Effects of Exercise on Glycemic Control and Body Mass in Type 2 Diabetes Mellitus

A Meta-analysis of Controlled Clinical Trials

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Context Exercise is widely perceived to be beneficial for glycemic control and weight loss in patients with type 2 diabetes. However, clinical trials on the effects of exercise in patients with type 2 diabetes have had small sample sizes and conflicting results.

Objective To systematically review and quantify the effect of exercise on glycosylated hemoglobin (HbA_{1c}) and body mass in patients with type 2 diabetes.

Data Sources Database searches of MEDLINE, EMBASE, Sport Discuss, Health Star, Dissertation Abstracts, and the Cochrane Controlled Trials Register for the period up to and including December 2000. Additional data sources included bibliographies of textbooks and articles identified by the database searches.

Study Selection We selected studies that evaluated the effects of exercise interventions (duration ≥8 weeks) in adults with type 2 diabetes. Fourteen (11 randomized and 3 nonrandomized) controlled trials were included. Studies that included drug cointerventions were excluded.

Data Extraction Two reviewers independently extracted baseline and postintervention means and SDs for the intervention and control groups. The characteristics of the exercise interventions and the methodological quality of the trials were also extracted.

Data Synthesis Twelve aerobic training studies (mean [SD], 3.4 [0.9] times/week for 18 [15] weeks) and 2 resistance training studies (mean [SD], 10 [0.7] exercises, 2.5 [0.7] sets, 13 [0.7] repetitions, 2.5 [0.4] times/week for 15 [10] weeks) were included in the analyses. The weighted mean postintervention HbA_{1c} was lower in the exercise groups compared with the control groups (7.65% vs 8.31%; weighted mean difference, –0.66%; $P<.001$). The difference in postintervention body mass between exercise groups and control groups was not significant (83.02 kg vs 82.48 kg; weighted mean difference, 0.54; $P = .76$).

Conclusion Exercise training reduces HbA_{1c} by an amount that should decrease the risk of diabetic complications, but no significantly greater change in body mass was found when exercise groups were compared with control groups.

JAMA. 2001;286:1218-1227 www.jama.com

FOR MANY YEARS, EXERCISE, ALONG with diet and medication, has been considered 1 of the 3 cornerstones of diabetes therapy.[1] Regular physical activity is recommended for patients with type 2 diabetes since it may have beneficial effects on metabolic risk factors for the development of diabetic complications.[2] The low-cost, nonpharmacological nature of physical activity further enhances its therapeutic appeal.

Two of the major goals of diabetes therapy are to reduce hyperglycemia and body fat. Chronic hyperglycemia is associated with significant long-term complications, particularly damage to the kidneys, eyes, nerves, heart, and blood vessels.[3] Obesity, especially abdominal obesity, is associated with insulin resistance, hyperinsulinemia, hyperglycemia, dyslipidemia, and hypertension[4,5]; these abnormalities tend to cluster and are often referred to as the "metabolic syndrome."[6] Elements of the metabolic syndrome are strong risk factors for cardiovascular disease,[7,8] and regular exercise in nondiabetic subjects has beneficial effects on virtually all aspects of the syndrome.[4,9,10]

Although there have been numerous small studies on the effects of exercise in patients with type 2 diabetes, their findings have varied. There have been no large studies with adequate statistical power to guide practitioners in recommending exercise plans for their patients with diabetes. Exercise interventions reduced glycosylated hemoglobin (HbA_{1c}) in some studies,[11-15] but not in others.[16-22] Meta-analysis may be especially useful in summarizing and

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analyzing prior research when the number of subjects per study is small and the results are somewhat conflicting,[23] as is the case for exercise interventions in patients with type 2 diabetes.

The main objective of this study was to systematically review the effect of exercise interventions on glycemic control as represented by HbA_{1c} and body mass, measured as body weight in kilograms or body mass index (calculated as weight in kilograms divided by the square height in meters) in adults with type 2 diabetes.

METHODS

Study Selection

Literature searches of computer databases were performed for the period up to and including December 2000 (MEDLINE 1966-2000, EMBASE 1980-2000, Sport Discuss 1949-2000, Health Star 1975-2000, Dissertation Abstracts 1861-2000, and the Cochrane Controlled Trials Register). The reference lists of major textbooks, review articles, and of all included articles identified by the search were hand searched to find other potentially eligible studies. Potential missing articles and unpublished literature were sought from experts. Non-English studies were included.

The computer-based search strategy included common text words and Medical Subject Headings related to exercise and type 2 diabetes. MEDLINE and EMBASE searches were limited to human subjects and used a validated and highly sensitive search filter for randomized controlled trials and nonrandomized controlled clinical trials (CCTs).[24] If studies reported data for which it was impossible to discriminate between participants with type 2 diabetes and those with impaired glucose tolerance, we attempted to contact authors for the individual patient data.

We limited the analyses to exercise interventions lasting at least 8 weeks since our main outcome of interest, HbA_{1c}, reflects average blood glucose concentration from the previous 8 to 12 weeks. An exercise intervention was defined as a predetermined program of physical activity described in terms of type, frequency, intensity, and duration. Studies in which the intervention consisted only of recommending increased physical activity were not included within the analyses since it would be impossible to quantify the exercise intervention and compliance. To be included, compliance with exercise interventions had to be verified by direct supervision or through exercise diaries. Studies that included drug cointerventions were excluded from the analysis.

