

Changes in Body Fat Distribution and Fitness Are Associated With Changes in Hemoglobin A_{1c} After 9 Months of Exercise Training

Results from the HART-D study

MARTIN SÉNÉCHAL, PHD^{1,2,3}
DAMON L. SWIFT, PHD³
NEIL M. JOHANNSEN, PHD³
STEVEN N. BLAIR, PED⁴

CONRAD P. EARNEST, PHD⁵
CARL J. LAVIE, MD^{3,6}
TIMOTHY S. CHURCH, MD, MPH, PHD³

OBJECTIVE—To investigate the associations between changes in body composition and fitness after exercise training and changes in hemoglobin A_{1c} (HbA_{1c}) in individuals with type 2 diabetes.

RESEARCH DESIGN AND METHODS—Participants ($n = 201$) were randomized to aerobic, resistance, or combined training for 9 months. HbA_{1c}, waist circumference, total and trunk fat mass, appendicular fat mass, lean body mass, isokinetic leg muscle strength, peak O₂ uptake, and estimated METs were assessed at baseline and follow-up. Change in HbA_{1c} was evaluated across quartiles of change in body composition and fitness.

RESULTS—Change in HbA_{1c} was associated with changes in body weight ($r = 0.13$, $P = 0.052$), waist circumference ($r = 0.17$, $P = 0.013$), trunk fat mass ($r = 0.19$, $P = 0.005$), and estimated METs ($r = -0.16$, $P = 0.023$). There was a trend in change in HbA_{1c} across quartiles of waist circumference ($P = 0.011$), trunk fat mass ($P = 0.020$), and estimated METs ($P = 0.011$). Participants with increased estimated METs and reduced trunk fat mass had greater odds of having reduced HbA_{1c} after training (3.48, 1.46–8.31). Finally, participants with increased estimated METs and reduced waist circumference were 2.81 (1.13–6.98) times more likely to have reduced HbA_{1c} and type 2 diabetes medication use than those without improved fitness and central adiposity.

CONCLUSIONS—In patients with type 2 diabetes, a reduction in central adiposity and increase in fitness were the most prominent predictors of the change in HbA_{1c} in response to exercise training.

Diabetes Care 36:2843–2849, 2013

Hemoglobin A_{1c} (HbA_{1c}) is the most widely used indicator of glucose control in individuals with type 2 diabetes, and exercise training is recommended along with standard care to improve glucose control and overall health status (1–5). Strong evidence from our

data (6) and that of others (7,8) has established that a combination of aerobic and resistance training is effective in reducing HbA_{1c}, whereas still others have reported that this combination is more effective than aerobic training or resistance training alone (7). However, only few studies

specifically address what changes in cardiometabolic factors of exercise training (i.e., changes in cardiorespiratory fitness, muscle strength, body composition) are associated with improvement in HbA_{1c} (9–12).

Previous studies have found that reductions in fat mass (10) and central adiposity (9,11) and increases in fitness (11,12) and muscle strength (12,13) are associated with reductions in HbA_{1c} after exercise training. In a large ($n = 251$) randomized trial, Larose et al. (12) found that change in cardiorespiratory fitness was the strongest predictor of change in HbA_{1c} after aerobic and aerobic combined with resistance training. However, with resistance training only, the change in muscle strength was the strongest predictor of the change in HbA_{1c}. In a smaller sample ($n = 40$), Bacchi et al. (11) showed that an increase in fitness and a reduction in trunk fat mass result in the largest decrease in HbA_{1c} after aerobic or resistance training alone in individuals with type 2 diabetes. Of note, previous studies evaluating the effects of body fat distribution, muscle strength, and fitness on long-term glucose control generally are limited by the absence of a control group (11), a small sample size (8), or a homogeneous study population (9). Herein, we performed secondary analyses based on data from the Health Benefits of Aerobic and Resistance Training in Individuals with Type 2 Diabetes (HART-D) trial, which investigated the contribution of 9 months of aerobic training, resistance training, or a combination of both interventions on changes in HbA_{1c}. Although the purpose of the original HART-D trial (6) was to evaluate the effect of exercise, the current study expands on the previous findings by investigating the predictors of change in HbA_{1c} in individuals with type 2 diabetes. Therefore, the primary aim of this study was to investigate the association between changes in body composition and fat distribution, leg

From the ¹Manitoba Institute of Child Health, Winnipeg, Manitoba, Canada; the ²Department of Pediatrics and Child Health, Faculty of Medicine, University of Manitoba, Winnipeg, Manitoba, Canada; the ³Pennington Biomedical Research Center, Department of Preventive Medicine, Baton Rouge, Louisiana; the ⁴Arnold School of Public Health, University of South Carolina, Columbia, South Carolina; the ⁵Sport Health and Exercise Science, Department for Health, University of Bath, Bath, U.K.; and the ⁶John Ochsner Heart and Vascular Institute, Ochsner Clinical School, The University of Queensland School of Medicine, New Orleans, Louisiana.

Corresponding author: Timothy S. Church, timothy.church@pbr.edu.

Received 21 November 2012 and accepted 7 March 2013.

DOI: 10.2337/dc12-2428. Clinical trial reg. no. NCT00458133, clinicaltrials.gov.

© 2013 by the American Diabetes Association. Readers may use this article as long as the work is properly cited, the use is educational and not for profit, and the work is not altered. See <http://creativecommons.org/licenses/by-nc-nd/3.0/> for details.

muscle strength, and cardiorespiratory fitness and change in HbA_{1c}.

