

# Physical Activity Advice Only or Structured Exercise Training and Association With HbA<sub>1c</sub> Levels in Type 2 Diabetes

## A Systematic Review and Meta-analysis

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EXERCISE IS A CORNERSTONE OF diabetes management, along with dietary and pharmacological interventions.<sup>1,2</sup> 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.<sup>1,2</sup> Previous meta-analyses<sup>3-6</sup> demonstrated that structured exercise training including aerobic and resistance exercises reduces hemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>) 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<sub>1c</sub> levels.<sup>5</sup> Since publication of this meta-analysis, 2 large randomized trials<sup>7,8</sup> were published that reported contradictory findings regarding the types of

**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<sub>1c</sub> (HbA<sub>1c</sub>) 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<sub>1c</sub> 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<sub>1c</sub> 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<sub>1c</sub> level (−0.67%; 95% confidence interval [CI], −0.84% to −0.49%; *I*<sup>2</sup>, 91.3%) compared with control participants. In addition, structured aerobic exercise (−0.73%; 95% CI, −1.06% to −0.40%; *I*<sup>2</sup>, 92.8%), structured resistance training (−0.57%; 95% CI, −1.14% to −0.01%; *I*<sup>2</sup>, 92.5%), and both combined (−0.51%; 95% CI, −0.79% to −0.23%; *I*<sup>2</sup>, 67.5%) were each associated with declines in HbA<sub>1c</sub> levels compared with control participants. Structured exercise durations of more than 150 minutes per week were associated with HbA<sub>1c</sub> reductions of 0.89%, while structured exercise durations of 150 minutes or less per week were associated with HbA<sub>1c</sub> reductions of 0.36%. Overall, interventions of physical activity advice (24 studies) were associated with lower HbA<sub>1c</sub> levels (−0.43%; 95% CI, −0.59% to −0.28%; *I*<sup>2</sup>, 62.9%) compared with control participants. Combined physical activity advice and dietary advice was associated with decreased HbA<sub>1c</sub> (−0.58%; 95% CI, −0.74% to −0.43%; *I*<sup>2</sup>, 57.5%) as compared with control participants. Physical activity advice alone was not associated with HbA<sub>1c</sub> changes.

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

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and questions on p 1817.

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structured exercise associated with declines in HbA<sub>1c</sub> levels. Sigal et al<sup>7</sup> 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<sup>8</sup> observed that only the combination, but not aerobic and resistance training alone, reduced HbA<sub>1c</sub> 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.<sup>9</sup> 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<sub>1c</sub> 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<sub>1c</sub> 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,<sup>10</sup> 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.<sup>11</sup>

### 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<sub>1c</sub> as an outcome, and reported means or differences between means and respective dispersion values of HbA<sub>1c</sub> 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<sub>1c</sub> 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, drop-out rates, and adverse events were also extracted.

### Assessment of Risk of Bias

Risk of bias was evaluated according to the PRISMA recommendation.<sup>12</sup> 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  $\kappa$  agreement rate between reviewers was  $\kappa=0.96$  for quality assessment.

### Data Analyses

Absolute changes in HbA<sub>1c</sub> 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 base-

line 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  $\alpha$  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.<sup>13</sup> 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<sub>1c</sub> 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<sub>1c</sub> plus exercise frequency (defined as the number of exercise sessions per week [model 1]); baseline HbA<sub>1c</sub> 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<sub>1c</sub> 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<sub>1c</sub> plus exercise intensity plus total exercise time spent in the program (model 4). Model 4 included covariates that were not significant in uni-

variate 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.<sup>14,15</sup> 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*.<sup>13</sup> Imputation and/or transformation methods were used for few studies that showed results as confidence intervals (CIs) or interquartile ranges.<sup>16</sup>

Publication bias was assessed using a contour-enhanced funnel plot of each trial's effect size against the standard error.<sup>17</sup> 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.<sup>18,19</sup> 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 data-

bases 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<sub>1c</sub>)**  
**Structured Exercise Training: Aerobic, Resistance, or Both.** The overall association of any structured exercise vs control with absolute HbA<sub>1c</sub> reduction

