Physical Activity Advice Only or Structured Exercise Training and Association With HbA_{1c} Levels in Type 2 Diabetes

A Systematic Review and Meta-analysis

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Context Regular exercise improves glucose control in diabetes, but the association of different exercise training interventions on glucose control is unclear.

Objective To conduct a systematic review and meta-analysis of randomized controlled clinical trials (RCTs) assessing associations of structured exercise training regimens (aerobic, resistance, or both) and physical activity advice with or without dietary cointervention on change in hemoglobin A_{1c} (HbA_{1c}) in type 2 diabetes patients.

Data Sources MEDLINE, Cochrane-CENTRAL, EMBASE, ClinicalTrials.gov, LILACS, and SPORTDiscus databases were searched from January 1980 through February 2011.

Study Selection RCTs of at least 12 weeks' duration that evaluated the ability of structured exercise training or physical activity advice to lower HbA_{1c} levels as compared with a control group in patients with type 2 diabetes.

Data Extraction Two independent reviewers extracted data and assessed quality of the included studies.

Data Synthesis Of 4191 articles retrieved, 47 RCTs (8538 patients) were included. Pooled mean differences in HbA_{1c} levels between intervention and control groups were calculated using a random-effects model. Overall, structured exercise training (23 studies) was associated with a decline in HbA_{1c} level (−0.67%; 95% confidence interval [CI], −0.84% to −0.49%; I^2, 91.3%) compared with control participants. In addition, structured aerobic exercise (−0.73%; 95% CI, −1.06% to −0.40%; I^2, 92.8%), structured resistance training (−0.57%; 95% CI, −1.14% to −0.01%; I^2, 92.5%), and both combined (−0.51%; 95% CI, −0.79% to −0.23%; I^2, 67.5%) were each associated with declines in HbA_{1C} levels compared with control participants. Structured exercise durations of more than 150 minutes per week were associated with HbA_{1c} reductions of 0.89%, while structured exercise durations of 150 minutes or less per week were associated with HbA_{1C} reductions of 0.36%. Overall, interventions of physical activity advice (24 studies) were associated with lower HbA_{1c} levels (−0.43%; 95% CI, −0.59% to −0.28%; I^2, 62.9%) compared with control participants. Combined physical activity advice and dietary advice was associated with decreased HbA_{1c} (−0.58%; 95% CI, −0.74% to −0.43%; I^2, 57.5%) as compared with control participants. Physical activity advice alone was not associated with HbA_{1c} changes.

Conclusions Structured exercise training that consists of aerobic exercise, resistance training, or both combined is associated with HbA_{1c} reduction in patients with type 2 diabetes. Structured exercise training of more than 150 minutes per week is associated with greater HbA_{1c} declines than that of 150 minutes or less per week. Physical activity advice is associated with lower HbA_{1c}, but only when combined with dietary advice.

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Exercise is a cornerstone of diabetes management, along with dietary and pharmacological interventions.[1,2] Current guidelines recommend that patients with type 2 diabetes should perform at least 150 minutes per week of moderate-intensity aerobic exercise and should perform resistance exercise 3 times per week.[1,2] Previous meta-analyses[3-6] demonstrated that structured exercise training including aerobic and resistance exercises reduces hemoglobin A_{1c} (HbA_{1c}) levels by approximately 0.6%. However, only 1 previous review separately analyzed associations of aerobic exercise, resistance training, and the combination of aerobic exercise and resistance training on change in HbA_{1c} levels.[5] Since publication of this meta-analysis, 2 large randomized trials[7,8] were published that reported contradictory findings regarding the types of

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CME available online at www.jamaarchivescme.com and questions on p 1817.

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structured exercise associated with declines in HbA_{1c} levels. Sigal et al[7] found that aerobic or resistance exercise training alone improved glycemic control but the effects were more pronounced with both combined. In contrast, Church et al[8] observed that only the combination, but not aerobic and resistance training alone, reduced HbA_{1c} levels.

In contrast to structured exercise training, physical activity is defined as any bodily movement produced by skeletal muscle contractions resulting in increased energy expenditure.[9] Although structured exercise training may be available to a subset of patients with type 2 diabetes, physical activity advice is more feasible and should be offered to most patients with type 2 diabetes. However, meta-analyses have not been performed to determine whether physical activity advice is associated with similar declines in HbA_{1c} as compared with those associated with structured exercise. This study consists of a systematic review with meta-analysis of randomized controlled clinical trials (RCTs) on the associations of structured exercise training and physical activity advice, respectively, on changes in HbA_{1c} levels in patients with type 2 diabetes. Structured exercise training is categorized according to whether it consists of aerobic exercise, resistance training, or a combination of both.