RESEARCH DESIGN AND METHODS

Participants

The full methodology for HART-D has been previously described in the main outcomes paper (6). Briefly, the HART-D study enrolled 262 sedentary individuals aged 30–75 years with type 2 diabetes. Participants were excluded if they had a BMI of ≥ 48.0 kg/m², blood pressure $\geq 160/100$ mmHg, fasting triglyceride level ≥ 500 mg/dL, urine protein level >100 mg/dL, and serum creatinine level >1.5 mg/dL; used an insulin pump; or had a history of stroke, advanced neuropathy or retinopathy, or any serious medical condition that prevented them from adhering to the protocol or exercising safely. Demographic information was collected by self-report questionnaire. Information about type 2 diabetes medications (dose and class) were documented with a detailed questionnaire and confirmed by a visual inspection of the medication bottle. The Pennington Biomedical Research Center institutional review board annually approved the protocol, and all participants provided written informed consent.

Study design

The current study was a secondary analysis of the HART-D data. Of the 262 participants randomized in HART-D, 61 were excluded from this analysis because of either missing baseline ($n = 1$), follow-up exercise ($n = 54$), or follow-up body composition ($n = 5$) data. One participant was excluded from the control group because she gained 6 kg of trunk fat mass. The final analysis included 201 participants (Fig. 1).

Exercise intervention

Aerobic training. Participants in the aerobic training group exercised 3–5 days per week at an exercise intensity of 50–80% of their maximal cardiorespiratory fitness for a total dose of 12 kcal/kg body weight per week. Participants were weighed weekly to calculate their prescribed caloric dose. During weeks 12 and 24, we reduced the exercise dose by one-third to provide a recuperation week. American College of Sports Medicine equations were used to estimate caloric expenditure rate and, therefore, the time required per session (14).

Resistance training. Participants exercised 3 days per week, with each session consisting of two sets of four upper-body exercises (bench press, seated row, shoulder press, and lat pull down), three sets of

three lower-body exercises (leg press, leg extension, and leg curl), and two sets of abdominal crunches and back extensions. Each set comprised 10–12 repetitions. The prescribed weight was increased when the participant was able to complete 12 repetitions of the final set of each exercise on two consecutive sessions.

Combination training. We selected an aerobic exercise dose of 10 kcal/kg body weight per week and two sessions of resistance training per week for the combination training group. Resistance training comprised one set of 10–12 repetitions of the same nine exercises, using a similar progressive resistance program as the resistance training group. The combination training group was consistent with federal physical activity guidelines (15) and ensured equal time commitment among all exercise groups.

Control group. Participants randomized to the nonexercise control group were offered weekly stretching and relaxation classes once per week and were asked to maintain their current lifestyle.

Outcomes and measurements

Cardiorespiratory fitness. Cardiorespiratory fitness was evaluated by a modified Balke treadmill test (Trackmaster 425; Carefusion, Newton, KS), with respiratory gases sampled by a TrueMax 2400