**Table 1.** Characteristics of the Structured Exercise Studies Included

Source	Age, Mean (SD), y <sup>a</sup>	Control Group Intervention	Dietary Cointervention	Chronic Comorbidities	Frequency, Sessions/wk	Weekly Duration, min <sup>b</sup>	Program Duration, wk	Adherence to Exercise Training, %	Dropouts, %
Aerobic training									
Bjorgaas et al, <sup>20</sup> 2005	57 (8)	Diet advice care, no exercise	Yes	Hypertension	2	90	12	77	20
Church et al, <sup>8</sup> 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, <sup>21</sup> 2003	59 (6)	Usual care	No	NR	3	75	16	92	0
Dela et al, <sup>22</sup> 2004	52 (7)	Usual care	No	None	5	30-40	12	100	NR
Giannoupolou et al, <sup>23</sup> 2005	58 (6)	Dietary planning, no exercise	Yes	NR	3-4	60	14	NR	17
Goldhaber-Fiebert et al, <sup>24</sup> 2003	59 (10)	Nutrition classes, no exercise	Yes	Hypertension, dyslipidemia	3	60	12	NR	Aerobic, 17.5; control, 20
Kadoglou et al, <sup>25</sup> 2007	62 (5)	Usual care	No	Hypertension	4	30-45	26	92	Aerobic, 3; control, 10
Kadoglou et al, <sup>26</sup> 2007	59 (8)	Usual care	No	Hypertension	4	45-60	16	NR	Aerobic, 6.5; control, 13
Kadoglou et al, <sup>27</sup> 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, <sup>28</sup> 2008	52 (8)	Usual care	No	No major complications	3	50	12	≥85	Aerobic, 5; control, 11
Ligtenberg et al, <sup>29</sup> 1997	62 (5)	Educational program, no exercise instructions	No	No major complications	3	50	12	97	Aerobic, 17; control, 7
Middlebrooke et al, <sup>30</sup> 2006	63 (8)	Usual care	No	Neuropathy, hypertension	3	30	26	99	Aerobic, 24; control, 0
Raz et al, <sup>31</sup> 1994	57 (7)	Lifestyle maintenance	No	Obesity, hypertension, CAD, PAD	3	45	12	68	Aerobic, 5; control, 5
Ribeiro et al, <sup>32</sup> 2008	55 (10)	Sedentary lifestyle	No	None	3	40	16	≥75	0
Sigal et al, <sup>7</sup> 2007	54 (7)	Sedentary habitual lifestyle	No	Hypertension, depression	3	45	26	80	Aerobic, 20; control, 5
Sridhar et al, <sup>33</sup> 2010	61 (3)	Sedentary habitual lifestyle	No	Hypertension	5	30	52	NR	NR
Vancea et al, <sup>34</sup> 2009	57 (6)	Spontaneous exercise counseling	No	NR	3 or 5	30	20	NR	0
Verity and Ismail, <sup>35</sup> 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 <sup>a</sup>	Control Group Intervention	Dietary Cointervention	Chronic Comorbidities	Frequency, Sessions/wk	Weekly Duration, min <sup>b</sup>	Program Duration, wk	Adherence to Exercise Training, %	Dropouts, %
Resistance training Castaneda et al, <sup>36</sup> 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, <sup>8</sup> 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, <sup>37</sup> 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, <sup>7</sup> 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, <sup>38</sup> 2004	61 (9)	Lifestyle maintenance	No	Hypertension	3	60	52	>90	Combined, 18; control, 9
Church et al, <sup>8</sup> 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, <sup>21</sup> 2003	63 (7)	Usual care	No	NR	3	75	16	92	0
Lambers et al, <sup>28</sup> 2008	56 (10)	Usual care	No	No major complications	3	50	12	≥85	Combined, 11; control, 11
Loimaala et al, <sup>39</sup> 2003	53 (5)	Usual care	No	Hypertension	4	≥30 Aerobic; 24 sets of resistance exercises	52	NR	Combined, 4; control, 0
Sigal et al, <sup>7</sup> 2007	53 (7)	Sedentary habitual lifestyle	No	Hypertension, depression	3	Aerobic and resistance programs	26	86	Combined, 13; control, 5
Tessier et al, <sup>40</sup> 2000	69 (5)	Lifestyle maintenance	No	NR	3	40	16	>90	13

Abbreviations: CAD, coronary artery disease; NR, not reported; PAD, peripheral arterial disease.

<sup>a</sup>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.<sup>b</sup>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<sub>1c</sub> 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<sub>1c</sub> 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<sub>1c</sub> 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<sub>1c</sub> 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). Struc-