Data Extraction

For the variables of interest, we extracted sample sizes as well as baseline and postintervention means and SDs for the intervention and control groups. The authors of potentially eligible studies were contacted when necessary to resolve ambiguities in reported methods or results and to seek additional information. In some cases,[12,19,25] postintervention SDs were not available. In these instances, we imputed the baseline SD. This was assumed to be valid since the baseline and postintervention SDs were found to be similar within the other trials included in the meta-analysis (for example, the postintervention SDs were on average 0.14 units lower than the baseline SDs). Where necessary, means and measures of dispersion were approximated from figures in the manuscripts using an image scanner (RT6l5CTW [resolution 200 dpi], Compaq Computer Corp, Houston, Tex), as described previously.[26]

The characteristics of the exercise interventions were extracted, including the type, frequency, duration, intensity, and energy cost. The Compendium of Physical Activities[27] was used to estimate the exercise intensity in terms of metabolic equivalents (METs). Exercise volume (total energy expenditure on exercise, in METs per hour) was calculated by multiplying the intensity in METs by total time spent exercising (number of exercise sessions multiplied by duration of each exercise session). The methodological quality of each included trial was assessed using a validated 5-point scale as described by Jadad et al.[28] The instrument assigned scores for reported randomization, blinding, and withdrawals. In addition to this quality scoring, we recorded separately whether allocation concealment was adequate, as described by Schulz et al.[29]

Two of the authors (N.G.B. and E.H.) independently performed the literature search, quality assessment, and data extraction. Any disagreements on inclusion of trials or quality assessment were resolved by discussion with a third author (R.J.S.).

Statistical Analysis

Statistical analysis was performed with Review Manager Software (RevMan 4.1, Cochrane Collaboration, Oxford, England) and JMP Software (Version 3.1.6.2, SAS Institute Inc, Cary, NC). In each study, the effect size for the intervention was calculated by the difference between the means of the exercise and control groups at the end of the intervention. Each mean difference was weighted according to the inverse of its variance, and the average was taken (weighted mean difference [WMD]). When the same outcome was measured by different scales (ie, body mass represented by body weight in some studies and body mass index in others), the mean difference was standardized by dividing it by the within-group SD; the results were then weighted and the average taken (standardized mean difference [SMD]). The WMD or SMD in each study was pooled with a fixed-effects model.[30] The χ^2 test for heterogeneity was performed, and when significant heterogeneity was found, the analysis was redone with a random-effects model.[30] The funnel plot technique[31] was used to detect publication bias.

We performed a meta-regression analysis to explore whether effects of the exercise interventions on HbA_{1c} were mediated by effects on body mass, by the exercise intensity, or by exercise volume. In all meta-regression

models, studies were weighted by sample size. In the first model, the mean difference in end-of-study HbA_{1c} for individual studies was regressed on the corresponding mean difference in body mass at the same time point. In the second model, we corrected for baseline values by regressing the difference between exercise and control groups' change from baseline in HbA_{1c} on the corresponding values for body mass change. In the third model, the mean difference in end-of-study HbA_{1c} was regressed on the exercise intensity (METs). In the fourth model, exercise volume was used (total METs per hour). In the fifth model, body mass, exercise intensity, and exercise volume were entered simultaneously.

RESULTS

Participants, Study Design, and Exercise Interventions

The computer searches yielded approximately 2700 potential articles. After the application of the filter for CCTs, the number of potential studies was 1487. The most common reasons for exclusion were: review article only, nonhuman subjects, lack of type 2 diabetic control group, lack of an exercise training intervention, duration of intervention less than 8 weeks, and/or absence of exercise supervision or exercise diaries. Eventually, 14 trials were deemed appropriate for inclusion, but in some cases there were multiple publications from the same trial.[32-40]

Two of the 14 trials presented data for 2 comparisons, therefore 16 comparisons were included (TABLE). One of these trials[12] had a 2 × 2 factorial design in which participants were assigned to 4 groups (exercise, diet, exercise and diet, and control). For this trial, we were able to analyze 2 comparisons: exercise and diet vs diet alone; and exercise alone vs control. The second trial, Vanninen et al,[21] had data analyzed separately for men and women. In the article by Wing et al,[22] the results of 2 separate studies were presented.

Of the studies otherwise meeting inclusion criteria, one study[41] was excluded because the exercise intervention alternated between 3 months of exercise and 3 months without exercise, and another study[42] was excluded because program participation was not associated with a significant increase in physical activity. Two studies[43,44] were excluded because we were unable to differentiate between participants with and without diabetes and 3 others[45-47] were excluded because postintervention HbA_{1c} and body mass values were not available. In the study by Kaplan et al,[18] the combined exercise and diet group was excluded from the analysis because only the last 5 of the 10 weeks included exercise.