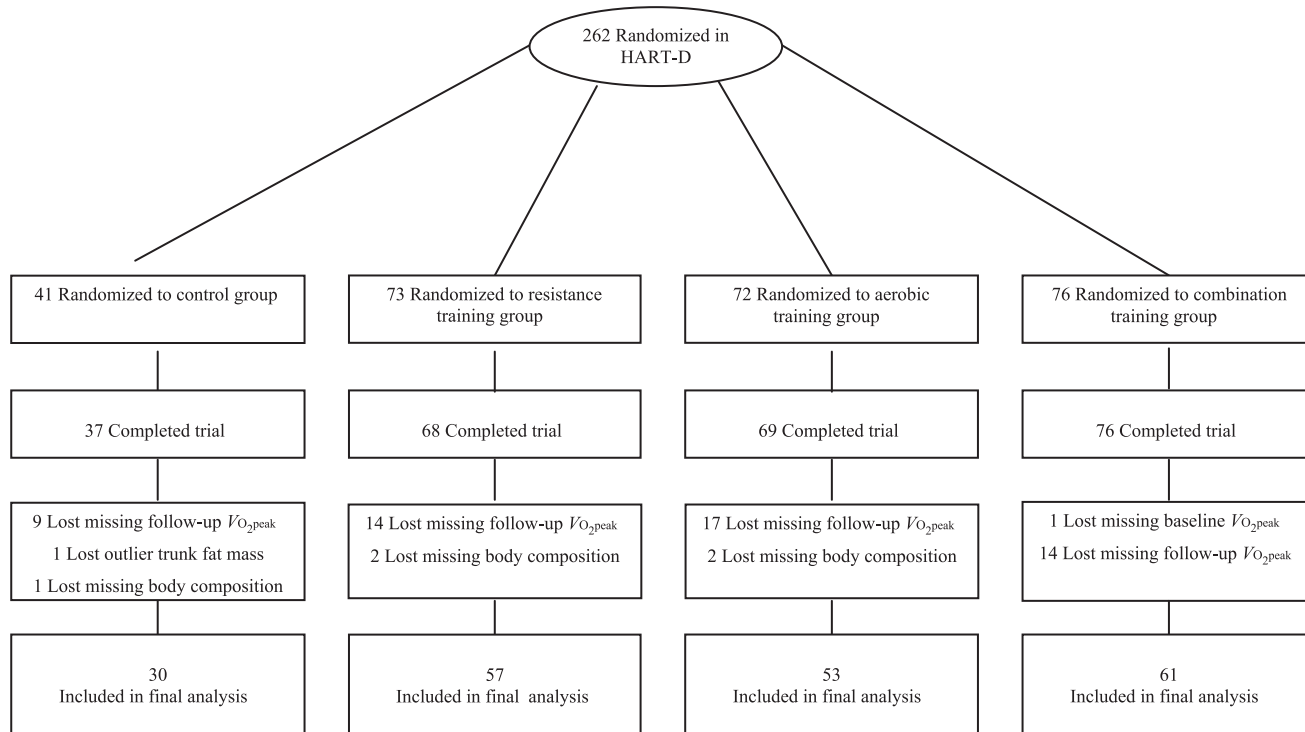


Figure 1—Consort diagram.

Metabolic Measurement Cart (ParvoMedics, Salt Lake City, UT). Briefly, participants self-selected a walking pace at a level grade, and the grade increased by 2% every 2 min until they reached voluntary exhaustion. Peak O_2 uptake (VO_{2peak}) was reported relative to total and lean body mass.

Estimated METs. METs are strongly correlated with cardiorespiratory fitness, and measured VO_2 is not available in most cardiology and clinical exercise settings. Therefore, it is relevant to quantify estimated METs from a clinical perspective. Estimated METs were derived from the maximal speed and grade reached during the cardiorespiratory fitness test at baseline and follow-up, using equations from the American College of Sports Medicine (14).

Leg muscle strength. Concentric isokinetic knee extension torque was assessed with a Biodex System 3 dynamometer (Biodex Medical Systems, Shirley, NY), and peak torque was determined as the highest measured torque over five maximal repetitions.

HbA_{1c}. Baseline and postintervention HbA_{1c} was obtained by venipuncture after a 10-h fast and analyzed with Beckman Coulter DxC 600 Pro (Brea, CA).

Anthropometric measures and body composition. Weight was measured on a GSE 450 electronic scale (GSE, Livonia, MI), and height was measured with a standard stadiometer. BMI was calculated as body weight in kilograms divided by height in meters squared. Waist circumference was measured to the nearest 0.1 cm at the level of the iliac crest while the subject was at minimal expiration. Body composition was measured by dual-energy X-ray absorptiometry (DEXA) with the QDR 4500A whole-body scanner (Hologic Inc., Bedford, MA).

Statistical analysis

All analyses were performed with SAS version 9.2 (SAS Institute Inc., Cary, NC) statistical software. Baseline continuous data are presented as mean \pm SD, whereas categorical variables are presented as *n* (%). A one-way ANOVA was performed to identify baseline differences between groups for continuous variables. A χ^2 test was used to assess baseline differences among groups in categorical variables. Spearman correlations were performed to determine the associations between changes in body composition, cardiorespiratory fitness, and isokinetic leg

muscle strength and change in HbA_{1c}. A multiple linear regression model was performed to test the impact of intervention on changes in HbA_{1c}. Unadjusted and adjusted multiple linear regression models revealed that intervention groups were not significantly associated with changes in HbA_{1c} (unadjusted $P = 0.17$, adjusted $P = 0.18$); therefore, a combined analysis strategy was used. Multiple linear regression models were used to identify differences of change in HbA_{1c} across quartiles of change in body composition, cardiorespiratory fitness, and isokinetic leg muscle strength and are presented as adjusted least squares mean with 95% CI.

Multiple logistic regression was used to determine the odds of improving HbA_{1c} ($\Delta < 0\%$) on the basis of estimated METs and trunk fat mass as well as estimated METs and waist circumference response after the intervention. A dichotomous variable was coded for estimated METs and trunk fat mass to indicate a favorable response (Δ estimated METs > 0 , Δ trunk fat mass < 0 kg) and an unfavorable response or no change (Δ estimated METs ≤ 0 , Δ trunk fat mass ≥ 0 kg) after exercise training. The responses for estimated METs and trunk fat mass were combined to determine the effect on the odds of a favorable response in HbA_{1c}. A similar dichotomous variable was computed for waist circumference and estimated METs. These models were adjusted for age, sex, race/ethnicity, smoking, medication changes, duration of diabetes, and baseline HbA_{1c} value.

Change in HbA_{1c} ($\leq -0.5\%$) or in type 2 diabetes medication use (decrease or discontinuation) suggests an improvement in long-term glucose control (6). Thus, multiple logistic regression was used to determine the odds of reducing HbA_{1c} ($\leq -0.5\%$) or type 2 diabetes medications for glucose control (decrease or discontinuation) on the basis of exercise-induced changes in estimated METs and trunk fat mass as well as estimated METs and waist circumference (see previous paragraph). In this analysis, a dichotomous variable was created for change in HbA_{1c} (Δ HbA_{1c} $\leq -0.5\% = 1$, Δ HbA_{1c} $> -0.5\% = 0$), and a dichotomous variable was created for change in type 2 diabetes medications (reduction/discontinuation = 1, increase = 0, no change = 0). These dichotomous variables were coded into a single dependent variable, and the models were adjusted for age, sex, race/ethnicity, smoking, baseline

HbA_{1c} value, and duration of diabetes. Data are presented as odds ratio (OR) (95% CI). Statistical significance was defined as a two-tailed $P \leq 0.05$.