tured exercise of more than 150 minutes per week (18 observations, 826 patients) was associated with an absolute HbA<sub>1c</sub> 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<sub>1c</sub> (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 <sup>a</sup>	Control Group Intervention	Chronic Comorbidities	Frequency, Sessions/wk	Program Duration, wk	Weekly Duration, min	Preintervention	Dropouts, %
Dietary cointervention								
Aas et al, <sup>41</sup> 2005	56	Insulin treatment, no lifestyle intervention	NR	2	52	120	No	PA, 23; control, 25
Agurs-Collins et al, <sup>42</sup> 1997	62 (6)	Usual care, nutrition information	NR	3	26	90	No	PA, 6; control, 12
Christian et al, <sup>43</sup> 2008	53 (11)	Diabetes, diet, and exercise materials	No major complications	NR	52	NR	No	PA, 9; control, 13
Dasgupta et al, <sup>44</sup> 2006	52 (NR)	Individualized dietary counseling	Cardiovascular disease	3	24	135	Yes	24
Di Loreto et al, <sup>45</sup> 2003	62 (10)	Usual care, dietary counseling	No major complications	NR	104	>10 MET-h	No	PA, 2; control, 0
Hordern et al, <sup>46</sup> 2009	56 (10)	Usual care	Myocardial dysfunction	NR	52	≥150	Yes	PA, 21; control, 21
Kim et al, <sup>47</sup> 2006	54 (9)	Basic dietary education	Hypertension	30	26	150	No	0
Jakicic et al, <sup>48</sup> 2009	59 (7)	Diabetes support, education	Hypertension, cardiovascular disease	5	52	175	Yes	PA, 3; control, 4
Mayer Davis et al, <sup>49</sup> 2004	61 (9)	Usual care	Hypertension	NR	52	150	Yes	19
Ménard et al, <sup>50</sup> 2005	55 (8)	Usual care	Hypertension, dyslipidemia	3	52	45	Yes	PA, 6; control, 3
Vanninen et al, <sup>51</sup> 1992	53 (7)	Basic health education	Hypertension, CAD	3	52	158	Yes	0
Wing et al, <sup>52</sup> 1988	56 (7)	Health habits education, self-monitoring	No major complications	3	52	NR	Yes	0
No dietary cointervention								
Brun et al, <sup>53</sup> 2008	60 (10)	Repeated health evaluations	No major complications	2	52	75	Yes	0
Cheung et al, <sup>54</sup> 2009	60 (8)	Lifestyle maintenance	NR	5	16	150	Yes	PA, 5; control, 11
Diedrich et al, <sup>55</sup> 2010	56 (12)	Education, diabetes self-management	NR	NR	12	NR	Yes	PA, 41; control, 38
Kim et al, <sup>56</sup> 2006	55 (7)	Usual care, basic dietary education	Hypertension	3-5	12	90-150	No	0
Kirk et al, <sup>57</sup> 2003	58 (8)	Usual care	Hypertension	5	26	150	No	PA, 9; control, 11
Kirk et al, <sup>58</sup> 2009	61 (10)	Usual care	NR	5	52	150	No	PA, 9; control, 9
Krousel-Wood et al, <sup>59</sup> 2008	57 (10)	Self-management, education, exercise encouragement	No major complications	5	12	150	No	PA, 18; control, 20
Leehey et al, <sup>60</sup> 2009	66	Usual care, diabetes education	Chronic kidney disease, obesity	3	24	≥120	Yes	PA, 0; control, 33
Rönnemaa et al, <sup>61</sup> 1986	53	Usual care	Hypertension, retinopathy	5-7	16	225-315	No	PA, 13; control, 20
Samaras et al, <sup>62</sup> 1997	61 (8)	Usual care	NR	NR	26	NR	Yes	0
Tudor-Locke et al, <sup>63</sup> 2004	53 (5)	Usual care	Hypertension, dyslipidemia, allergies	NR	16	NR	Yes	PA, 20; control, 23
Van Rooijen et al, <sup>64</sup> 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.

<sup>a</sup>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<sub>1c</sub> of 0.43% (95% CI, -0.59% to -0.28%;  $I^2$ , 62.9%;  $P$  for heterogeneity <.001) (FIGURE 2).

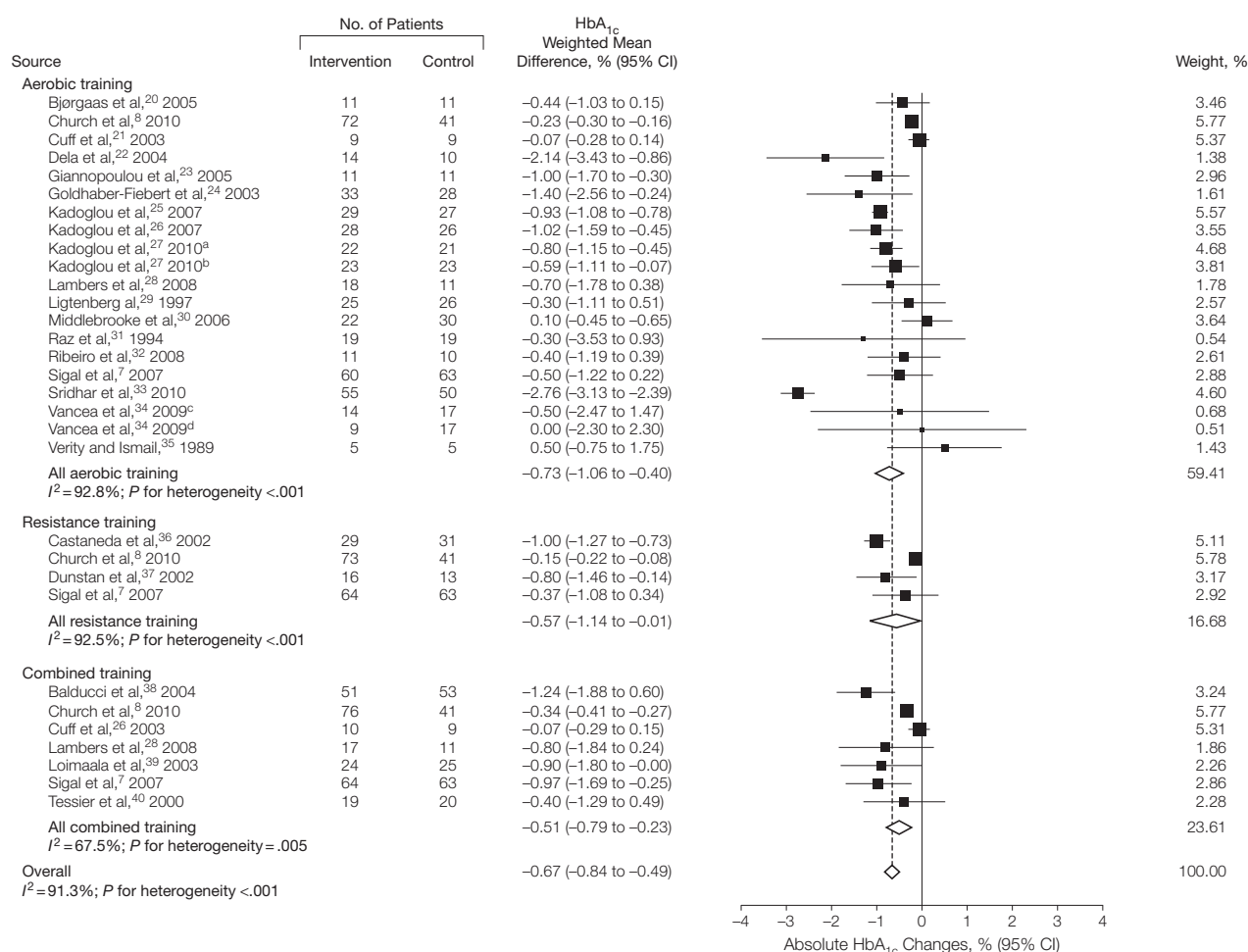
Covariates used in univariate analysis did not explain heterogeneity (eTable 4). Similarly, a multivariate meta-regression using baseline HbA<sub>1c</sub> and dietary recommendation (model 1) as covariates did not explain the between-studies variance (overall,  $P$  = .17).