METHODS

Search Strategy and Study Selection

We searched the following electronic databases covering the period from January 1980 through February 2011: MEDLINE (accessed by PubMed), Cochrane Central Register of Controlled Trials, EMBASE, ClinicalTrials.gov, SPORTdiscus, and LILACS. In addition, we searched the references of published studies manually. The initial search comprised the terms *exercise*, *diabetes mellitus*, *physical activity*, and related entry terms associated with a high-sensitivity strategy for the search of RCTs,[10] and was not limited by language. The complete search strategy used for the PubMed database is shown in eBox 1 (available at http://www.jama.com). Only eligible full texts in English, Portuguese, or Spanish were considered for review. This systematic review and meta-analysis is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[11]

Eligibility Criteria

We included RCTs that compared any category of structured exercise training (aerobic, resistance, or a combination of both) or physical activity advice with a control group of patients with type 2 diabetes older than 18 years, that evaluated HbA_{1c} as an outcome, and reported means or differences between means and respective dispersion values of HbA_{1c} at baseline and after the intervention. Structured exercise training was defined as an intervention in which patients were engaged in planned, individualized, and supervised exercise programs. Physical activity advice was defined as an intervention in which patients were partially or not engaged in supervised exercise training, but received formal instructions to exercise regularly with or without an individualized exercise prescription. Eligible studies included only individuals able to exercise, with no clinical manifestations limiting physical activity. Exclusion criteria are as follows: (1) studies of patients with type 1 diabetes or gestational diabetes; (2) RCTs that did not provide information regarding the associations of the intervention with HbA_{1c} in the experimental group, the control group, or both; (3) duplicate publications or substudies of included trials; and (4) studies with less than 12 weeks of follow-up.

Data Extraction

Titles and abstracts of retrieved articles were independently evaluated by 2 investigators (D.U. and P.A.B.R.). Reviewers were not blinded to authors, institutions, or manuscript journals. Abstracts that did not provide enough information regarding the inclusion and exclusion criteria were retrieved for full-text evaluation. Reviewers independently evaluated full-text articles and determined study eligibility. Disagreements were solved by consensus and if disagreement persisted, by a third reviewer (B.D.S.). To avoid possible double counting of patients included in more than 1 report by the same authors or working groups, patient recruitment periods were evaluated and if necessary, authors were contacted for clarification. The corresponding author was contacted as needed to obtain data not included in the published report.

Two reviewers (D.U. and P.A.B.R.) independently conducted data extraction. Disagreements were solved by consensus or by a third reviewer (B.D.S.). Adherence to protocols, dropout rates, and adverse events were also extracted.

Assessment of Risk of Bias

Risk of bias was evaluated according to the PRISMA recommendation.[12] Study quality assessment included adequate sequence generation, allocation concealment, blinding of outcomes assessors, use of intention-to-treat analysis, and description of losses and exclusions. Studies without clear descriptions of an adequate sequence generation or how the allocation list was concealed were considered not to have fulfilled these criteria. Quality assessment was independently performed by 2 unblinded reviewers (D.U. and P.A.B.R) and disagreements were solved by consensus or by a third reviewer (B.D.S). The κ agreement rate between reviewers was $\kappa = 0.96$ for quality assessment.

Data Analyses

Absolute changes in HbA_{1c} were reported as differences between arithmetic means before and after interventions. Data from intention-to-treat analyses were entered whenever available in included RCTs.

Pooled-effect estimates were obtained by comparing the least squares mean percentage change from baseline to the end of the study for each group, and were expressed as the weighted mean difference between groups. Calculations were performed using a random-effects model. Four comparisons were made with each group being compared with a no-intervention (control) group: structured aerobic exercise training, structured resistance exercise training, structured combined aerobic/resistance exercise training, and physical activity advice. An α value=.05 was considered statistically significant.

Statistical heterogeneity of the treatment effect among studies was assessed using Cochran Q test, a threshold P value of .1 was considered statistically significant, and the inconsistency I^2 test in which values greater than 50% were considered indicative of high heterogeneity.[13] We explored heterogeneity between studies using 3 strategies. First, we reran the meta-analyses removing each study at a time to check if a particular study was explaining heterogeneity. Second, stepwise meta-regression analyses were carried out. Using univariate meta-regression models, we assessed clinical and methodological variables that influenced the association of exercise with HbA_{1c} levels. Likewise, similar procedures were undertaken to analyze particular variables that could explain heterogeneity in the physical activity advice meta-analysis. Thereafter, based on univariate meta-regression analyses, we constructed 4 multivariate models including baseline HbA_{1c} plus exercise frequency (defined as the number of exercise sessions per week [model 1]); baseline HbA_{1c} plus total exercise time spent in the program (defined as the cumulative product of exercise frequency, session duration, and number of weeks of training [model 2]); baseline HbA_{1c} plus a variable indicating total exercise time of 150 minutes or less per week or more than 150 minutes per week [model 3]); and baseline HbA_{1c} plus exercise intensity plus total exercise time spent in the program (model 4). Model 4 included covariates that were not significant in univariate regression, but were included based on clinical judgment of their importance. We evaluated the goodness of fit of each model using the adjusted R^2, which denotes the proportion of between-study variation explained by the covariates.[14,15] Third, we performed sensitivity analyses to evaluate subgroups of studies most likely to yield valid estimates of the intervention based on prespecified relevant clinical information and on meta-regression analyses. For the structured exercise training meta-analysis results, we used a cutoff of 150 minutes per week to stratify studies according to their weekly amounts of exercise. RCTs evaluating physical activity advice were grouped according to the presence vs absence of a simultaneous dietary recommendation.

