Available online at www.sciencedirect.com

Metabolism

www.metabolismjournal.com

Change of energy expenditure from physical activity is the most powerful determinant of improved insulin sensitivity in overweight patients with coronary artery disease participating in an intensive lifestyle modification program

Marie C. Audelin[*,1], *Patrick D. Savage, Michael J. Toth, Jean Harvey-Berino, David J. Schneider, Janice Y. Bunn, Maryann Ludlow, Philip A. Ades*

Divisions of Cardiology, Nutrition, and Biometry, University of Vermont College of Medicine, Burlington VT

ARTICLE INFO

Article history:
Received 24 November 2010
Accepted 7 October 2011

ABSTRACT

The objective was to evaluate the determinants of change (Δ) in insulin sensitivity in overweight coronary artery disease male patients without diabetes after an intensive lifestyle intervention. All patients received nutritional counseling and performed 4 months of exercise training (ET) according to 1 of 2 protocols: aerobic ET (65%-70% of peak aerobic capacity [VO_2]) 25 to 40 minutes 3 times a week (n = 30) or walking (50%-60% of peak VO_2) 45 to 60 minutes at least 5 times a week (n = 30). Data from participants of both ET groups were pooled, and post–intensive lifestyle intervention results were compared with baseline data. The primary outcome was Δ insulin sensitivity (*m*-value) assessed by the criterion standard technique, the euglycemic-hyperinsulinemic clamp. Changes in weight, body mass index, total and percentage fat mass (by dual-energy x-ray absorptiometry scan), waist circumference, total abdominal and visceral fat (by computed tomographic scan), high-sensitivity C-reactive protein, peak VO_2, daily energy intake, and physical activity energy expenditure (PAEE) (by doubly labeled water technique) were also assessed. Daily energy intake decreased by 335 kcal, and PAEE increased by 482 kcal/d (all $P < .0001$). The mean weight loss was 6.4 kg, and the mean improvement in *m*-value was 1.6 mg/kg fat-free mass per minute. Univariate determinants of Δ *m*-value were low baseline PAEE, walking protocol, Δ weight, Δ body mass index, Δ total and percentage fat mass, Δ waist circumference, Δ total abdominal and visceral fat, and Δ PAEE (all $P < .05$). In multivariate analysis, the only significant determinant of Δ *m*-value was Δ PAEE ($P < .02$). In this analysis, the most powerful determinant of improved insulin sensitivity in overweight coronary artery disease patients is the change in PAEE.

Author contributions: MCA was responsible for statistical analysis, data interpretation, literature review, and manuscript writing; PDS was responsible for study design and conduct, data collection, and manuscript revision and edition; MJT was responsible for study design and manuscript revision and edition, and contributed to discussion; JHB was responsible for study design and manuscript revision; DJS was responsible for study design and manuscript revision; JYB was responsible for statistical analysis guidance and manuscript revision; ML was responsible for data collection and manuscript revision; and PAA was responsible for study design and conduct, data collection, and manuscript revision and edition, and contributed to discussion.

* *Corresponding author*. Division of Cardiology, Quebec Heart and Lung Institute, Quebec City (QC), Canada, G1V 4G5. Tel.: +1 418 656 4767; fax: +1 418 656 4581.

E-mail address: Marie-Chantal.Audelin@criucpq.ulaval.ca (M.C. Audelin).

[1] Current affiliation of Dr Audelin: Division of Cardiology, Quebec Heart and Lung Institute, Quebec City, Quebec, Canada.