A total of 504 participants were included in the 14 trials. The mean (SD) age of participants in studies for which this information was available was 55.0 (7.2) years, duration of diabetes was 4.3 (4.6) years, and 50% of participants were women (Table). The quality of the trials according to the scale described by Jadad et al[28] was moderate to low. The mean (SD) score was 1.6 (0.5) out of a possible 5 points. The quality assessment criterion that permitted the greatest discrimination between studies was randomization since the studies obtained similar scores on other methodological quality characteristics. Of the 14 trials, 11 were randomized controlled trials and 3 were CCTs (Table). None of the trials was double blind or had adequate allocation concealment. Nine trials had adequately described dropouts,[11-16,18-20] there were no dropouts in 2 of the studies,[17,25] while 3 studies did not comment on dropouts.[21,22]

The compliance to the exercise interventions was relatively high. In 9 studies,[11-14,18,20-22] the mean participation rate was above 80%, 2 articles[15,19] indicated that compliance was good, and 3 studies[16,17,25] did not comment on compliance. Dietary compliance was assessed in all but 1 study[21] that prescribed dietary cointerventions, using food diaries or weekly meetings with a dietician. Medication was altered for a small number of participants during 1 study.[21] In this study, 6 participants started taking glybenclamide and it was not stated how many of these participants had been assigned to the exercise group. More details on the medications taken by participants and dietary cointerventions are provided in the Table.

The exercise interventions in each study are described in the Table. The exercise interventions typically prescribed 3 workouts per week, each lasting a mean (SD) of 53 (17) minutes (including 10 minutes of warm-up and cool-down) for 18 (15) weeks. The intensity of the aerobic exercise was moderate and typically consisted of walking or cycling. Two studies[16,17] used resistance exercise training as an intervention and 1 study[20] added resistance training with elastic bands to its aerobic training program. Resistance training was composed of 2 to 3 sets ranging from 10 to 20 repetitions. One study[16] described the initial resistance to be at 50% to 55% of the participants' repetition maximum, while the other did not specify the intensity.[17] Both studies stated that the resistance was progressively increased.[16,17]

The results are presented for 2 types of comparisons. The exercise vs nonexercise control comparisons included studies in which there was no diet cointervention or in which the same diet cointervention was given to both the exercise and control groups. The second set of comparisons was between combined exercise and diet interventions vs nondieting/nonexercising control groups.

Effect of Exercise on Glycemic Control

Baseline and postintervention HbA_{1c} values were described in 12 studies (14 comparisons). For the 11 comparisons between exercise and nonexercise control groups there were no significant baseline differences in HbA_{1c} (WMD, 0.08%; $P = .65$). As shown in FIGURE 1, when the postintervention results were pooled, HbA_{1c} was significantly lower in the exercise groups compared with the control groups (7.65% vs 8.31%; WMD, –0.66%; $P < .001$). Figure 1 also illustrates the effects on HbA_{1c} of interventions combining exercise and diet compared with nonexercise, nondiet

controls. When diet and exercise were combined, the effect on HbA_{1c} was similar to the effect of exercise alone (WMD, –0.76%; $P=.008$).

A sensitivity analysis identified no significant differences between the results from randomized controlled trials and CCTs. The postintervention WMD between exercise and control groups for the 9 randomized comparisons was –0.63% (95% confidence interval [CI], –1.01% to –0.25%; $P=.001$), whereas the corresponding WMD for the 2 CCTs was –0.75% (95% CI, –1.36% to –0.14%; $P=.02$). Further subgroup analysis comparing aerobic or resistance training groups with the control group revealed no significant difference. The WMD for aerobic training vs control was –0.67% (95% CI, –1.04% to –0.30%; $P<.001$) and was –0.64% (95% CI, –1.29% to 0.01%; $P=.05$) for resistance training vs control.

There was only 1 study[20] in which participation was limited to participants with diabetes who were older than 65 years. The age of the participants in this study was much higher than the overall mean (SD) age of the participants in this meta-analysis (69.4 [4.7] years vs 55.0 [7.2] years, respectively). The intervention in this study was not successful in reducing HbA_{1c}. If this study were excluded, the overall WMD for HbA_{1c} would have been –0.74% (95% CI, –1.09% to –0.39%).

Effect of Exercise on Body Mass

In all but 2 of 14 trials, the details on the changes in body mass were given in kilograms (Raz et al[14] and Vanninen et al[21] only presented body mass index values). In the body mass comparisons for the 13 exercise groups vs nonexercise control groups, no significant postintervention differences were found (SMD, 0.06; $P=.60$; FIGURE 2). The effect of exercise vs nonexercise control was similar when only the 12 studies that measured body mass in kilograms were considered separately (83.02 kg vs 82.48 kg; WMD, 0.54 [95% CI, –2.91 to 3.99]; $P=.76$). There were no significant differences between the 2 groups when randomized controlled trials, CCTs, aerobic training studies, and resistance training studies were considered separately. In the studies comparing combined exercise and diet interventions vs control (Figure 2), the postintervention body mass difference also did not reach statistical significance (SMD, –0.20; $P=.25$).

The average baseline to postintervention changes in body weight were approximately –0.9 kg ($P=.70$) in the exercise groups, –3.4 kg ($P=.11$) in the combined exercise and diet groups, –2.5 kg ($P=.29$) in the diet groups, and 0.8 kg ($P=.73$) in the control groups.