Because some studies compared multiple exercise interventions with a single control group, we split this shared group into 2 or more groups with smaller sample sizes weighted in relation to different exercise interventions. This approach was applied in order to have reasonably independent comparisons and overcome a unit-of-analysis error for studies that could contribute to multiple and correlated comparisons, as suggested by the *Cochrane Handbook for Systematic Reviews of Interventions*.[13] Imputation and/or transformation methods were used for few studies that showed results as confidence intervals (CIs) or interquartile ranges.[16]

Publication bias was assessed using a contour-enhanced funnel plot of each trial's effect size against the standard error.[17] Funnel plot asymmetry was evaluated by Begg and Egger tests, and a significant publication bias was considered if the P value was less than .10. The trim-and-fill computation was used to estimate the effect of publication bias on the interpretation of results.[18,19] All analyses were conducted using Stata software version 11.0 (Stata Inc, College Station, Texas).

RESULTS

Description of Studies

From 4191 potentially relevant citations retrieved from electronic databases and searches of reference lists, 47 RCTs (including 23 RCTs of structured exercise training and 24 RCTs of physical activity advice) met the inclusion criteria. A flow diagram of search and selection is shown in eFigure 1. Included studies had a total of 8538 patients. Of these, 848 patients were included in studies of structured aerobic exercise training, 261 in structured resistance exercise studies, 404 in structured combined aerobic/resistance exercise training studies, and 7025 in physical activity advice studies. Characteristics of these studies are summarized in TABLE 1 and TABLE 2.

Fifteen studies of structured exercise reported data on adherence. Of these, 14 trials reported adherence rates of more than 75%. Dropout rates were less than 20% in all but 2 of the 21 studies that reported this measure (Table 1). Adherence rates were not reported for the physical activity studies because of lack of accuracy (ie, self-reported data and reliance on patient recall). Dropout rates were less than 20% for 19 of the 24 physical activity intervention studies (Table 2).

No major adverse effects were reported (eTable 1). Minor adverse events for the structured exercise interventions and physical activity interventions most commonly included cardiovascular disease events that were not related to the intervention and musculoskeletal injury or discomfort (eTable 1). One study of a physical activity intervention included a high rate of hypoglycemia. Of 47 RCTs, 30 studies did not report data on adverse events (eTable 1).

Quality (Risk of Bias) and Publication Bias Assessment

Among the included studies, 36% presented adequate sequence generation (17 of 47), 17% reported allocation concealment (8 of 47), 17% had blinded assessment of outcomes (8 of 47), 96% described losses to follow-up and exclusions (45 of 47), and 13% used the intention-to-treat principle for statistical analyses (6 of 47) (eTable 2 and eTable 3).

Contour-enhanced funnel plots and the Egger regression test suggested an asymmetry in the analysis of structured exercise training ($P=.02$). However, the trim-and-fill computation revealed that publication bias did not interfere with the interpretation of results (eFigure 2, panel A). Regarding physical activity advice studies, neither the Egger regression test nor the trim-and-fill computation showed any publication bias ($P>.10$) (eFigure 2, panel B).

Association of Interventions With the Primary End Point (HbA_{1c})

Structured Exercise Training: Aerobic, Resistance, or Both. The overall association of any structured exercise vs control with absolute HbA_{1c} reduction

Table 1. Characteristics of the Structured Exercise Studies Included

Source	Age, Mean (SD), y[a]	Control Group Intervention	Dietary Cointervention	Chronic Comorbidities	Frequency, Sessions/wk	Weekly Duration, min[b]	Program Duration, wk	Adherence to Exercise Training, %	Dropouts, %
Aerobic training									
Bjorgaas et al,[20] 2005	57 (8)	Diet advice care, no exercise	Yes	Hypertension	2	90	12	77	20
Church et al,[8] 2010	54 (9)	Weekly stretching classes	No	Cardiovascular diseases, neuropathy, cancer	3	No fixed duration; target, 150	≈39	NR	Aerobic, 4; control, 10
Cuff et al,[21] 2003	59 (6)	Usual care	No	NR	3	75	16	92	0
Dela et al,[22] 2004	52 (7)	Usual care	No	None	5	30-40	12	100	NR
Giannoupolou et al,[23] 2005	58 (6)	Dietary planning, no exercise	Yes	NR	3-4	60	14	NR	17
Goldhaber-Fiebert et al,[24] 2003	59 (10)	Nutrition classes, no exercise	Yes	Hypertension, dyslipidemia	3	60	12	NR	Aerobic, 17.5; control, 20
Kadoglou et al,[25] 2007	62 (5)	Usual care	No	Hypertension	4	30-45	26	92	Aerobic, 3; control, 10
Kadoglou et al,[26] 2007	59 (8)	Usual care	No	Hypertension	4	45-60	16	NR	Aerobic, 6.5; control, 13
Kadoglou et al,[27] 2010	59 (8)	One subgroup maintained habitual activities; other received add-on rosiglitazone therapy	No	NR	4	30-45	52	88	Aerobic, 16; control, 12; aerobic plus rosiglitazone, 8; control plus rosiglitazone, 8
Lambers et al,[28] 2008	52 (8)	Usual care	No	No major complications	3	50	12	≥85	Aerobic, 5; control, 11
Ligtenberg et al,[29] 1997	62 (5)	Educational program, no exercise instructions	No	No major complications	3	50	12	97	Aerobic, 17; control, 7
Middlebrooke et al,[30] 2006	63 (8)	Usual care	No	Neuropathy, hypertension	3	30	26	99	Aerobic, 24; control, 0
Raz et al,[31] 1994	57 (7)	Lifestyle maintenance	No	Obesity, hypertension, CAD, PAD	3	45	12	68	Aerobic, 5; control, 5
Ribeiro et al,[32] 2008	55 (10)	Sedentary lifestyle	No	None	3	40	16	≥75	0
Sigal et al,[7] 2007	54 (7)	Sedentary habitual lifestyle	No	Hypertension, depression	3	45	26	80	Aerobic, 20; control, 5
Sridhar et al,[33] 2010	61 (3)	Sedentary habitual lifestyle	No	Hypertension	5	30	52	NR	NR
Vancea et al,[34] 2009	57 (6)	Spontaneous exercise counseling	No	NR	3 or 5	30	20	NR	0
Verity and Ismail,[35] 1989	59 (4)	Lifestyle maintenance	No	Hypertension	3	60-90	16	NR	0