RESULTS—Baseline characteristics are shown in Table 1. The study sample comprised 56.2% non-Hispanic white, 63.7% women, 1.5% current smokers, and 28.9% former smokers. The mean age of the sample was 56.7 ± 8.0 years, and the mean BMI was 34.3 ± 5.7 kg/m². Relative VO_{2peak} was 19.5 ± 4.3 mL·kg⁻¹·min⁻¹, and mean type 2 diabetes duration was 7.3 ± 5.6 years. Significant differences were observed among exercise groups at baseline for race/ethnicity ($P = 0.048$) and HbA_{1c} ($P = 0.037$).

The associations between change in HbA_{1c} and changes in body composition, cardiorespiratory fitness, and isokinetic leg muscle strength after 9 months of intervention are shown in Table 2. Unadjusted change in HbA_{1c} was associated with changes in body weight ($P = 0.052$), waist circumference ($P = 0.013$), and trunk fat mass ($P = 0.005$) and inversely associated with estimated METs ($P = 0.023$).

Adjusted change in anthropometry, body composition, fitness, and strength measures across quartiles of changes in HbA_{1c} are shown in Table 3. A significant trend was observed for decrease in body weight ($P = 0.013$), BMI ($P = 0.025$), and trunk fat mass ($P = 0.020$) across quartiles of changes in HbA_{1c}. Similarly, a significant trend was observed for decrease in waist circumference ($P = 0.011$), with the greatest reduction in HbA_{1c} in the highest quartile. No significant trend was observed for decrease in total fat mass across quartiles of changes in HbA_{1c} ($P = 0.154$). A significant trend was observed for increase in estimated METs ($P = 0.011$) across quartiles of changes in HbA_{1c}. No other fitness measures (VO_{2peak} , muscle strength) were significantly associated with change in HbA_{1c} ($P > 0.05$ for trend).

Table 4 describes the odds of reducing HbA_{1c} on the basis of a favorable response for estimated METs and trunk fat mass (Δ estimated METs > 0 , Δ trunk fat mass < 0 kg) or estimated METs and waist circumference (Δ estimated METs > 0 , Δ waist circumference < 0 cm). The likelihood of a favorable response (Δ HbA_{1c} $< 0\%$) was 3.48 (95% CI 1.46–8.31) in participants who had increased estimated METs and decreased trunk fat mass and 4.57 (1.80–11.65) in

Table 1—Baseline characteristics

	Control (n = 30)	Aerobic (n = 53)	Resistance (n = 57)	Combined (n = 61)	P value
General characteristics					
Age (years)	58.6 ± 8.5	55.1 ± 8.3	58.1 ± 8.3	55.9 ± 7.2	0.122
Male	11 (36.6)	18 (33.9)	24 (42.1)	20 (32.7)	0.733
Race/ethnicity					
Non-Hispanic white	17 (56.6)	33 (62.3)	32 (56.1)	31 (50.8)	0.679
African American	11 (36.6)	20 (37.7)	24 (42.1)	24 (39.3)	0.954
Hispanic/other	2 (6.6)	0 (0.0)	1 (1.7)	6 (9.8)	0.048
Smoking					
Current	1 (3.3)	0 (0.0)	1 (1.7)	1 (1.6)	0.675
Former	10 (33.3)	14 (26.4)	19 (33.3)	15 (24.5)	0.672
Body composition					
Weight (kg)	98.9 ± 20.6	94.4 ± 14.8	96.2 ± 15.9	96.5 ± 18.5	0.718
BMI (kg/m ²)	35.3 ± 6.3	34.0 ± 5.6	33.9 ± 5.4	34.7 ± 5.9	0.614
Waist circumference (cm)	110.6 ± 14.8	108.9 ± 12.2	111.3 ± 11.9	112.0 ± 13.0	0.632
Body fat (%)	38.7 ± 7.2	37.3 ± 7.6	36.7 ± 8.0	38.5 ± 6.9	0.505
Total fat mass (kg)	38.9 ± 12.1	35.4 ± 9.4	35.8 ± 10.5	37.8 ± 11.1	0.400
Peripheral fat mass (kg)	13.3 ± 4.5	12.0 ± 4.0	11.9 ± 4.4	12.7 ± 4.6	0.442
Trunk fat mass (kg)	20.2 ± 6.9	18.9 ± 4.9	19.5 ± 5.4	20.3 ± 5.9	0.518
Total LBM (kg)	57.9 ± 11.9	56.8 ± 11.0	58.4 ± 10.9	57.0 ± 11.6	0.867
Peripheral LBM (kg)	26.7 ± 5.8	25.7 ± 5.5	26.3 ± 5.4	26.0 ± 6.0	0.857
Exercise test variables					
Absolute V _{O₂} peak (L/min)	1.8 ± 0.4	1.9 ± 0.5	1.9 ± 0.5	1.8 ± 0.4	0.668
Relative V _{O₂} peak (mL·kg ⁻¹ ·min ⁻¹)	18.7 ± 3.7	20.4 ± 5.1	19.8 ± 4.5	18.9 ± 3.3	0.209
Relative V _{O₂} peak (mL·LBM ⁻¹ ·min ⁻¹)	31.6 ± 4.3	33.5 ± 5.4	32.2 ± 4.8	31.7 ± 3.7	0.175
Estimated METs	6.8 ± 1.2	7.1 ± 1.6	7.0 ± 1.3	6.8 ± 1.0	0.453
Isokinetic leg muscle strength (Nm)	127.7 ± 39.1	133.2 ± 45.4	129.7 ± 45.4	124.2 ± 49.0	0.763
Diabetes					
HbA _{1c} (%)	7.6 ± 1.4	7.0 ± 0.9	7.1 ± 1.0	7.2 ± 1.1	0.037
Diabetes duration (years)	7.3 ± 5.0	7.2 ± 5.8	7.6 ± 5.8	6.9 ± 5.6	0.933