Abdominal obesity was represented by waist-to-hip ratio or waist circumference. This information was available in 4 studies.[12,13,16,19] The postintervention WMDs were –0.02 U ($P=.05$) for waist-to-hip ratio and –4.53 cm ($P<.001$) for waist circumference. However, much of this difference could be accounted for by baseline differences in abdominal adiposity favoring the exercise groups (waist-to-hip ratio, –0.01; $P=.40$; waist circumference, –3.52 cm; $P<.001$). Only 1 study[13] in our meta-analysis directly measured abdominal obesity by magnetic resonance imaging. The aerobic training program in that study (55 minutes, 3 times/week, 10 weeks) resulted in a significant reduction in both abdominal subcutaneous adipose tissue (227.3 cm^2 to 186.7 cm^2; $P<.05$) and visceral adipose tissue (156.1 cm^2 to 80.4 cm^2; $P<.05$) while no significant reductions were found in the control group. In the same study, waist circumference and waist-to-hip ratio were not significantly reduced (98.4 cm to 97.4 cm and 0.97 to 0.94 U, respectively). Only 2 studies, 1 of aerobic training[13] and 1 of resistance training,[16] presented data on the sum of skinfolds and neither study found a significant exercise effect on this outcome. There were no significant changes in body fat percentage within the 2 aerobic training studies[13,19] that measured this variable. In the study by Mourier et al,[13] magnetic resonance imaging indicated that the mid-thigh muscle cross-sectional area was significantly increased after aerobic training (149.3 cm^2 to 183.5 cm^2; $P<.05$).

Meta-Regression Analysis

The postintervention mean difference in body weight did not predict the postintervention mean difference in HbA_{1c} ($r^2=.003$; $P=.84$ for model 1). Even after correcting for baseline values, no significant association between these variables was found ($r^2=.09$; $P=.31$ for model 2). Exercise intensity (METs) was not associated with the postintervention mean difference in HbA_{1c} ($r^2=.07$, $P=.35$ for model 3). Similarly, exercise volume (total MET hours) was not associated with the postintervention mean difference in HbA_{1c} ($r^2=.04$; $P=.51$ for model 4). When body mass (SMD), exercise intensity (METs), and exercise volume (total MET hours) were entered simultaneously as independent variables (model 5), a nonsignificant 8% of the variance in HbA_{1c} was explained ($P=.79$).

Evaluation of Potential Bias

The funnel plot technique[31] was used to evaluate publication bias. The postintervention WMDs in HbA_{1c} were plotted against the sample size of the study. The plot did not show any asymmetry, an indication that significant publication bias was not likely. We did not find an unpublished study meeting the inclusion criteria. To statistically pool results from different studies using a fixed-effects model, the values must be relatively homogenous between studies. The results from the various analyses were consistent and homogeneous, however, there was 1 exception. The χ^2 tests suggested that there was heterogeneity in the baseline HbA_{1c} values for the combined exercise and diet vs control comparison (Figure 2). This analysis was repeated with a random-effects model; the baseline WMD was reduced to 0.02% ($P>.99$) and the postintervention WMD was not changed (WMD, –0.76% [95% CI, –1.32 to –0.20]; $P=.008$).

COMMENT

Postintervention HbA_{1c} values were significantly reduced in the exercise groups compared with control groups while body mass was not. The postintervention HbA_{1c} values were 0.66%