(continued)

Table 1. Characteristics of the Structured Exercise Studies Included (continued)

Source	Age, Mean (SD), y[a]	Control Group Intervention	Dietary Cointervention	Chronic Comorbidities	Frequency, Sessions/wk	Weekly Duration, min[b]	Program Duration, wk	Adherence to Exercise Training, %	Dropouts, %
Resistance training									
Castaneda et al,[36] 2002	66 (8)	Usual care	No	Cardiovascular disease, hypertension	3	≈35 min, 5 exercises, 15 sets	16	90	Resistance, 6; control, 0
Church et al,[8] 2010	57 (9)	Weekly stretching classes	No	Cardiovascular diseases, neuropathy, cancer	3	9 Exercises, 21 sets	≈39	NR	Resistance, 5; control, 10
Dunstan et al,[37] 2002	67 (5)	Dietary intervention and stretching classes	Yes	Hypertension, arthritis, neuropathy, retinopathy	3	≈45 min, 9 exercises, 27 sets	26	88	Resistance, 16; control, 24
Sigal et al,[7] 2007	55 (7)	Sedentary habitual lifestyle	No	Hypertension, depression	3	7 Exercises, 21 sets	26	85	Resistance, 11; control, 5
Combined training									
Balducci et al,[38] 2004	61 (9)	Lifestyle maintenance	No	Hypertension	3	60	52	>90	Combined, 18; control, 9
Church et al,[8] 2010	55 (8)	Weekly stretching classes	No	Cardiovascular diseases, neuropathy, cancer	3	No fixed time for aerobic; 9 sets of resistance exercises	≈39	NR	Combined, 5; control, 10
Cuff et al,[21] 2003	63 (7)	Usual care	No	NR	3	75	16	92	0
Lambers et al,[28] 2008	56 (10)	Usual care	No	No major complications	3	50	12	≥85	Combined, 11; control, 11
Loimaala et al,[39] 2003	53 (5)	Usual care	No	Hypertension	4	≥30 Aerobic; 24 sets of resistance exercises	52	NR	Combined, 4; control, 0
Sigal et al,[7] 2007	53 (7)	Sedentary habitual lifestyle	No	Hypertension, depression	3	Aerobic and resistance programs	26	86	Combined, 13; control, 5
Tessier et al,[40] 2000	69 (5)	Lifestyle maintenance	No	NR	3	40	16	>90	13

Abbreviations: CAD, coronary artery disease; NR, not reported; PAD, peripheral arterial disease.
[a] Age data represent weighted mean (SD) between intervention and control groups. In studies with more than 2 interventions, age data represent mean (SD) of each intervention group.
[b] Exercise characteristics do not include warm-up or cool-down periods.

(23 studies; 1533 patients) was −0.67% (95% CI; −0.84% to −0.49%; I^2, 91.3%; P for heterogeneity, <.001) (FIGURE 1). Eighteen studies (848 patients) demonstrated that structured aerobic exercise training was associated with an absolute HbA_{1c} reduction of 0.73% (95% CI, −1.06% to −0.40%; I^2, 92.8%; P for heterogeneity <.001) as compared with control.

Four articles (261 patients) demonstrated that structured resistance exercise training was associated with a decline in absolute HbA_{1c} of 0.57% (95% CI, −1.14% to −0.01%; I^2, 92.5%; P for heterogeneity <.001) as compared with control.

Seven articles (404 patients) demonstrated that the combination of aerobic and resistance exercise were associated with an HbA_{1c} reduction of 0.51% (95% CI, −0.79% to −0.23%; I^2, 67.5%; P for heterogeneity <.001) as compared with control participants.

