	**0.4 ± 1.1**	0.1 ± 0.5	−0.1 ± 0.5	0.01 ± 0.06	0.2 ± 0.4	−5.9 ± 6.9	−4.0 ± 3.3
—	−40 ± 13 S, −16 ± 20 V	—	—	—	—	—	—	—
—	−5.4 ± 4.9 S, −3.5 ± 10.0 V	—	—	—	—	—	—	—
—	—	—	−0.2 ± 0.3	0.2 ± 0.4	0.05 ± 0.05	−0.4 ± 0.6	—	—
—	—	—	0.04 ± 0.27	0.0 ± 0.3	0.02 ± 0.07	0.3 ± 1.3	—	—
—	—	—	—	—	—	—	—	—
	−2 ± 16	−8.4 ± 3.4 S, −7.5 ± 6.2 V	−0.0 ± 2.0	0.2 ± 0.8	**2.7 ± 0.7**	0.09 ± 0.20	−0.5 ± 0.9	—
−1.6 ± 5.4	—	—	−0.2 ± 0.6	—	0.06 ± 0.12	0.3 ± 2.9	—	—
−15 ± 37	—	−3.2 ± 6.2	—	0.2 ± 0.4	—	—	—	—
—	—	—	−0.3 ± 0.6	−0.1 ± 0.4	−0.03 ± 0.09	−0.2 ± 1.1	—	—
10 ± 41	−13 ± 18 S, **−48 ± 15** V	−1.0 ± 8.6	—	—	—	—	—	—
—	—	—	−0.1 ± 0.6	—	0.00 ± 0.16	−0.2 ± 0.4	—	—
—	—	—	—	—	—	—	—	—
—	—	—	−0.3 ± 0.8	−0.0 ± 0.7	0.03 ± 0.09	—	—	—
—	—	—	−0.4 ± 0.5	—	0.06 ± 0.14	−0.9 ± 0.5	—	—
—	—	—	−0.2 ± 0.5	—	0.08 ± 0.15	−0.3 ± 0.8	—	—
—	—	—	—	—	—	—	—	—
—	—	—	0.5 ± 0.6	—	−0.04 ± 0.16	0.8 ± 0.6	2.0 ± 7.8	2.0 ± 4.0
—	—	—	−0.3 ± 0.5	—	−0.04 ± 0.12	−0.9 ± 0.5	4 ± 13	2.0 ± 7.7
7.4 ± 9.0	—	—	−0.1 ± 0.6	—	**0.20 ± 0.26**	—	—	—
	−11 (−20, −1)	−1.2 (−3.0, 0.6)	−0.2 (−0.3, 0.0)	0.1 (−0.1, 0.3)	0.02 (−0.01, 0.05)	−0.4 (−0.7, 0.0)	−3.5 (−7.6, 0.6)	−1.8 (−4.6, 1.0)
−9.8 ± 5.6	—	—	0.3 ± 0.5	0.4 ± 0.7	0.05 ± 0.11	−0.2 ± 0.7	—	—
−5.5 ± 8.1	—	−4.1 ± 3.7	−0.1 ± 0.4	−0.6 ± 0.6	0.06 ± 0.13	−0.3 ± 0.3	—	—
—	—	0.0 ± 18	—	—	—	—	—	—
—	—	−0.7 ± 2.0	0.2 ± 0.5	0.2 ± 0.5	−0.05 ± 0.11	−0.2 ± 0.5	−1.1 ± 8.7	−2.7 ± 4.5
−0.9 ± 4.9	—	−0.2 ± 3.6	0.4 ± 0.5	0.4 ± 0.5	−0.01 ± 0.11	−0.1 ± 0.4	−4.2 ± 8.7	−3.5 ± 5.7
—	—	—	−0.5 ± 0.7	−0.4 ± 0.5	−0.05 ± 0.19	−0.0 ± 0.8	2.0 ± 9.6	2.0 ± 4.8
−27 ± 58	—	—	—	—	—	—	—	—
	−4 (−16, 10)	−2.0 (−4.6, 0.7)	0.1 (−0.2, 0.4)	0.0 (−0.3, 0.3)	0.02 (−0.03, 0.07)	0.1 (−0.6, 0.8)	−1.3 (−6.5, 3.9)	−1.3 (−5.4, 2.8)
−10 ± 8	—	−3.2 ± 4.6	−0.1 ± 0.3	−0.0 ± 0.3	0.17 ± 0.09	−0.6 ± 0.4	−5.3 ± 6.2	−5.5 ± 2.9
—	−7.8 ± 6.2 S, −10.2 ± 9.8 V	—	—	—	—	—	—	—
—	—	—	—	—	—	—	−5.7 ± 4.6	—
−9 ± 29	—	−1.3 ± 3.5	0.0 ± 0.5	0.1 ± 0.5	0.10 ± 0.24	—	—	—
—	—	—	—	—	—	—	—	—
	−15 (−26, −2)	−0.8 (−3.3, 1.7)	0.3 (−0.4, 0.4)	0.1 (−0.4, 0.5)	0.13 (0.07, 0.20)	−0.3 (−1.4, 0.8)	−5.6 (−9.3, −1.8)	−5.5 (−9.9, −1.1)