Data are mean ± SD on n (%). LBM, lean body mass; Nm, newton meter.

participants who had increased estimated METs and decreased waist circumference compared with those with an unfavorable response. However, the interactions between increase in estimated METs and decrease in trunk fat mass ($P = 0.435$) or decrease in waist circumference ($P = 0.863$) were not significantly associated with change in HbA_{1c}. Additionally, in participants with increased estimated METs and decreased waist circumference, the likelihood of a favorable response (improve HbA_{1c}, reduced diabetes medications, or both) was 2.81 (1.13–6.98) compared with those with an unfavorable response after the intervention. Similarly, the interaction between an increase in estimated METs and a decrease in trunk fat mass ($P = 0.760$) or waist circumference ($P = 0.884$) was not significant.

CONCLUSIONS—The primary results of the current study suggest that reducing central adiposity and increasing fitness in a large sample of men and

women with type 2 diabetes are critical factors to improving glycemic control (HbA_{1c}) after an exercise training program. Additionally, the data suggest that a decrease in central adiposity and an increase in fitness increase the likelihood of achieving a favorable HbA_{1c} response (>0.5% decrease) or reducing the number of medications required for the treatment of type 2 diabetes. These findings have clinical implications for the design of exercise training programs used to treat individuals with type 2 diabetes because they suggest that a concomitant reduction in central adiposity and increase in fitness should be the main focus of an exercise intervention aiming to improve glycemic control.

The relationship between the change in central adiposity and change in HbA_{1c} is supported by previous studies (9,11,16). Bacchi et al. (11) found that change in trunk fat mass was the strongest predictor for change in HbA_{1c} after 4 months of aerobic or resistance training

alone in patients with type 2 diabetes. Castaneda et al. (9) investigated the impact of resistance training on body composition and glycemic control in individuals with type 2 diabetes and found that a decrease in trunk fat mass was accompanied by a reduction of 1.1% in HbA_{1c} after resistance training. Doyon et al. (17) reported an association between trunk fat mass measured by DEXA and visceral fat mass measured by CT scan before ($r = 0.61$, $P \leq 0.01$) and after ($r = 0.67$, $P \leq 0.01$) an intervention of weight loss with or without resistance training in a cohort of obese postmenopausal women. Therefore, loss in visceral fat may, at least in part, be responsible for the reduction in HbA_{1c} observed in the current study because previous research suggests that a reduction in visceral fat improves glycemic control in individuals with type 2 diabetes (18–20). In support of this hypothesis, a study by Giannopoulou et al. (21) suggested that exercise is mandatory to decrease visceral fat in

Table 2—Spearman correlation coefficients between change in body composition, fitness measures, and isokinetic leg muscle strength and change in HbA_{1c}

Variable	Change in HbA _{1c}	
	r	P value
Weight	0.13	0.052
BMI	0.12	0.089
Waist circumference	0.17	0.013
Total body fat	0.10	0.146
Total fat mass	0.10	0.130
Peripheral fat mass	0.06	0.386
Trunk fat mass	0.19	0.005
Total lean body mass	0.03	0.659
Peripheral lean body mass	-0.04	0.529
Absolute VO _{2 peak} (L/min)	0.04	0.495
Relative VO _{2 peak} (mL·kg ⁻¹ ·min ⁻¹)	-0.01	0.940
Relative VO _{2 peak} (mL·LBM ⁻¹ ·min ⁻¹)	0.02	0.761
Estimated METs	-0.16	0.023
Isokinetic leg muscle strength	0.01	0.947

individuals with type 2 diabetes. This decrease in visceral fat mass would decrease free fatty acid flux and improve glucose disposal (22), which would improve glycemic control. Secondary analyses revealed that trunk fat mass measured by

DEXA was significantly associated with waist circumference ($r = 0.87$, $P < 0.0001$), which supports that waist circumference is an appropriate surrogate measure to evaluate the improvement in central adiposity from exercise training because trunk and visceral fat mass are not evaluated in most clinical and exercise settings. We also found that a reduction in central adiposity (measured by trunk fat mass or waist circumference) was associated with a reduction in HbA_{1c}. Additionally, when this reduction in central adiposity occurred with an improvement in estimated METs, it was associated with a greater odds of improving glucose control or decreasing the number of diabetes medications. Therefore, the current results suggest that a reduction in central adiposity is associated with an improvement in HbA_{1c}, which is optimized by the concomitant increase in fitness, in individuals with type 2 diabetes.