In univariate meta-regression, baseline HbA_{1c} level, exercise frequency, total time spent in exercise during the study, and weekly exercise duration of more than 150 minutes per week or of 150 minutes or less per week partially explained heterogeneity between structured exercise training studies (eTable 4). These covariates also were significant in the multivariate meta-regression models (eTable 4). Structured exercise of more than 150 minutes per week (18 observations, 826 patients) was associated with an absolute HbA_{1c} reduction of 0.89% (95% CI, −1.26% to −0.51%; I^2, 91.4%; P for heterogeneity <.001). Structured exercise of 150 minutes or less per week (12 observations, 687 patients) was associated with an absolute reduction of 0.36% of HbA_{1c} (95% CI, −0.50% to −0.23%; I^2, 78.6%; P for heterogeneity <.001) (eFigure 3). When studies were omitted individually from the meta-analysis to assess possible individual influences on results, heterogeneity and weighted mean differences were unchanged.

Physical Activity Advice. Twenty-four articles comparing physical activity

Table 2. Characteristics of the Physical Activity Advice Studies Included

Source	Age, Mean (SD), y[a]	Control Group Intervention	Chronic Comorbidities	Frequency, Sessions/wk	Program Duration, wk	Weekly Duration, min	Preintervention	Dropouts, %
Dietary cointervention								
Aas et al,[41] 2005	56	Insulin treatment, no lifestyle intervention	NR	2	52	120	No	PA, 23; control, 25
Agurs-Collins et al,[42] 1997	62 (6)	Usual care, nutrition information	NR	3	26	90	No	PA, 6; control, 12
Christian et al,[43] 2008	53 (11)	Diabetes, diet, and exercise materials	No major complications	NR	52	NR	No	PA, 9; control, 13
Dasgupta et al,[44] 2006	52 (NR)	Individualized dietary counseling	Cardiovascular disease	3	24	135	Yes	24
Di Loreto et al,[45] 2003	62 (10)	Usual care, dietary counseling	No major complications	NR	104	>10 MET-h	No	PA, 2; control, 0
Hordern et al,[46] 2009	56 (10)	Usual care	Myocardial dysfunction	NR	52	≥150	Yes	PA, 21; control, 21
Kim et al,[47] 2006	54 (9)	Basic dietary education	Hypertension	30	26	150	No	0
Jakicic et al,[48] 2009	59 (7)	Diabetes support, education	Hypertension, cardiovascular disease	5	52	175	Yes	PA, 3; control, 4
Mayer Davis et al,[49] 2004	61 (9)	Usual care	Hypertension	NR	52	150	Yes	19
Ménard et al,[50] 2005	55 (8)	Usual care	Hypertension, dyslipidemia	3	52	45	Yes	PA, 6; control, 3
Vanninen et al,[51] 1992	53 (7)	Basic health education	Hypertension, CAD	3	52	158	Yes	0
Wing et al,[52] 1988	56 (7)	Health habits education, self-monitoring	No major complications	3	52	NR	Yes	0
No dietary cointervention								
Brun et al,[53] 2008	60 (10)	Repeated health evaluations	No major complications	2	52	75	Yes	0
Cheung et al,[54] 2009	60 (8)	Lifestyle maintenance	NR	5	16	150	Yes	PA, 5; control, 11
Diedrich et al,[55] 2010	56 (12)	Education, diabetes self-management	NR	NR	12	NR	Yes	PA, 41; control, 38
Kim et al,[56] 2006	55 (7)	Usual care, basic dietary education	Hypertension	3-5	12	90-150	No	0
Kirk et al,[57] 2003	58 (8)	Usual care	Hypertension	5	26	150	No	PA, 9; control, 11
Kirk et al,[58] 2009	61 (10)	Usual care	NR	5	52	150	No	PA, 9; control, 9
Krousel-Wood et al,[59] 2008	57 (10)	Self-management, education, exercise encouragement	No major complications	5	12	150	No	PA, 18; control, 20
Leehey et al,[60] 2009	66	Usual care, diabetes education	Chronic kidney disease, obesity	3	24	≥120	Yes	PA, 0; control, 33
Rönnemaa et al,[61] 1986	53	Usual care	Hypertension, retinopathy	5-7	16	225-315	No	PA, 13; control, 20
Samaras et al,[62] 1997	61 (8)	Usual care	NR	NR	26	NR	Yes	0
Tudor-Locke et al,[63] 2004	53 (5)	Usual care	Hypertension, dyslipidemia, allergies	NR	16	NR	Yes	PA, 20; control, 23
Van Rooijen et al,[64] 2004	55	Relaxation intervention	Hypertension, arthritis	5	12	225	No	PA, 6; control, 4

Abbreviations: CAD, coronary artery disease; MET, metabolic equivalent task; NR, not reported; PA group, physical activity advice group.
[a] Age data represent weighted mean (SD) between intervention and control groups.

advice (3529 patients) vs control (3496 patients) demonstrated that physical activity advice was associated with a decline in HbA_{1c} of 0.43% (95% CI, −0.59% to −0.28%; I^2, 62.9%; *P* for heterogeneity <.001) (**Figure 2**).

Covariates used in univariate analysis did not explain heterogeneity (eTable 4). Similarly, a multivariate meta-regression using baseline HbA_{1c} and dietary recommendation (model 1) as covariates did not explain the between-studies variance (overall, *P*=.17).