In sensitivity analyses, physical activity associated with dietary advice (12 studies, 6313 patients) was associated with a 0.58% absolute HbA<sub>1c</sub> 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<sub>1c</sub> 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<sub>1c</sub> 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<sub>1c</sub>) than structured exercise duration of 150 minutes or less per week (0.36% reduction in HbA<sub>1c</sub>). Structured exercise

**Figure 1.** Absolute Changes in HbA<sub>1c</sub> of Individual Studies of Structured Exercise Training vs No Intervention



CI indicates confidence interval. Changes in hemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>) (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.

<sup>a</sup>Exercise and control subgroups.

<sup>b</sup>Exercise and control subgroups with rosiglitazone treatment as cointervention.

<sup>c</sup>Subgroup with exercise frequency of 3 sessions per week.

<sup>d</sup>Subgroup with exercise frequency of 5 sessions per week.

training was associated with a more pronounced HbA<sub>1c</sub> reduction compared with physical activity advice. A recommendation to increase physical activity was beneficial (0.43% HbA<sub>1c</sub> reduction), but only if combined with dietary recommendations.

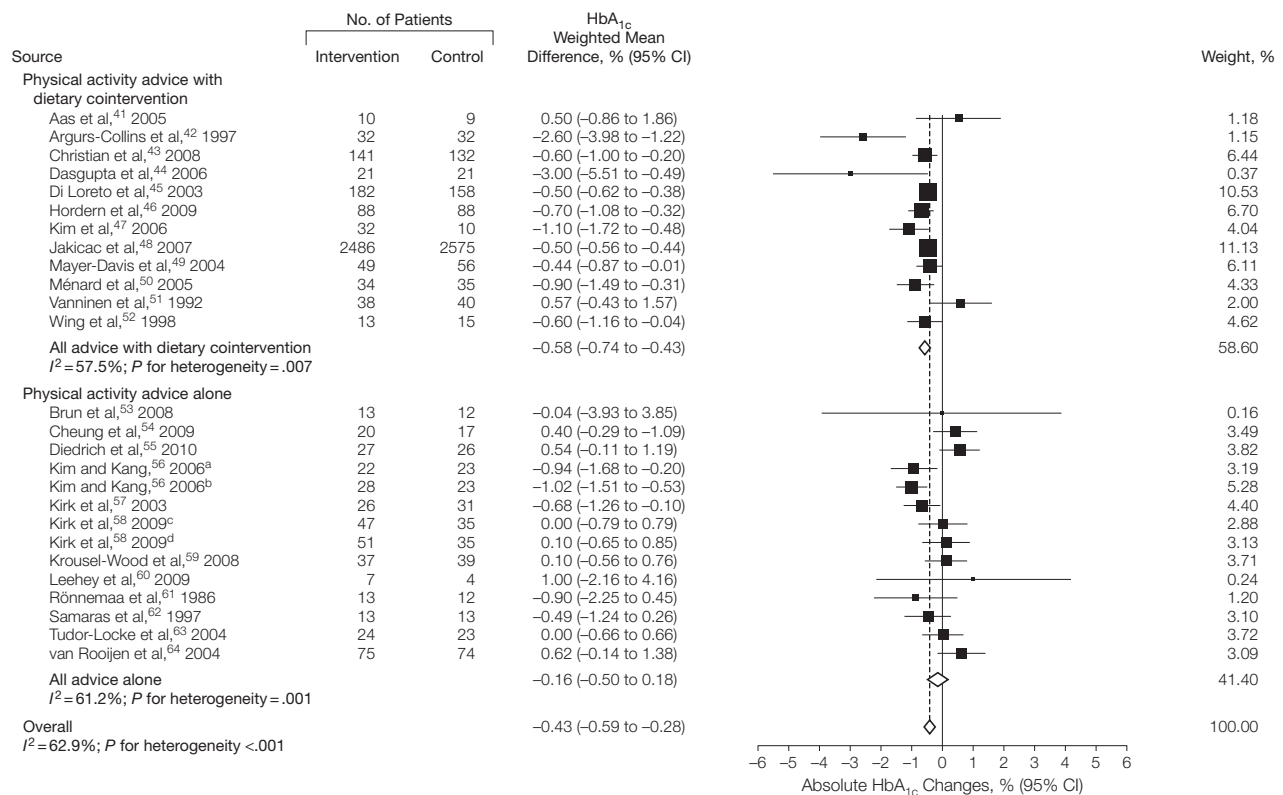
This systematic review and meta-analysis of RCTs demonstrates important findings regarding the prescription of structured exercise training. First, aerobic, resistance, and combined training are each associated with HbA<sub>1c</sub> decreases, and the magnitude of this reduction is similar across the 3 exercise modalities. Interestingly, the weighted mean difference of -0.67% in HbA<sub>1c</sub> levels favorably compares with the decline in HbA<sub>1c</sub>