Of note, the results show an association between the change in fitness (measured by estimated METs) and change in HbA_{1c} but not VO_{2peak}. The change in cardiorespiratory fitness was associated with a change in estimated METs ($P < 0.0001$), but the variability between the measures was surprisingly low ($\sim 31\%$, $r = 0.56$). In contrast, in a similar study, Larose et al. (12) showed that cardiorespiratory fitness measured by a VO_{2max}

treadmill test was a strong predictor of change in HbA_{1c}, whereas treadmill time to exhaustion was only marginally associated with a reduction in HbA_{1c}. This result is controversial because the current study found a strong association between changes in treadmill time to exhaustion and change in HbA_{1c} (data not shown [$P = 0.01$ for trend]). The discrepancy between the current results and those of Larose et al. may lie on the statistical analysis strategy used (per group versus combined groups), differences in exercise dose in the combined group (full aerobic and full resistance training versus a reduced dose in HART-D for the combined group), and overall intervention design. Although the specific rationale explaining the lack of a relationship between VO_{2max} and HbA_{1c} is unknown, the estimated METs and workload on a treadmill are associated with cardiovascular and all-cause mortality in individuals with type 2 diabetes (23–25). Furthermore, other exercise training studies found that reductions in HbA_{1c} are associated with an increase in treadmill time to exhaustion (26,27). Considering that treadmill time to exhaustion and estimated METs were associated with changes in HbA_{1c}, the current findings may have relevant clinical applications because these fitness measures typically are evaluated in clinical settings. However, the fitness results

Table 3—Changes in exposure variables across quartiles of change in HbA_{1c}

Exposure variable	Δ HbA _{1c}				P for trend
	Quartile 1 (range 0.25 to 4.40%)	Quartile 2 (range -0.10 to 0.20%)	Quartile 3 (range -0.55 to -0.10%)	Quartile 4 (range -3.55 to -0.60%)	
Weight (kg)	0.11 (-0.78 to 1.01)	-0.03 (-0.93 to 0.86)	-1.69 (-2.60 to -0.78)	-1.07 (-1.97 to -0.17)	0.013
BMI (kg/m ²)	0.02 (-0.30 to 0.34)	-0.06 (-0.38 to 0.26)	-0.61 (-0.94 to -0.28)	-0.36 (-0.68 to -0.03)	0.025
Waist circumference (cm)	-0.84 (-1.95 to 0.27)	-1.15 (-2.26 to -0.04)	-2.02 (-3.15 to -0.90)	-2.72 (-3.83 to -1.60)	0.011
Total body fat (%)	-0.38 (-0.87 to 0.10)	-0.64 (-1.12 to -0.15)	-1.09 (-1.58 to -0.59)	-0.67 (-1.15 to -0.18)	0.250
Total fat mass (kg)	-0.54 (-1.23 to 0.15)	-0.85 (-1.54 to -0.15)	-1.67 (-2.37 to -0.97)	-1.03 (-1.73 to -0.34)	0.154
Peripheral fat mass (kg)	-0.15 (-0.45 to 0.13)	-0.20 (-0.49 to 0.08)	-0.42 (-0.71 to -0.12)	-0.24 (-0.54 to 0.04)	0.476
Trunk fat mass (kg)	-0.13 (-0.57 to 0.29)	-0.49 (-0.92 to -0.05)	-1.11 (-1.55 to -0.67)	-0.72 (-1.15 to -0.28)	0.020
Total LBM (kg)	0.18 (-0.38 to 0.75)	0.50 (-0.07 to 1.07)	-0.08 (-0.66 to 0.49)	-0.02 (-0.60 to 0.54)	0.360
Peripheral LBM (kg)	-0.02 (-0.37 to 0.31)	0.24 (-0.09 to 0.58)	0.10 (-0.23 to 0.45)	0.18 (-0.15 to 0.52)	0.502
Absolute VO _{2 peak} (L/min)	0.02 (-0.02 to -0.08)	0.01 (-0.03 to 0.07)	0.01 (-0.04 to 0.07)	0.03 (-0.02 to 0.09)	0.888
Relative VO _{2 peak} (mL·kg ⁻¹ ·min ⁻¹)	0.26 (-0.37 to -0.91)	0.25 (-0.38 to 0.88)	0.48 (-0.16 to 1.13)	0.53 (-0.10 to 1.18)	0.479
Relative VO _{2 peak} (mL·LBM ⁻¹ ·min ⁻¹)	0.38 (-0.61 to 1.38)	0.23 (-0.75 to 1.21)	0.23 (-0.76 to 1.24)	0.38 (-0.61 to 1.38)	0.998
Estimated METs	0.11 (-0.15 to 0.39)	0.46 (0.19 to 0.73)	0.73 (0.45 to 1.00)	0.56 (0.29 to 0.83)	0.011
Isokinetic leg muscle strength (Nm)	5.04 (-1.13 to 11.21)	3.83 (-2.33 to 10.01)	8.73 (2.49 to 14.98)	4.03 (-2.14 to 10.21)	0.900

Data are adjusted mean (95% CI). Analyses were adjusted for age, sex, smoking, race/ethnicity, medication changes, and baseline HbA_{1c}. LBM, lean body mass; Nm, newton meter.