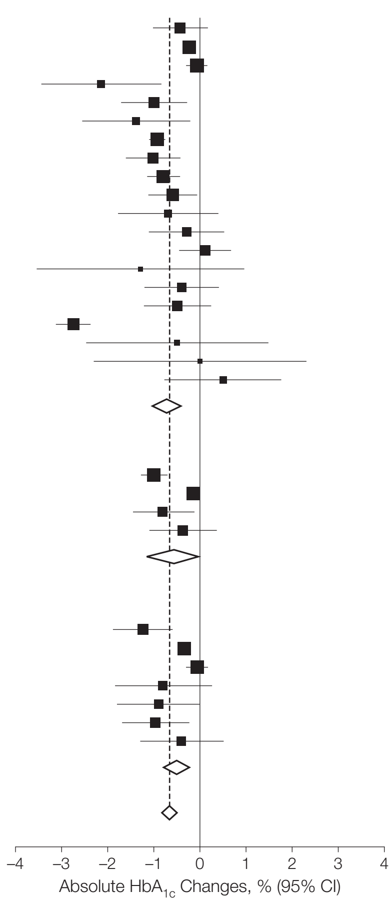
In sensitivity analyses, physical activity associated with dietary advice (12 studies, 6313 patients) was associated with a 0.58% absolute HbA_{1c} reduction (95% CI, −0.74% to −0.43%; I^2, 57.5%; *P* for heterogeneity=.007) as compared with control. Physical activity advice alone (14 studies, 712 patients) was not associated with HbA_{1c} changes as compared with control (Figure 2). When studies were individually omitted from the meta-analysis, heterogeneity and weighted mean differences were unchanged.

COMMENT

Our results demonstrate that in patients with type 2 diabetes, structured aerobic, resistance, or combined exercise training is associated with a HbA_{1c} decline of −0.67%. Our analyses also demonstrate that structured exercise duration of more than 150 minutes per week was associated with greater benefit (0.89% reduction in HbA_{1c}) than structured exercise duration of 150 minutes or less per week (0.36% reduction in HbA_{1c}). Structured exercise

Figure 1. Absolute Changes in HbA_{1c} of Individual Studies of Structured Exercise Training vs No Intervention

Source	No. of Patients: Intervention	No. of Patients: Control	HbA_{1c} Weighted Mean Difference, % (95% CI)	Weight, %
Aerobic training				
Bjørgaas et al,[20] 2005	11	11	−0.44 (−1.03 to 0.15)	3.46
Church et al,[8] 2010	72	41	−0.23 (−0.30 to −0.16)	5.77
Cuff et al,[21] 2003	9	9	−0.07 (−0.28 to 0.14)	5.37
Dela et al,[22] 2004	14	10	−2.14 (−3.43 to −0.86)	1.38
Giannopoulou et al,[23] 2005	11	11	−1.00 (−1.70 to −0.30)	2.96
Goldhaber-Fiebert et al,[24] 2003	33	28	−1.40 (−2.56 to −0.24)	1.61
Kadoglou et al,[25] 2007	29	27	−0.93 (−1.08 to −0.78)	5.57
Kadoglou et al,[26] 2007	28	26	−1.02 (−1.59 to −0.45)	3.55
Kadoglou et al,[27] 2010[a]	22	21	−0.80 (−1.15 to −0.45)	4.68
Kadoglou et al,[27] 2010[b]	23	23	−0.59 (−1.11 to −0.07)	3.81
Lambers et al,[28] 2008	18	11	−0.70 (−1.78 to 0.38)	1.78
Ligtenberg al,[29] 1997	25	26	−0.30 (−1.11 to 0.51)	2.57
Middlebrooke et al,[30] 2006	22	30	0.10 (−0.45 to −0.65)	3.64
Raz et al,[31] 1994	19	19	−0.30 (−3.53 to 0.93)	0.54
Ribeiro et al,[32] 2008	11	10	−0.40 (−1.19 to 0.39)	2.61
Sigal et al,[7] 2007	60	63	−0.50 (−1.22 to 0.22)	2.88
Sridhar et al,[33] 2010	55	50	−2.76 (−3.13 to −2.39)	4.60
Vancea et al,[34] 2009[c]	14	17	−0.50 (−2.47 to 1.47)	0.68
Vancea et al,[34] 2009[d]	9	17	0.00 (−2.30 to 2.30)	0.51
Verity and Ismail,[35] 1989	5	5	0.50 (−0.75 to 1.75)	1.43
All aerobic training I^2=92.8%; *P* for heterogeneity <.001			−0.73 (−1.06 to −0.40)	59.41
Resistance training				
Castaneda et al,[36] 2002	29	31	−1.00 (−1.27 to −0.73)	5.11
Church et al,[8] 2010	73	41	−0.15 (−0.22 to −0.08)	5.78
Dunstan et al,[37] 2002	16	13	−0.80 (−1.46 to −0.14)	3.17
Sigal et al,[7] 2007	64	63	−0.37 (−1.08 to 0.34)	2.92
All resistance training I^2=92.5%; *P* for heterogeneity <.001			−0.57 (−1.14 to −0.01)	16.68
Combined training				
Balducci et al,[38] 2004	51	53	−1.24 (−1.88 to 0.60)	3.24
Church et al,[8] 2010	76	41	−0.34 (−0.41 to −0.27)	5.77
Cuff et al,[26] 2003	10	9	−0.07 (−0.29 to 0.15)	5.31
Lambers et al,[28] 2008	17	11	−0.80 (−1.84 to 0.24)	1.86
Loimaala et al,[39] 2003	24	25	−0.90 (−1.80 to −0.00)	2.26
Sigal et al,[7] 2007	64	63	−0.97 (−1.69 to −0.25)	2.86
Tessier et al,[40] 2000	19	20	−0.40 (−1.29 to 0.49)	2.28
All combined training I^2=67.5%; *P* for heterogeneity=.005			−0.51 (−0.79 to −0.23)	23.61
Overall I^2=91.3%; *P* for heterogeneity <.001			−0.67 (−0.84 to −0.49)	100.00