More research is needed for confident conclusions about other factors that could affect the outcomes of an exercise program, especially the effect of sex of the patients. In the meantime, it is reasonably clear that there is a small additional benefit for those with more severe disease, a reassuring finding for those prescribing exercise to patients. There was little synergistic effect of a dietary cointervention; this finding can also reassure clinicians that the effects of diet will add linearly to those of exercise, although the apparent small harmful effects of a dietary cointervention on LDL and total cholesterol need to be clarified. The effect of duration of the exercise program on A1C was consistent with the turnover time for Hb, but, otherwise, the effect of total exercise time on A1C and the other measures was at best trivial. This finding is consistent with most patients reaching a stable state in their exercise programs and gaining no extra benefit from more exercise. An in-

Table 3—*Meta-analyzed effects of various modes of exercise and the moderating effects of study characteristics on measures of glucose control and related physiological parameters*

	Mode of exercise			Aerobic − resistance difference	Combined − aerobic difference	Initial mean value (+2 SD)	Male − female difference	Exercise total time (×2)	Exercise intensity (+2 levels)	Dietary cointervention	Random effect
	Aerobic	Resistance	Combined								
A1C	−0.37 ± 0.16 small	−0.29 ± 0.25 small	−0.43 ± 0.29 small	−0.08 ± 0.30 unclear	−0.06 ± 0.34 unclear	−0.36 ± 0.40 small	−0.29 ± 0.37 small	0.00 ± 0.14 trivial	−0.29 ± 0.43 small	0.03 ± 0.29 unclear	0.24 ± 0.23 small
Fasting glucose	−0.20 ± 0.15 small	−0.10 ± 0.31 unclear	−0.53 ± 0.31 small	−0.09 ± 0.33 trivial	−0.34 ± 0.35 small	−0.40 ± 0.48 small	−0.16 ± 0.38 unclear	−0.01 ± 0.15 trivial	−0.04 ± 0.35 unclear	−0.27 ± 0.28 small	0.02 ± 0.21 trivial
Postprandial glucose*	*−0.44 ± 0.20 small*	*−0.10 ± 0.53 unclear*	*−0.28 ± 0.46 small*	*−0.35 ± 0.57 unclear*	*0.16 ± 0.53 unclear*	—	*−0.51 ± 0.83 unclear*	*−0.10 ± 0.35 unclear*	***1.06 ± 0.65 mod. harm***	*−0.03 ± 0.73 unclear*	—
Insulin sensitivity	0.74 ± 0.47 moderate	0.34 ± 0.52 small	2.20 ± 1.85 large	0.40 ± 0.76 unclear	1.46 ± 1.90 unclear	—	1.24 ± 1.24 large	0.03 ± 0.78 unclear	−0.54 ± 0.81 unclear	−0.50 ± 1.02 unclear	0.15 ± 0.35 unclear
Fasting insulin	−0.47 ± 0.63 moderate	−0.78 ± 0.97 moderate	−0.15 ± 1.89 unclear	−0.31 ± 1.23 unclear	0.32 ± 1.92 unclear	—	1.93 ± 2.39 unclear	−0.05 ± 0.64 unclear	0.59 ± 1.16 unclear	0.99 ± 1.38 unclear	0.81 ± 0.73 moderate
Body mass	−0.09 ± 0.03 trivial	0.03 ± 0.05 trivial	−0.32 ± 0.16 small	−0.13 ± 0.06 trivial	−0.22 ± 0.16 small	—	*0.07 ± 0.09 trivial*	*0.00 ± 0.03 trivial*	*0.07 ± 0.13 trivial*	*−0.06 ± 0.08 trivial*	−0.02 ± 0.04 trivial
Body fat	−0.35 ± 0.31 small	−0.12 ± 0.40 unclear	−0.46 ± 0.40 small	−0.23 ± 0.47 trivial	−0.11 ± 0.27 trivial	—	−0.32 ± 0.62 unclear	**0.23 ± 0.29 small harm**	0.04 ± 0.52 unclear	−0.03 ± 0.56 unclear	0.29 ± 0.30 small
Waist circumference*	*−0.10 ± 0.15 trivial*	*−0.17 ± 0.23 trivial*	*−0.07 ± 0.21 trivial*	*0.07 ± 0.29 unclear*	*0.03 ± 0.30 unclear*	—	*0.11 ± 0.32 unclear*	*−0.01 ± 0.09 trivial*	*−0.04 ± 0.60 unclear*	*0.25 ± 0.16 small*	—
Total cholesterol	−0.14 ± 0.15 trivial	0.09 ± 0.26 trivial	0.03 ± 0.36 unclear	−0.23 ± 0.33 small	0.17 ± 0.42 unclear	−0.06 ± 0.58 unclear	−0.09 ± 0.43 unclear	0.01 ± 0.14 trivial	−0.04 ± 0.58 unclear	**0.23 ± 0.28 small harm**	0.21 ± 0.69 small
LDL cholesterol	0.09 ± 0.22 trivial	0.02 ± 0.31 unclear	0.09 ± 0.50 unclear	0.06 ± 0.37 unclear	0.00 ± 0.54 unclear	−0.02 ± 0.32 unclear	−0.40 ± 0.72 unclear	0.03 ± 0.15 trivial	0.13 ± 0.71 unclear	**0.21 ± 0.30 small harm**	−0.10 ± 0.21 trivial
HDL cholesterol	*0.07 ± 0.09 trivial*	*0.08 ± 0.19 trivial*	*0.49 ± 023 small*	*−0.00 ± 0.24 unclear*	*0.41 ± 0.27 small*	*−0.10 ± 0.26 trivial*	*0.08 ± 0.34 unclear*	*0.03 ± 0.09 trivial*	*−0.23 ± 0.33 small*	*−0.03 ± 0.15 unclear*	—
Triglycerides	−0.23 ± 0.23 small	0.04 ± 0.45 unclear	−0.14 ± 0.70 unclear	−0.27 ± 0.58 unclear	0.09 ± 0.76 unclear	0.38 ± 1.80 unclear	−0.30 ± 0.69 unclear	−0.11 ± 0.23 trivial	−0.32 ± 1.02 unclear	0.09 ± 0.35 unclear	0.24 ± 0.27 small
Systolic blood pressure†	*−0.22 ± 0.26 small*	*−0.08 ± 0.33 unclear*	*−0.35 ± 0.24 small*	*−0.13 ± 0.41 unclear*	*−0.13 ± 0.35 unclear*	—	—	—	—	—	—
Diastolic blood pressure†	*−0.21 ± 0.32 small*	*−0.15 ± 0.47 unclear*	*−0.63 ± 0.50 moderate*	*−0.06 ± 0.57 unclear*	*−0.42 ± 0.60 small*	—	—	—	—	—	—