Table. Description of Exercise Interventions*

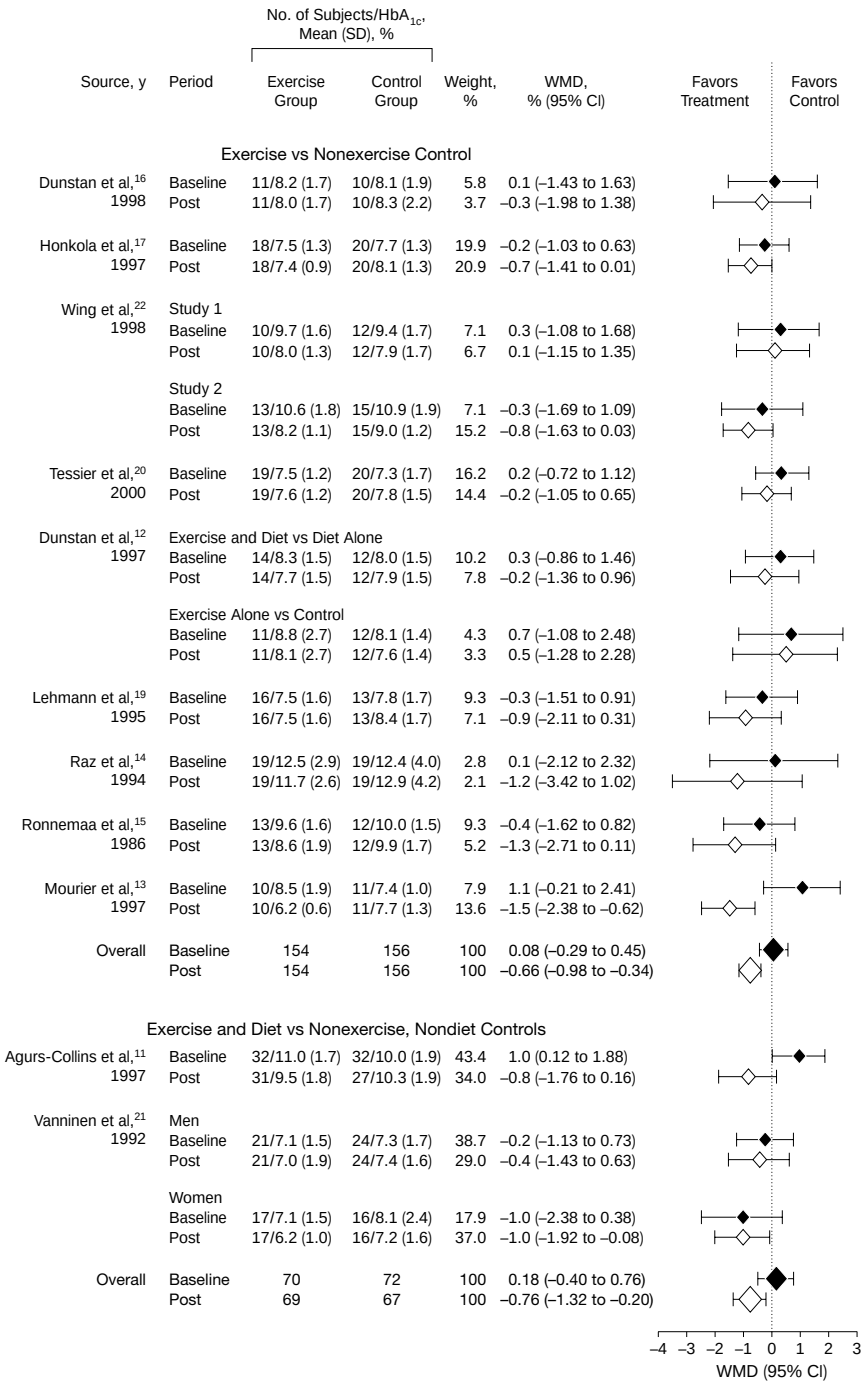
Source, y	Study Location	Age, y†	Women, %	Duration of Type 2 Diabetes Mellitus, y†	Prestudy vs Poststudy Medication	Exercise Group		Control
						No. of Subjects	Medication Use	No. of Subjects
								Exercise vs Nonexercise
Dunstan et al,[12] 1997	Australia							
Exercise and diet vs diet alone		53.3 (7.7)	23	5.4 (4.3)	No change	14	11 Taking oral hypoglycemic agent	12
Exercise alone vs control		52.7 (7.6)	26	4.1 (3.7)	No change	11	8 Taking oral hypoglycemic agent	12
Fujii et al,[25] 1982	Japan	39.5 (6.3)	40	ND	No change	10	No medication	15
Kaplan et al,[18] 1987	United States	54.1 (8.4)	58	NA	19 Taking insulin and 29 taking oral hypoglycemic agent prestudy	18	NA	15
Lehmann et al,[19] 1995	Switzerland	55.5 (9.8)	48	7.8 [1-25]	No change	16	10 Taking oral hypoglycemic agent	13
Mourier et al,[13] 1997	France	45.5 (8.5)	17	4.9 (2.0)	20 Taking oral hypoglycemic agent (3 sulfonylureas; 14 metformin) for >3 mo prestudy	10	NA	11
Raz et al,[14] 1994	Israel	56.6 (6.5)	65	NA	NA	19	Glibenclamide and metformin	19
Ronnemaa et al,[15] 1986	Finland	52.5 [45-60]	33	7.1 [1-13]	18 Taking sulfonylureas and 10 taking sulfonylureas and metformin combined prestudy	13	NA	12
Wing et al,[22] 1988	United States				NA			
Study 1		54.2 (8.3)	84	4.6 (5.0)		10	6 Taking oral hypoglycemic agent	12
Study 2		55.6 (6.8)	70	7.0 (5.7)		13	10 Taking oral hypoglycemic agent and 3 taking insulin	15
Tessier et al,[20] 2000	Canada	69.4 (4.7)	41	6.5 (5.8)	No change	19	10 Taking glyburide and 14 taking metformin	20
								Exercise vs Nonexercise Control
Dunstan et al,[16] 1998	Australia	50.7 (6.8)	37	5.2 (4.2)	No change	11	7 Taking oral hypoglycemic agent	10
Honkola et al,[17] 1997	Finland	64.7 (8.7)	55	8.0 (8.5)	NA	18	4 Taking oral hypoglycemic agent and 5 taking insulin	20
								Exercise and Diet vs Control
Agurs-Collins et al,[11] 1997	United States	61.7 (5.8)	77	NA	NA	31	15 Taking oral hypoglycemic agent and 16 taking insulin	27
Vanninen et al,[21] 1992	Finland				1 Taking glybenclamide prestudy and 7 taking glybenclamide poststudy			
For men		53.0 (7.0)	0	ND		21	NA	24
For women		54.0 (6.0)	100	ND		17	NA	16
Total						251		253
Average		55.0 (7.2)	50	4.3 (4.6)				

*RCT indicates randomized controlled trial; Vo_{2max}, maximum oxygen consumption; Vo_{2peak}, peak oxygen consumption; ND, newly diagnosed; CCT, nonrandomized controlled trial; and NA, data not available.
†Values are expressed as mean (SD) or median [range].