associated with the addition of noninsulin antidiabetic drugs to maximal metformin therapy.<sup>65</sup> Second, our findings demonstrate that structured exercise of more than 150 minutes per week is associated with greater declines in HbA<sub>1c</sub> 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.<sup>1,2</sup> Although high-intensity exercise has been previously shown to have an association with HbA<sub>1c</sub> reduction,<sup>4</sup> our findings did not demonstrate that more intensive exercise was associated with greater declines in HbA<sub>1c</sub>. It is important to mention

that, due to a great variability in exercise intensity descriptions, we used an intensity rating as previously reported.<sup>5</sup> Baseline HbA<sub>1c</sub> was one of the variables explaining the heterogeneity between studies, which underscores the greater magnitude of intervention effects in HbA<sub>1c</sub> among individuals with baseline HbA<sub>1c</sub> levels of greater than 7%, when compared with those with baseline HbA<sub>1c</sub> levels of less than 7%.<sup>7,8,66,67</sup>

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<sub>1c</sub> than the studies evalu-

**Figure 2.** Absolute Changes in HbA<sub>1c</sub> of Individual Studies of Physical Activity Advice vs No Intervention



CI indicates confidence interval. Changes in hemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>) 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.

<sup>a</sup>Subgroup received advice in printed material.

<sup>b</sup>Subgroup received advice through a Web system.

<sup>c</sup>Subgroup received advice from an individual.

<sup>d</sup>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<sub>1c</sub>.<sup>68</sup>

This review demonstrates that physical activity advice is only associated with HbA<sub>1c</sub> 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<sub>1c</sub> 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<sup>1</sup> have distinct mechanisms to elicit these effects, it is expected that these interventions applied together would result in greater metabolic effects.<sup>2,69</sup> 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.<sup>1,2</sup>

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<sub>1c</sub>) 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<sub>1c</sub>. Structured exercise training reduced HbA<sub>1c</sub> to a larger degree than physical activity advice. Physical activity advice is beneficial only if associated with dietary recommendations.

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## REFERENCES

1. American Diabetes Association. Standards of medical care in diabetes—2011. *Diabetes Care*. 2011; 34(suppl 1):S11-S61.
2. Colberg SR, Sigal RJ, Fernhall B, et al; American College of Sports Medicine; American Diabetes

Association. Exercise and type 2 diabetes: the American College of Sports Medicine and the American Diabetes Association: joint position statement. *Diabetes Care*. 2010;33(12):e147-e167.