Table 4—Odds of improving HbA_{1c} and decreasing type 2 diabetes medications across group of change in fitness and central adiposity

Variable	Δ HbA _{1c} ^a	Δ HbA _{1c} and/or Δ medications ^b
Trunk fat mass		
Decrease estimated METs and increase TFM (Δ estimated METs \leq 0, Δ TFM \geq 0 kg)	1.00	1.00
Decrease estimated METs and decrease TFM (Δ estimated METs \leq 0, Δ TFM $<$ 0 kg)	1.22 (0.52–2.84)	1.54 (0.67–3.55)
Increase estimated METs and increase TFM (Δ estimated METs $>$ 0, Δ TFM \geq 0 kg)	1.66 (0.54–5.08)	2.06 (0.70–6.08)
Increase estimated METs and decrease TFM (Δ estimated METs $>$ 0, Δ TFM $<$ 0 kg)	3.48 (1.46–8.31)	1.84 (0.79–4.25)
Waist circumference		
Decrease estimated METs and increase WC (Δ estimated METs \leq 0, Δ WC \geq 0 cm)	1.00	1.00
Decrease estimated METs and decrease WC (Δ estimated METs \leq 0, Δ WC $<$ 0 cm)	1.97 (0.81–4.80)	2.30 (0.93–5.62)
Increase estimated METs and increase WC (Δ estimated METs $>$ 0, Δ WC \geq 0 cm)	2.62 (0.78–8.77)	1.82 (0.56–5.88)
Increase estimated METs and decrease WC (Δ estimated METs $>$ 0, Δ WC $<$ 0 cm)	4.57 (1.80–11.65)	2.81 (1.13–6.98)

Data are OR (95% CI). Δ HbA_{1c} is adjusted for age, sex, smoking, race/ethnicity, diabetes duration, medication changes, and baseline HbA_{1c}, whereas Δ HbA_{1c} and/or diabetes medication is adjusted for age, sex, smoking, race/ethnicity, diabetes duration, and baseline HbA_{1c}. TFM, trunk fat mass; WC, waist circumference. ^a Δ HbA_{1c} $<$ 0% = 1, Δ HbA_{1c} \geq 0% = 0. ^b Δ HbA_{1c} \leq -0.5% = 1, Δ HbA_{1c} $>$ -0.5% = 0 and/or reduction/discontinuation = 1, increase/no change = 0.

are especially relevant to exercise clinicians, who should prescribe training programs that can safely promote the greatest reduction in central adiposity and improvement in fitness in individuals with type 2 diabetes.

In the current study, improvement in muscle strength was not related to reductions in HbA_{1c}, which is in contrast with previous studies (7,12) that found that the combination of resistance and aerobic training were the most beneficial for improvement in glucose control. Perhaps resistance training contributes either to the improvement in fitness or the reduction in central adiposity. In HART-D, the combined training group had the greatest reduction in trunk fat mass, even when compared with the aerobic group, and a significant improvement in treadmill time to exhaustion. In contrast to the current results, Larose et al. (12) reported that change in muscle strength was associated with change in HbA_{1c}. The observed disparity may be explained by the different muscle limb measurement (upper versus lower) or methodology used to quantify change in muscle strength (one repetition maximum versus Biodex). It has been reported that using dissimilar training and testing modalities might compromise the capability to quantify muscle strength changes (28). Nevertheless, previous studies performed in individuals with type 2 diabetes support our observation. For example, Ishii et al. (29) and Ibañez et al. (30) did not observe an association between changes in muscle strength and changes in HbA_{1c}, despite a 16 and 17% increase in muscle strength, respectively.

A potential limitation of our study is the lack of gold standard measures for visceral fat mass and oral glucose

tolerance test, which could have given insight into the mechanism underlying the improvement in HbA_{1c}. Strengths of our study were the large sample size and the standardized and tightly supervised exercise training session. Another strength was that HART-D participants had excellent compliance ($>$ 80%) to exercise training, and we adjusted the analyses for potential confounding variables that may affect HbA_{1c}. Finally, the sample was diverse in terms of age, sex, and race/ethnicity (39.3% African American), which makes the findings generalizable, although the overall study group was generally middle-aged, obese, and with relatively poor baseline fitness.

In conclusion, this study suggests that trunk fat mass and estimated METs are both associated with changes in HbA_{1c}. From a clinical standpoint, the goals behind physical activity programs in individuals with type 2 diabetes should be to maximize the increase in fitness and decrease in central fat mass (especially waist circumference) to reduce HbA_{1c}. Future research should investigate the specific mechanisms by which exercise training-related increases in fitness and central adiposity reduction improve HbA_{1c} in individuals with type 2 diabetes.

Acknowledgments—This work was supported by National Institutes of Health Grant DK-068298. The National Institutes of Health T32 postdoctoral fellowship program (Obesity from Genes to Man) and the Manitoba Health Research Council supported the salary and training of D.L.S. and M.S., respectively.

No potential conflicts of interest relevant to this article were reported.

The sponsor had no role in the design, protocol development, or conducting of the

trial, data collection, data analysis, or preparation of the manuscript.

M.S. analyzed the data and wrote the manuscript. D.L.S. wrote and reviewed the manuscript. N.M.J. researched data, analyzed data, and wrote and reviewed the manuscript. S.N.B., C.P.E., and C.J.L. edited and reviewed the manuscript. T.S.C. edited and reviewed the manuscript and was the primary investigator of the HART-D study. T.S.C. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

References

- Colberg SR, Albright AL, Blissmer BJ, et al; American College of Sports Medicine; American Diabetes Association. Exercise and type 2 diabetes: American College of Sports Medicine and the American Diabetes Association: joint position statement. *Exercise and type 2 diabetes*. *Med Sci Sports Exerc* 2010;42:2282–2303
- 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 executive summary. *Diabetes Care* 2010;33:2692–2696
- Pate RR, Pratt M, Blair SN, et al. Physical activity and public health. A recommendation from the Centers for Disease Control and Prevention and the American College of Sports Medicine. *JAMA* 1995; 273:402–407
- Zinman B, Ruderman N, Campagne BN, Devlin JT, Schneider SH; American Diabetes Association. Physical activity/exercise and diabetes mellitus. *Diabetes Care* 2003;26(Suppl. 1):S73–S77
- U.S. Department of Health and Human Services. *Physical Activity and Health: A Report of the Surgeon General*. Atlanta, GA,