Group			Exercise Intervention					
Medication Use	Type of Trial	Diet Cointervention	Type	No. of Times/wk	No. of Weeks	Length, min	Intensity	Metabolic Equivalent, h/wk‡
Control (Aerobic Training)								
	RCT							
8 Taking oral hypoglycemic agent		<30% kcal/d as fat (<10% saturated fat), <100 mmol/d sodium, and 1 fish meal/d (3.6 g of omega-3 fatty acids/d)	Cycling	3	8	40	50%-65% Vo_{2max}	8.8
8 Taking oral hypoglycemic agent		Same as other group but no fish	Cycling	3	8	40	50%-65% Vo_{2max}	8.8
No medication	CCT	Caloric restriction: 30-35 kcal/kg of ideal body weight	Jogging	5	26	30	Approximately 40% Vo_{2max}	10.0
NA	RCT	1200 kcal/d (50% as carbohydrates, 30% as fat, 20% as protein)	Walking	3	10	80	60%-70% Vo_{2max}	12.5
6 Taking oral hypoglycemic agent	CCT	1664 kcal/d (39% as carbohydrates, 44% as fat, and 17% as protein)	Walking, cycling, jogging, rowing, stair climbing	3	13	90	50%-70% Vo_{2max}	16.9
NA	RCT	Half of each group took branched-chain amino acid supplements, the other half took placebo	Cycling	3	10	55	75% Vo_{2peak} intervals	11.6
Glibenclamide and metformin	RCT	None	Cycling, rowing, swimming, treadmill	3	12	55	65%Vo_{2max}	12.5
NA	RCT	None	Walking, jogging, skiing	6	17.5	45	70% Vo_{2max}	24.8
6 Taking oral hypoglycemic agent	RCT	Goal: lose 1 kg/wk (prebody weight [kg] × 26-1000 kcal/d); increase complex carbohydrates and decrease fat	Walking	3	10	60	4.8 km/session	9.9
9 Taking oral hypoglycemic agent and 5 taking insulin	RCT	Same as study 1	Walking	3	10	60	4.8 km/session	9.9
12 Taking glyburide and 15 taking metformin	RCT	None	Walking, cycling, weight training	3	16	60	Aerobic: 60%-79% Vo_{2max}; resistance training: 2 sets, 20 repetitions, 9 exercises	11.0
(Resistance Training)								
8 Taking oral hypoglycemic agent	RCT	Reminded not to alter diet	Cycling, weight training	3	8	60	2-3 sets, 10-15 repetitions, 10 exercises, 50%-55% repetition maximum (adjusted at wk 4)	11.4
6 Taking oral hypoglycemic agent and 7 taking insulin	CCT	Prestudy diet	Cycling, weight training	2	22	45	2 sets, 12-15 repetitions, 8-10 exercises (progressively increased intensity)	8.3
(Aerobic Training)								
14 Taking oral hypoglycemic agent and 14 taking insulin	RCT	Exercise group: 55%-60% as carbohydrates, 12%-20% as protein, and <30% fat; goal: lose 4.5 kg over 6 mo	Cycling, rowing, aerobics (low impact), treadmill	3	13	30	Low-impact aerobic activity	5.8
	RCT							
NA		Prestudy reduction of kcal/d, cholesterol, and fat. Exercise group: continued kcal/d and fat restriction	Walking, jogging, cycling, swimming, skiing	3.5	52	45	Heart rate, 110-140/min	13.1
NA		Same as men	Walking, jogging, cycling, swimming, skiing	3.5	52	45	Heart rate, 110-140/min	13.1
	11§							
				3.3	18	53		11.8

‡Amount of energy expenditure per week during programmed exercise (1 metabolic equivalent equals 210 mL of oxygen per kilogram).
§Total number of RCTs.

Figure 1. Differences in Glycosylated Hemoglobin (HbA_{1c}) From Baseline to Postintervention