- 3. Boulé NG, Haddad E, Kenny GP, Wells GA, Sigal RJ. Effects of exercise on glycemic control and body mass in type 2 diabetes mellitus: a meta-analysis of controlled clinical trials. *JAMA*. 2001;286(10):1218-1227.
- 4. Boulé NG, Kenny GP, Haddad E, Wells GA, Sigal RJ. Meta-analysis of the effect of structured exercise training on cardiorespiratory fitness in type 2 diabetes mellitus. *Diabetologia*. 2003;46(8):1071-1081.
- 5. Snowling NJ, Hopkins WG. Effects of different modes of exercise training on glucose control and risk factors for complications in type 2 diabetic patients: a meta-analysis. *Diabetes Care*. 2006;29(11):2518-2527.
- 6. Thomas DE, Elliott EJ, Naughton GA. Exercise for type 2 diabetes mellitus. *Cochrane Database Syst Rev*. 2006;3:CD002968.
- 7. Sigal RJ, Kenny GP, Boulé NG, et al. Effects of aerobic training, resistance training, or both on glycemic control in type 2 diabetes: a randomized trial. *Ann Intern Med*. 2007;147(6):357-369.
- 8. Church TS, Blair SN, Cocroham S, et al. Effects of aerobic and resistance training on hemoglobin A<sub>1c</sub> levels in patients with type 2 diabetes: a randomized controlled trial. *JAMA*. 2010;304(20):2253-2262.
- 9. Sigal RJ, Kenny GP, Wasserman DH, Castaneda-Sceppa C. Physical activity/exercise and type 2 diabetes. *Diabetes Care*. 2004;27(10):2518-2539.
- 10. Robinson KA, Dickersin K. Development of a highly sensitive search strategy for the retrieval of reports of controlled trials using PubMed. *Int J Epidemiol*. 2002; 31(1):150-153.
- 11. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med*. 2009;151(4):264-269, W64.
- 12. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *Ann Intern Med*. 2009;151(4):W65-W94.
- 13. Higgins JPT. Analysing data and undertaking meta-analysis. In: Higgins JPT, Green S, eds. *Cochrane Handbook for Systematic Reviews of Interventions*. Version 5.1.0 [updated March 2011]. <http://www.cochrane-handbook.org>. Accessed February 3, 2011.
- 14. Harbord RM, Higgins JPT. Meta-regression in Stata. In: Sterne JAC, Newton HJ, Cox NJ, eds. *Meta-analysis in Stata*. College Station, TX: Stata Press; 2009.
- 15. Indrayan A. *Medical Biostatistics*. 2nd ed. Boca Raton, FL: Chapman & Hall/CRC; 2008.
- 16. Wiebe N, Vandermeer B, Platt RW, Klassen TP, Moher D, Barrowman NJ. A systematic review identifies a lack of standardization in methods for handling missing variance data. *J Clin Epidemiol*. 2006; 59(4):342-353.
- 17. Peters JL, Sutton AJ, Jones DR, Abrams KR, Rushton L. Contour-enhanced meta-analysis funnel plots help distinguish publication bias from other causes of asymmetry. *J Clin Epidemiol*. 2008;61(10):991-996.
- 18. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003; 327(7414):557-560.
- 19. Duval S, Tweedie R. Trim and fill: a simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. *Biometrics*. 2000; 56(2):455-463.
- 20. Bjørngaas M, Vik JT, Saeterhaug A, et al. Relationship between pedometer-registered activity, aerobic