- U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, 1996
6. Church TS, Blair SN, Cooreham S, et al. Effects of aerobic and resistance training on hemoglobin A1c levels in patients with type 2 diabetes: a randomized controlled trial. *JAMA* 2010;304:2253–2262
 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;147:357–369
 8. 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;27:841–842
 9. 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;25:2335–2341
 10. 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;25:1729–1736
 11. Bacchi E, Negri C, Zanolin ME, et al. Metabolic effects of aerobic training and resistance training in type 2 diabetic subjects: a randomized controlled trial (the RAED2 study). *Diabetes Care* 2012;35:676–682
 12. Larose J, Sigal RJ, Khandwala F, Prud'homme D, Boulé NG, Kenny GP; Diabetes Aerobic and Resistance Exercise (DARE) trial investigators. Associations between physical fitness and HbA_{1c} in type 2 diabetes mellitus. *Diabetologia* 2011;54:93–102
 13. Tokmakidis SP, Zois CE, Volaklis KA, Kotsa K, Touvra AM. The effects of a combined strength and aerobic exercise program on glucose control and insulin action in women with type 2 diabetes. *Eur J Appl Physiol* 2004;92:437–442
 14. American College of Sports Medicine. *ACSM's Guidelines for Exercise Testing and Prescription*. 7th ed. Philadelphia, Lippincott Williams & Wilkins, 2006
 15. U.S. Department of Health and Human Services. 2008 Physical activity guidelines for Americans [Internet], 2008. Washington, DC, U.S. Department of Health and Human Services. Available from <http://www.health.gov/paguidelines/pdf/paguide.pdf>. Accessed 29 March 2013
 16. 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;26:2977–2982
 17. Doyon CY, Brochu M, Messier V, et al. Association between abdominal fat (DXA) and its subcomponents (CT scan) before and after weight loss in obese postmenopausal women: a MONET study. *J Obes* 2011;2011:239516.
 18. Mourier A, Gautier JF, De Kerviler E, et al. Mobilization of visceral adipose tissue related to the improvement in insulin sensitivity in response to physical training in NIDDM. Effects of branched-chain amino acid supplements. *Diabetes Care* 1997;20:385–391
 19. Boudou P, De Kerviler E, Vexiau P, Fiet J, Cathelineau G, Gautier J. Effects of a single bout of exercise and exercise training on steroid levels in middle-aged type 2 diabetic men: relationship to abdominal adipose tissue distribution and metabolic status. *Diabetes Metab* 2000;26:450–457
 20. Boudou P, Sobngwi E, Mauvais-Jarvis F, Vexiau P, Gautier JF. Absence of exercise-induced variations in adiponectin levels despite decreased abdominal adiposity and improved insulin sensitivity in type 2 diabetic men. *Eur J Endocrinol* 2003;149:421–424
 21. Giannopoulou I, Ploutz-Snyder LL, Carhart R, et al. Exercise is required for visceral fat loss in postmenopausal women with type 2 diabetes. *J Clin Endocrinol Metab* 2005;90:1511–1518
 22. Park HS, Lee K. Greater beneficial effects of visceral fat reduction compared with subcutaneous fat reduction on parameters of the metabolic syndrome: a study of weight reduction programmes in subjects with visceral and subcutaneous obesity. *Diabet Med* 2005;22:266–272
 23. Church TS, Cheng YJ, Earnest CP, et al. Exercise capacity and body composition as predictors of mortality among men with diabetes. *Diabetes Care* 2004;27:83–88
 24. Church TS, LaMonte MJ, Barlow CE, Blair SN. Cardiorespiratory fitness and body mass index as predictors of cardiovascular disease mortality among men with diabetes. *Arch Intern Med* 2005;165:2114–2120
 25. Wei M, Gibbons LW, Kampert JB, Nichaman MZ, Blair SN. Low cardiorespiratory fitness and physical inactivity as predictors of mortality in men with type 2 diabetes. *Ann Intern Med* 2000;132:605–611
 26. Larose J, Sigal RJ, Boulé NG, et al. Effect of exercise training on physical fitness in type II diabetes mellitus. *Med Sci Sports Exerc* 2010;42:1439–1447
 27. 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;14:837–843
 28. Weiss EP, Racette SB, Villareal DT, et al; Washington University School of Medicine CALERIE Group. Lower extremity muscle size and strength and aerobic capacity decrease with caloric restriction but not with exercise-induced weight loss. *J Appl Physiol* 2007;102:634–640
 29. Ishii T, Yamakita T, Sato T, Tanaka S, Fujii S. Resistance training improves insulin sensitivity in NIDDM subjects without altering maximal oxygen uptake. *Diabetes Care* 1998;21:1353–1355
 30. Ibañez J, Izquierdo M, Argüelles I, et al. Twice-weekly progressive resistance training decreases abdominal fat and improves insulin sensitivity in older men with type 2 diabetes. *Diabetes Care* 2005;28:662–667