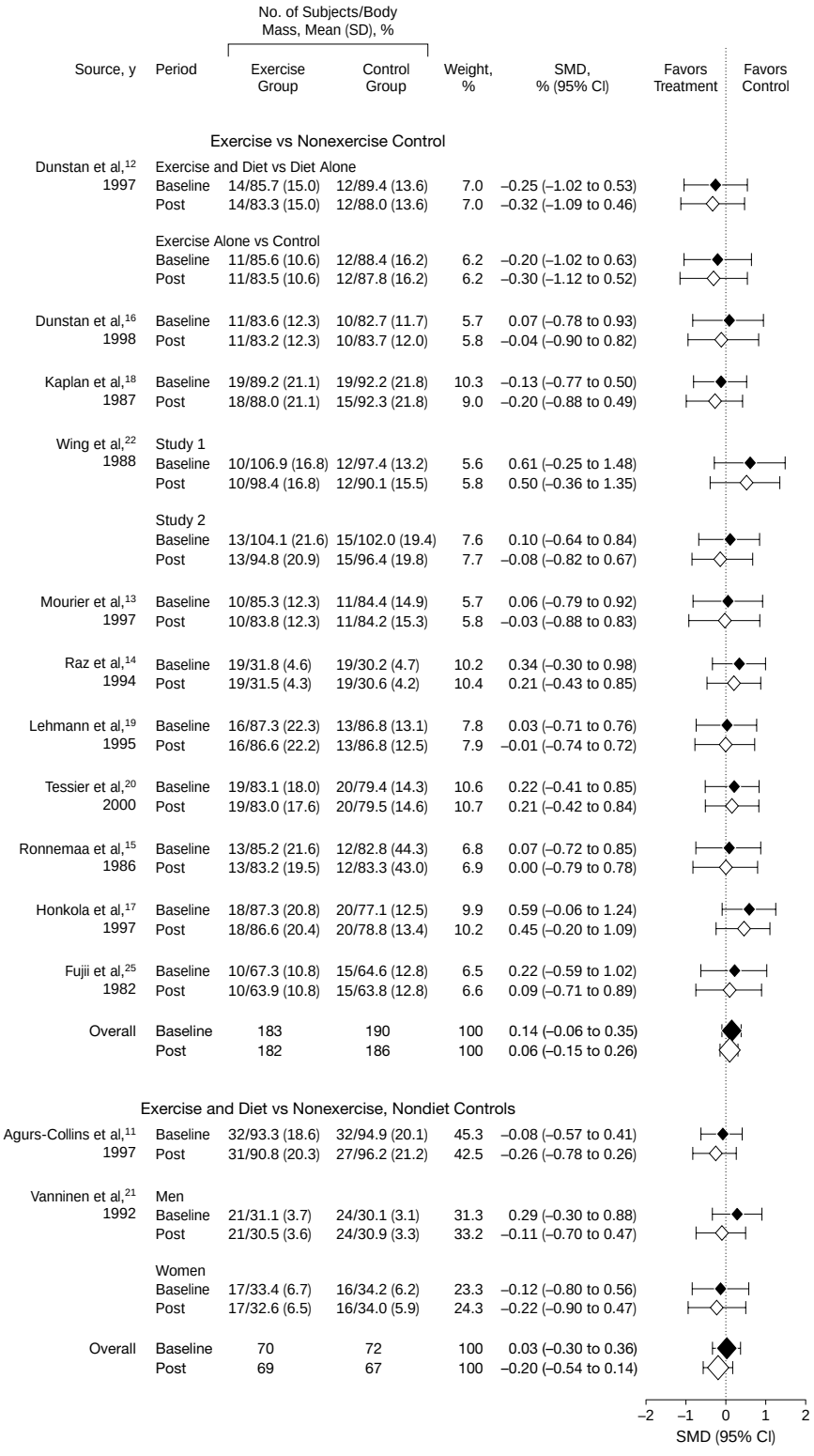


WMD indicates weighted mean difference; CI, confidence interval. Studies are placed in ascending order of the intensity of the exercise intervention and represent the mean difference and the 95% CI for baseline and postintervention measurements. Exercise vs nonexercise control: baseline values, the χ^2 test for heterogeneity was 4.78 ($P=.91$) and the z score for overall effect was 0.45 ($P=.65$); postintervention values, the χ^2 test for heterogeneity was 9.76 ($P=.46$) and the z score for overall effect was 4.01 ($P<.001$). Exercise and diet vs control: baseline values, the χ^2 test for heterogeneity was 6.77 ($P=.03$) and the z score for overall effect was 0.60 ($P=.55$); postintervention values, the χ^2 test for heterogeneity was 0.74 ($P=.69$) and the z score for overall effect was 2.66 ($P=.008$).

lower in the exercise groups when compared with nonexercise control groups. A reduction in HbA_{1c} of this magnitude is clinically significant and close to the difference between conventional and intensive glucose-lowering therapy in the United Kingdom Prospective Diabetes Study (UKPDS). In the UKPDS, subjects receiving intensive treatment with insulin or sulfonylureas had HbA_{1c} averaging 0.9% below the conventional treatment (7.0% vs 7.9%; $P<.001$) and had significant reduction in diabetes-related clinical end points (40.9 vs 46 events per 1000 patient-years; $P=.03$).[48-50] In UKPDS subjects randomized to intensive glycemic control with metformin, HbA_{1c} was only 0.6% lower than with conventional treatment but there were risk reductions of 32% ($P=.002$) for diabetes-related clinical end points and 42% for diabetes-related deaths ($P=.02$).[49] The potential importance of good glycemic control for the reduction of cardiovascular disease risk was supported in a recent meta-regression study, which demonstrated an exponential relationship between fasting glucose concentrations and the incidence of cardiovascular events.[51] We speculate that a greater reduction in cardiovascular complications might be anticipated with exercise than with insulin or sulfonylureas in the UKPDS since, unlike these medications, exercise is associated with other cardioprotective benefits[4,9,32,52-54] and does not cause weight gain.