CI indicates confidence interval. Changes in hemoglobin A_{1c} (HbA_{1c}) (absolute values) of individual studies included in the meta-analysis of structured exercise training (aerobic exercise, resistance training, and combined aerobic/resistance exercise) vs no intervention in patients with type 2 diabetes. Studies that included more than 1 modality or different training protocols within a same type of structured exercise training were evaluated as separate observations. Weights are from random-effects analysis.

[a] Exercise and control subgroups.
[b] Exercise and control subgroups with rosiglitazone treatment as cointervention.
[c] Subgroup with exercise frequency of 3 sessions per week.
[d] Subgroup with exercise frequency of 5 sessions per week.

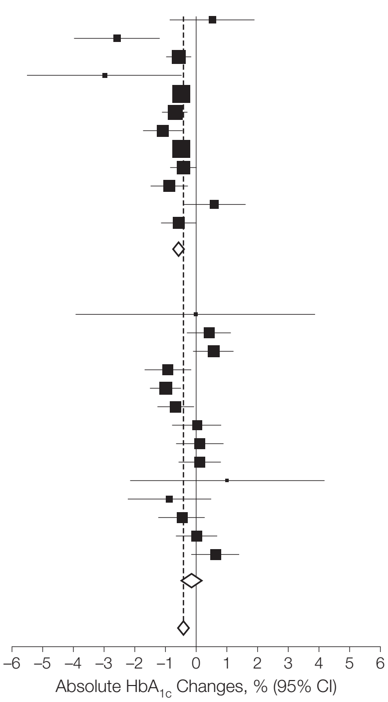
training was associated with a more pronounced HbA_{1c} reduction compared with physical activity advice. A recommendation to increase physical activity was beneficial (0.43% HbA_{1c} reduction), but only if combined with dietary recommendations.

This systematic review and meta-analysis of RCTs demonstrates important findings regarding the prescription of structured exercise training. First, aerobic, resistance, and combined training are each associated with HbA_{1c} decreases, and the magnitude of this reduction is similar across the 3 exercise modalities. Interestingly, the weighted mean difference of −0.67% in HbA_{1c} levels favorably compares with the decline in HbA_{1c} associated with the addition of noninsulin antidiabetic drugs to maximal metformin therapy.[65] Second, our findings demonstrate that structured exercise of more than 150 minutes per week is associated with greater declines in HbA_{1c} than structured exercise of 150 minutes or less per week in patients with type 2 diabetes. This finding is important because the current guideline-recommended exercise duration is at least 150 minutes per week.[1,2] Although high-intensity exercise has been previously shown to have an association with HbA_{1c} reduction,[4] our findings did not demonstrate that more intensive exercise was associated with greater declines in HbA_{1c}. It is important to mention that, due to a great variability in exercise intensity descriptions, we used an intensity rating as previously reported.[5] Baseline HbA_{1c} was one of the variables explaining the heterogeneity between studies, which underscores the greater magnitude of intervention effects in HbA_{1c} among individuals with baseline HbA_{1c} levels of greater than 7%, when compared with those with baseline HbA_{1c} levels of less than 7%.[7,8,66,67]

To our knowledge, this is the first systematic review to assess the association between physical activity advice interventions and glycemic control. Our results showed that physical activity advice was associated with lesser declines in HbA_{1c} than the studies evalu-

Figure 2. Absolute Changes in HbA_{1c} of Individual Studies of Physical Activity Advice vs No Intervention