- capacity and self-reported activity and fitness in patients with type 2 diabetes. *Diabetes Obes Metab*. 2005;7(6):737-744.
21. Cuff DJ, Meneilly GS, Martin A, Ignaszewski A, Tildesley HD, Frohlich JJ. Effective exercise modality to reduce insulin resistance in women with type 2 diabetes. *Diabetes Care*. 2003;26(11):2977-2982.
  22. Dela F, von Linstow ME, Mikines KJ, Galbo H. Physical training may enhance beta-cell function in type 2 diabetes. *Am J Physiol Endocrinol Metab*. 2004;287(5):E1024-E1031.
  23. Giannopoulou I, Fernhall B, Carhart R, et al. Effects of diet and/or exercise on the adipocytokine and inflammatory cytokine levels of postmenopausal women with type 2 diabetes. *Metabolism*. 2005;54(7):866-875.
  24. Goldhaber-Fiebert JD, Goldhaber-Fiebert SN, Tristán ML, Nathan DM. Randomized controlled community-based nutrition and exercise intervention improves glycemia and cardiovascular risk factors in type 2 diabetic patients in rural Costa Rica. *Diabetes Care*. 2003;26(1):24-29.
  25. Kadoglou NP, Iliadis F, Angelopoulou N, et al. The anti-inflammatory effects of exercise training in patients with type 2 diabetes mellitus. *Eur J Cardiovasc Prev Rehabil*. 2007;14(6):837-843.
  26. Kadoglou NP, Perrea D, Iliadis F, Angelopoulou N, Liapis C, Alevizos M. Exercise reduces resistin and inflammatory cytokines in patients with type 2 diabetes. *Diabetes Care*. 2007;30(3):719-721.
  27. Kadoglou NP, Iliadis F, Sailer N, et al. Exercise training ameliorates the effects of rosiglitazone on traditional and novel cardiovascular risk factors in patients with type 2 diabetes mellitus. *Metabolism*. 2010;59(4):599-607.
  28. Lambers S, Van Laethem C, Van Acker K, Calders P. Influence of combined exercise training on indices of obesity, diabetes and cardiovascular risk in type 2 diabetes patients. *Clin Rehabil*. 2008;22(6):483-492.
  29. Ligtnerberg PC, Hoekstra JB, Bol E, Zonderland ML, Erkelens DW. Effects of physical training on metabolic control in elderly type 2 diabetes mellitus patients. *Clin Sci (Lond)*. 1997;93(2):127-135.
  30. Middlebrooke AR, Elston LM, Macleod KM, et al. Six months of aerobic exercise does not improve microvascular function in type 2 diabetes mellitus. *Diabetologia*. 2006;49(10):2263-2271.
  31. Raz I, Hauser E, Bursztyn M. Moderate exercise improves glucose metabolism in uncontrolled elderly patients with non-insulin-dependent diabetes mellitus. *Isr J Med Sci*. 1994;30(10):766-770.
  32. Ribeiro IC, Iborra RT, Neves MQ, et al. HDL atheroprotection by aerobic exercise training in type 2 diabetes mellitus. *Med Sci Sports Exerc*. 2008;40(5):779-786.
  33. Sridhar B, Haleagrahara N, Bhat R, Kulur AB, Avabratha S, Adhikary P. Increase in the heart rate variability with deep breathing in diabetic patients after 12-month exercise training. *Tohoku J Exp Med*. 2010;220(2):107-113.
  34. Vancea DM, Vancea JN, Pires MI, Reis MA, Moura RB, Dib SA. Effect of frequency of physical exercise on glycemic control and body composition in type 2 diabetic patients. *Arq Bras Cardiol*. 2009;92(1):23-30.
  35. Verity LS, Ismail AH. Effects of exercise on cardiovascular disease risk in women with NIDDM. *Diabetes Res Clin Pract*. 1989;6(1):27-35.
  36. Castaneda C, Layne JE, Munoz-Orians L, et al. A randomized controlled trial of resistance exercise training to improve glycemic control in older adults with type 2 diabetes. *Diabetes Care*. 2002;25(12):2335-2341.
  37. Dunstan DW, Daly RM, Owen N, et al. High-intensity resistance training improves glycemic control in older patients with type 2 diabetes. *Diabetes Care*. 2002;25(10):1729-1736.
  38. Balducci S, Leonetti F, Di Mario U, Fallucca F. Is a long-term aerobic plus resistance training program feasible for and effective on metabolic profiles in type 2 diabetic patients? *Diabetes Care*. 2004;27(3):841-842.
  39. Loimaala A, Huikuri HV, Kööbi T, Rinne M, Nenonen A, Vuori I. Exercise training improves baroreflex sensitivity in type 2 diabetes. *Diabetes*. 2003;52(7):1837-1842.
  40. Tessier D, Ménard J, Fülöp T, et al. Effects of aerobic physical exercise in the elderly with type 2 diabetes mellitus. *Arch Gerontol Geriatr*. 2000;31(2):121-132.
  41. Aas AM, Bergstad I, Thorsby PM, Johannesen O, Solberg M, Birkeland KI. An intensified lifestyle intervention programme may be superior to insulin treatment in poorly controlled type 2 diabetic patients on oral hypoglycaemic agents: results of a feasibility study. *Diabet Med*. 2005;22(3):316-322.
  42. Agurs-Collins TD, Kumanyika SK, Ten Have TR, Adams-Campbell LL. A randomized controlled trial of weight reduction and exercise for diabetes management in older African-American subjects. *Diabetes Care*. 1997;20(10):1503-1511.
  43. Christian JG, Bessesen DH, Byers TE, Christian KK, Goldstein MG, Bock BC. Clinic-based support to help overweight patients with type 2 diabetes increase physical activity and lose weight. *Arch Intern Med*. 2008;168(2):141-146.
  44. Dasgupta K, Grover SA, Da Costa D, Lowenstein I, Yale JF, Rahme E. Impact of modified glucose target and exercise interventions on vascular risk factors. *Diabetes Res Clin Pract*. 2006;72(1):53-60.
  45. Di Loreto C, Fanelli C, Lucidi P, et al. Validation of a counseling strategy to promote the adoption and the maintenance of physical activity by type 2 diabetic subjects. *Diabetes Care*. 2003;26(2):404-408.