The meta-regression results suggest that the differences in HbA_{1c} found between the exercise groups and control groups after the intervention were not mediated by differences in weight loss, exercise intensity, or exercise volume. The finding that exercise does not need to reduce body weight to have a beneficial impact on glycemic control is clinically important. Exercise training decreases hepatic and muscle insulin resistance and increases glucose disposal through a number of mechanisms that would not necessarily be associated with body weight changes. The mechanisms were extensively re-

Figure 2. Differences in Body Mass From Baseline to Postintervention



SMD indicates standardized mean difference; CI, confidence interval. Studies are placed in ascending order of the duration of the exercise intervention and represent the mean difference and the 95% CI for baseline and postintervention measurements. Body mass was measured in kilograms except for the studies by Raz et al[14] and Vanninen et al[21] in which body mass index was measured in kilograms divided by meters squared. Exercise vs nonexercise control: baseline values, the χ^2 test for heterogeneity was 5.97 ($P=.92$) and the z score for overall effect was 1.37 ($P=.17$); postintervention values, the χ^2 test for heterogeneity was 5.28 ($P=.95$) and the z score for overall effect was 0.52 ($P=.60$). Exercise and diet vs control: baseline values, the χ^2 test for heterogeneity was 1.13 ($P=.57$) and the z score for overall effect was 0.15 ($P=.88$); postintervention values, the χ^2 test for heterogeneity was 0.13 ($P=.94$) and the z score for overall effect was 1.16 ($P=.24$).

viewed recently by Ivy et al,[55] and include increased postreceptor insulin signaling,[56] increased glucose transporter protein and messenger RNA,[57] increased activity of glycogen synthase[58] and hexokinase,[59] decreased release and increased clearance of free fatty acids,[55] increased muscle glucose delivery due to increased muscle capillary density,[59-61] and changes in muscle composition favoring increased glucose disposal.[59,62,63]

In the present meta-analysis, the exercise interventions produced no statistically significant reduction in body weight. There are several possible explanations for this. First, the exercise interventions were of relatively short duration and involved only moderate amounts of exercise. Second, exercise participants might have reduced their daily physical activities, partially counterbalancing the increased energy expenditure from the exercise intervention. Third, exercise group subjects might have increased their food intake, or decreased it less than control subjects. However, the studies' dietary intake records did not support this possibility. Fourth, in relatively inactive people, increasing physical activity can result in an increase in lean body mass.[64,65] Therefore, it is certainly possible that the amount of weight loss did not fully reflect the amount of fat loss. More accurate measures of body composition, such as computed tomography, magnetic resonance imaging, or

hydrostatic weighing, would be desirable in future studies to precisely measure changes in body composition.

The effect of exercise on HbA_{1c} and body mass was estimated from data obtained across different ethnicities (Northern Europeans, Southern Europeans, blacks, Asian, Middle-Easterners), medication status (no medication, oral hypoglycemic agents, insulin therapy), age groups, and dietary interventions. The results are therefore widely generalizable to middle-aged patients with type 2 diabetes. Because only 1 study[20] included many participants who were older than 65 years, we cannot be certain that the overall results are generalizable to people older than 65 years. Adherence rates to the exercise programs were relatively high in most studies (mean >80%, where reported). Adherence rates lower than these would presumably result in a lesser impact on HbA_{1c}.

There is little research on the effects of resistance training (such as weight lifting) in patients with type 2 diabetes; only 2 resistance exercise studies met inclusion criteria for this analysis. Several relevant resistance training studies were excluded from the present analysis because of the absence of an appropriate control group[66] or the inclusion of nondiabetic participants.[67-75] In the present meta-analysis, the postintervention WMD for HbA_{1c} in the resistance training groups vs nonexercise control groups was similar to aerobic training groups vs nonexercise control groups (–0.64% [95% CI, –1.29% to 0.01%] and –0.67% [95% CI, –1.04% to –0.30%], respectively). Well-designed studies on the effects of resistance training and aerobic training are needed to better understand the impact of increasing muscle mass and reducing fat mass (especially visceral fat) on glycemic control and other metabolic abnormalities.

In conclusion, although the individual trials on the effects of exercise in patients with type 2 diabetes have had partially conflicting results, the current meta-analysis suggests that exercise training reduces HbA_{1c} by approximately 0.66%, an amount that would be expected to reduce the risk of diabetic complications significantly. The studies reviewed in this meta-analysis did not find significantly greater weight loss in the exercise groups compared with the control groups. Therefore, exercise should be viewed as beneficial on its own, not merely as an avenue to weight loss. Future research should include longer interventions with better quantification of body composition changes. In the interim, our analysis using an evidence-based approach adds support to the idea that exercise is a cornerstone of diabetes therapy.

Author Contributions: *Study concept and design:* Boulé, Kenny, Wells, Sigal.
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Analysis and interpretation of data: Boulé, Haddad, Kenny, Wells, Sigal.
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Statistical expertise: Wells.
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Study supervision: Kenny, Wells, Sigal.
Funding/Support: Mr Boulé is supported by a postgraduate scholarship from the Natural Sciences and Engineering Research Council of Canada. Dr Kenny is supported by a Career Scientist Award from the Ontario Ministry of Health and Long Term Care. Dr Sigal is supported in part by a New Investigator Award from the Canadian Institutes of Health Research.
Acknowledgment: We thank Jessie McGowan, MLIS, for her assistance in planning the literature search and Beverley Shea, MSc, for her advice and critical feedback.

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