Source	No. of Patients: Intervention	No. of Patients: Control	HbA_{1c} Weighted Mean Difference, % (95% CI)	Weight, %
Physical activity advice with dietary cointervention				
Aas et al,[41] 2005	10	9	0.50 (−0.86 to 1.86)	1.18
Argurs-Collins et al,[42] 1997	32	32	−2.60 (−3.98 to −1.22)	1.15
Christian et al,[43] 2008	141	132	−0.60 (−1.00 to −0.20)	6.44
Dasgupta et al,[44] 2006	21	21	−3.00 (−5.51 to −0.49)	0.37
Di Loreto et al,[45] 2003	182	158	−0.50 (−0.62 to −0.38)	10.53
Hordern et al,[46] 2009	88	88	−0.70 (−1.08 to −0.32)	6.70
Kim et al,[47] 2006	32	10	−1.10 (−1.72 to −0.48)	4.04
Jakicac et al,[48] 2007	2486	2575	−0.50 (−0.56 to −0.44)	11.13
Mayer-Davis et al,[49] 2004	49	56	−0.44 (−0.87 to −0.01)	6.11
Ménard et al,[50] 2005	34	35	−0.90 (−1.49 to −0.31)	4.33
Vanninen et al,[51] 1992	38	40	0.57 (−0.43 to 1.57)	2.00
Wing et al,[52] 1998	13	15	−0.60 (−1.16 to −0.04)	4.62
All advice with dietary cointervention; I^2 = 57.5%; *P* for heterogeneity = .007			−0.58 (−0.74 to −0.43)	58.60
Physical activity advice alone				
Brun et al,[53] 2008	13	12	−0.04 (−3.93 to 3.85)	0.16
Cheung et al,[54] 2009	20	17	0.40 (−0.29 to −1.09)	3.49
Diedrich et al,[55] 2010	27	26	0.54 (−0.11 to 1.19)	3.82
Kim and Kang,[56] 2006[a]	22	23	−0.94 (−1.68 to −0.20)	3.19
Kim and Kang,[56] 2006[b]	28	23	−1.02 (−1.51 to −0.53)	5.28
Kirk et al,[57] 2003	26	31	−0.68 (−1.26 to −0.10)	4.40
Kirk et al,[58] 2009[c]	47	35	0.00 (−0.79 to 0.79)	2.88
Kirk et al,[58] 2009[d]	51	35	0.10 (−0.65 to 0.85)	3.13
Krousel-Wood et al,[59] 2008	37	39	0.10 (−0.56 to 0.76)	3.71
Leehey et al,[60] 2009	7	4	1.00 (−2.16 to 4.16)	0.24
Rönnemaa et al,[61] 1986	13	12	−0.90 (−2.25 to 0.45)	1.20
Samaras et al,[62] 1997	13	13	−0.49 (−1.24 to 0.26)	3.10
Tudor-Locke et al,[63] 2004	24	23	0.00 (−0.66 to 0.66)	3.72
van Rooijen et al,[64] 2004	75	74	0.62 (−0.14 to 1.38)	3.09
All advice alone; I^2 = 61.2%; *P* for heterogeneity = .001			−0.16 (−0.50 to 0.18)	41.40
Overall; I^2 = 62.9%; *P* for heterogeneity <.001			−0.43 (−0.59 to −0.28)	100.00



CI indicates confidence interval. Changes in hemoglobin A_{1c} (HbA_{1c}) for individual studies included in the meta-analysis of physical activity advice vs no intervention in patients with type 2 diabetes according to the association or not of dietary intervention. Two studies provided more than 1 observation and were analyzed as distinct interventions to deliver physical activity. Weights are from random-effects analysis.
[a] Subgroup received advice in printed material.
[b] Subgroup received advice through a Web system.
[c] Subgroup received advice from an individual.
[d] Subgroup received advice in written form.

ating structured exercise training. These results are consistent with a recent RCT demonstrating that supervised aerobic and resistance exercise training were more efficacious than physical activity advice alone in achieving declines in HbA_{1c}.[68]

This review demonstrates that physical activity advice is only associated with HbA_{1c} reduction when accompanied by a dietary cointervention. This highlights the need for a combined recommendation of these lifestyle interventions. Despite the fact that diet alone could improve glycemic control, most RCTs in our meta-analysis that evaluated physical activity plus a dietary intervention included a control group of a dietary intervention. Because HbA_{1c} reduction in type 2 diabetes is associated with improved insulin resistance, and both exercise training/physical activity and body weight reduction induced by low-calorie diets[1] have distinct mechanisms to elicit these effects, it is expected that these interventions applied together would result in greater metabolic effects.[2,69] Therefore, patients with type 2 diabetes should receive dietary recommendations in combination with advice to increase physical activity. Taken together, these results provide important information for clinical practice.[1,2]

This study has limitations. Data extraction was unblinded, which is a potential source of bias. Additionally, high heterogeneity was identified in the meta-analyses, especially in the structured exercise training meta-analysis. To address this, we have performed analyses to identify clinical (eg, baseline HbA_{1c}) and methodological differences (eg, amounts of exercise) between studies. Finally, the general quality of the studies was low, reflecting increased risk of bias in some studies. This may have contributed to the heterogeneity of our analyses.

CONCLUSIONS

Structured exercise, consisting of aerobic training, resistance training, or a combination of aerobic and resistance exercise training for at least 12 weeks, is associated with improved glycemic control in type 2 diabetic patients. Structured weekly exercise of more than 150 minutes per week was associated with greater declines in HbA_{1c}. Structured exercise training reduced HbA_{1c} to a larger degree than physical activity advice. Physical activity advice is beneficial only if associated with dietary recommendations.

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Acquisition of data: Umpierre, Ribeiro, Zucatti, Schaan.
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Online-Only Materials: The eBox, eTables 1-4, eFigures 1-3, and eReferences are available at http://www.jama.com.

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