Data are means ± 90% confidence limit. Effects are shown in units standardized by dividing by the baseline between-subject SD averaged over all studies. Magnitudes are based on the following scale: <0.20, trivial; 0.20–0.60, small; 0.60–1.20, moderate; and >1.20, large. Nontrivial magnitudes are beneficial, unless stated otherwise. Shaded cells indicate clear beneficial effects. Cells in boldface indicate clear harmful effects. Italics indicate estimates from a fixed-effects meta-analysis. *Random-effects analysis failed to produce estimates, even for the simplest model (mode of exercise as the only fixed effect). †Insufficient studies to include study characteristics in random- or fixed-effects analyses.

crease in exercise intensity was also generally unclear; this was a surprising finding given that most if not all physiological adaptations to exercise are sensitive to intensity (70). One possible explanation is that patient compliance with exercise programs of higher intensity was not as good as the authors claimed. Whatever the reason, the practical implication is that there may be little difference in the effectiveness of programs differing in intensity. Given the uncertainty in the estimates, a considerable number of additional studies will be required to resolve the effects of intensity. Alternatively, a large study with clearly defined monitoring of exercise programs differing in intensity could be definitive.

Our assessment of magnitudes of the meta-analyzed effects is based on a generic statistical approach using mean effects standardized with the between-subject SD of patients at baseline. An assessment of magnitude directly related to health outcomes would require a meta-analysis of controlled trials of the effects of exercise programs on morbidity and mortality of type 2 diabetic patients, but as far as we know, there are no such studies. However, there have been many prospective studies of the effects of A1C on health outcomes in these patients, and in a recent meta-analysis of those studies, an increase in A1C of 1.0% was associated with a relative risk of 1.18 for total cardiovascular disease (71). If we assume that the mean reduction in A1C produced by an exercise program in our meta-analysis (~0.8% for the longer studies) has the same association with cardiovascular disease, the reduction in risk would be ~1/1.14 or 0.88. Such a risk reduction would have to be regarded as only marginally beneficial, especially if one takes into account the fact that diabetes raises the risk of cardiovascular disease by a factor of ~2.5–3.0 (72,73). One should not conclude that exercise is not worth the effort. The reduction in A1C achieved with exercise is similar to that with long-term drug or insulin therapy (0.6–0.8%) (74,75). The effects of diet on A1C are also similar on average to those of exercise, although the reductions vary widely (as much as 1.7% in the short term for severe caloric restriction) (76). The combined small effects of drug therapy, diet, and exercise could well be moderate or even large. Further research addressing this issue should be a priority.

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