  46. Hordern MD, Coombes JS, Cooney LM, Jeffriess L, Prins JB, Marwick TH. Effect of exercise intervention on myocardial function in type 2 diabetes. *Heart*. 2009;95(16):1343-1349.
  47. Kim SH, Lee SJ, Kang ES, et al. Effects of lifestyle modification on metabolic parameters and carotid intima-media thickness in patients with type 2 diabetes mellitus. *Metabolism*. 2006;55(8):1053-1059.
  48. Jakicic JM, Jaramillo SA, Balasubramanyam A, et al; Look AHEAD Study Group. Effect of a lifestyle intervention on change in cardiorespiratory fitness in adults with type 2 diabetes: results from the Look AHEAD Study. *Int J Obes (Lond)*. 2009;33(3):305-316.
  49. Mayer-Davis EJ, D'Antonio AM, Smith SM, et al. Pounds off with empowerment (POWER): a clinical trial of weight management strategies for black and white adults with diabetes who live in medically underserved rural communities. *Am J Public Health*. 2004;94(10):1736-1742.
  50. Ménard J, Payette H, Baillargeon JP, et al. Efficacy of intensive multitherapy for patients with type 2 diabetes mellitus: a randomized controlled trial. *CMAJ*. 2005;173(12):1457-1466.
  51. Vanninen E, Uusitupa M, Siitonen O, Laitinen J, Lämsimies E. Habitual physical activity, aerobic capacity and metabolic control in patients with newly-diagnosed type 2 (non-insulin-dependent) diabetes mellitus: effect of 1-year diet and exercise intervention. *Diabetologia*. 1992;35(4):340-346.
  52. Wing RR, Epstein LH, Paternostro-Bayles M, Kriska A, Nowalk MP, Gooding W. Exercise in a behavioural weight control programme for obese patients with type 2 (non-insulin-dependent) diabetes. *Diabetologia*. 1988;31(12):902-909.
  53. Brun JF, Bordenave S, Mercier J, Jaussant A, Picot MC, Préfaut C. Cost-sparing effect of twice-weekly targeted endurance training in type 2 diabetics: a one-year controlled randomized trial. *Diabetes Metab*. 2008;34(3):258-265.
  54. Cheung NW, Cinnadaio N, Russo M, Marek S. A pilot randomised controlled trial of resistance exercise bands in the management of sedentary subjects with type 2 diabetes. *Diabetes Res Clin Pract*. 2009;83(3):e68-e71.
  55. Diedrich A, Munroe DJ, Romano M. Promoting physical activity for persons with diabetes. *Diabetes Educ*. 2010;36(1):132-140.
  56. Kim CJ, Kang DH. Utility of a Web-based intervention for individuals with type 2 diabetes: the impact on physical activity levels and glycemic control. *Comput Inform Nurs*. 2006;24(6):337-345.
  57. Kirk A, Mutrie N, MacIntyre P, Fisher M. Increasing physical activity in people with type 2 diabetes. *Diabetes Care*. 2003;26(4):1186-1192.
  58. Kirk A, Barnett J, Leese G, Mutrie N. A randomized trial investigating the 12-month changes in physical activity and health outcomes following a physical activity consultation delivered by a person or in written form in type 2 diabetes: Time2Act. *Diabet Med*. 2009;26(3):293-301.
  59. Krousel-Wood MA, Berger L, Jiang X, Blonde L, Myers L, Webber L. Does home-based exercise improve body mass index in patients with type 2 diabetes? results of a feasibility trial. *Diabetes Res Clin Pract*. 2008;79(2):230-236.
  60. Leehay DJ, Moinuddin I, Bast JP, et al. Aerobic exercise in obese diabetic patients with chronic kidney disease: a randomized and controlled pilot study. *Cardiovasc Diabetol*. 2009;8:62.
  61. Rönnemaa T, Mattila K, Lehtonen A, Kallio V. A controlled randomized study on the effect of long-term physical exercise on the metabolic control in type 2 diabetic patients. *Acta Med Scand*. 1986;220(3):219-224.
  62. Samaras K, Ashwell S, Mackintosh AM, Fleury AC, Campbell LV, Chisholm DJ. Will older sedentary people with non-insulin-dependent diabetes mellitus start exercising? a health promotion model. *Diabetes Res Clin Pract*. 1997;37(2):121-128.
  63. Tudor-Locke C, Bell RC, Myers AM, et al. Controlled outcome evaluation of the First Step Program: a daily physical activity intervention for individuals with type II diabetes. *Int J Obes Relat Metab Disord*. 2004;28(1):113-119.
  64. van Rooijen AJ, Rheeder P, Eales CJ, Becker PJ. Effect of exercise versus relaxation on haemoglobin A<sub>1c</sub> in Black females with type 2 diabetes mellitus. *QJM*. 2004;97(6):343-351.
  65. Phung OJ, Scholle JM, Talwar M, Coleman CI. Effect of noninsulin antidiabetic drugs added to metformin therapy on glycemic control, weight gain, and hypoglycemia in type 2 diabetes. *JAMA*. 2010;303(14):1410-1418.
  66. DeFronzo RA, Stonehouse AH, Han J, Wintle ME. Relationship of baseline HbA<sub>1c</sub> and efficacy of current glucose-lowering therapies: a meta-analysis of randomized clinical trials. *Diabet Med*. 2010;27(3):309-317.
  67. Gordon BA, Benson AC, Bird SR, Fraser SF. Resistance training improves metabolic health in type 2 diabetes: a systematic review. *Diabetes Res Clin Pract*. 2009;83(2):157-175.
  68. Balducci S, Zanuso S, Nicolucci A, et al; Italian Diabetes Exercise Study (IDES) Investigators. Effect of an intensive exercise intervention strategy on modifiable cardiovascular risk factors in subjects with type 2 diabetes mellitus: a randomized controlled trial: the Italian Diabetes and Exercise Study (IDES). *Arch Intern Med*. 2010;170(20):1794-1803.
  69. Ferrier KE, Nestel P, Taylor A, Drew BG, Kingwell BA. Diet but not aerobic exercise training reduces skeletal muscle TNF-alpha in overweight humans. *Diabetologia*. 2004;47(4):630-637.