0026-0495/$ – see front matter.
doi:10.1016/j.metabol.2011.10.001

1. Introduction

Type 2 diabetes mellitus and the metabolic syndrome (MS) markedly increase the rate of recurrent coronary events and the risk of mortality in patients with established coronary artery disease (CAD) [1-8]. In the cardiac rehabilitation (CR) setting, the percentage of patients with type 2 diabetes mellitus increased from 17% to 25% from 1996 to 2006; and more than 50% of CR participants now have the MS [9,10]. Moreover, the prevalence of obesity (body mass index [BMI] ≥30 kg/m^2) increased from 33% to 44% in 10 years; and more than 80% of CR participants are now overweight (BMI ≥25 kg/m^2) [9,11]. In view of the closely supervised environment and the willingness of participants to exercise, the CR population provides a unique group in which to test the effect of a variety of lifestyle and behavioral interventions to address the treatment of obesity and the MS in patients with CAD.

Several studies using intensive lifestyle intervention (ILI) for weight loss with nutritional counseling and physical activity have shown that it is possible to prevent the progression to overt diabetes in individuals at risk [12-15]. The Finnish Diabetes Prevention Study and the US Diabetes Prevention Program Trial randomly assigned subjects at risk of developing diabetes to ILI or placebo [12,13]. Both studies found a 58% relative risk reduction in the progression from impaired glucose tolerance to diabetes during a mean follow-up of 3 years. The Look AHEAD (Action for Health in Diabetes) study, a multicenter, randomized, controlled trial, was designed to examine the long-term effects of ILI combining diet modification and increased physical activity on the incidence of major cardiovascular disease events in patients with type 2 diabetes mellitus, 14% of whom had a history of cardiovascular disease at baseline [16]. Preliminary results have shown that, after 1 year, body weight was reduced among the active group compared with usual-care patients, with favorable effects on fasting glucose and hemoglobin A_{1c} despite a decrease in use of glucose-lowering medicines [17].

The effects of exercise training and behavioral weight loss counseling on measures of insulin resistance in patients with CAD at risk of diabetes and subsequent coronary events have only been minimally studied. We have recently shown that a combined program of exercise and weight reduction improves insulin-mediated glucose disposal in overweight patients with established CAD [18]. In the present analysis, our goal was to evaluate the determinants of the improvement in insulin sensitivity in overweight patients with CAD following an exercise and behaviorally oriented weight loss program. We hypothesized that the amount of increase in physical activity energy expenditure (PAEE) and the decrease in general and abdominal adiposity would be independent determinants of the improvement in insulin sensitivity.

2. Methods

2.1. Study design and patient characteristics

The present analysis is a substudy of a previously published randomized controlled trial that evaluated the effects of 2 types of exercise training protocol on weight loss and CAD risk factors in overweight patients with stable CAD [18]. Patients with a BMI greater than 27 kg/m^2 and a waist circumference (WC) greater than 102 cm for men (or >88 cm for women) were considered for participation. Diabetes patients (ie, on hypoglycemic medication or fasting glucose >126 mg/dL) were excluded because medication doses were susceptible to require adjustment after ILI. We also excluded subjects with severe deconditioning (peak aerobic capacity [VO_2] of <14 mL/[kg min]) because, in a preliminary nonrandomized trial, such subjects were unable to increase their exercise-related caloric expenditure and were less successful at accomplishing weight loss [19]. Finally, subjects who were hospitalized in the last 3 months were also excluded. A flow diagram of the recruiting process has already been published; but briefly, 116 subjects were screened for eligibility, and 42 were excluded because they did not meet inclusion criteria (22), they refused to participate (11), or of other reasons (9). The study population ultimately consisted of 74 individuals (60 men and 14 women); however, 3 patients (2 men and 1 woman) did not complete the study (because of personal reasons or failure to comply). For the current substudy, we used only male results because of the limited number of women in the trial, precluding a stratified analysis by sex and of the potential sex differences in metabolic response to weight loss and exercise training [20,21]. All patients participated in behavioral weight loss counseling with a daily caloric goal of 500 kcal less than predicted maintenance calories, and subjects participated in either of 2 exercise protocols (see below). For the current analysis, which has a different design than the mother trial, both exercise training groups were pooled together; and post-ILI results were compared with baseline data. The primary outcome was the change in insulin sensitivity (*m*-value) in response to a standardized insulin stimulus as assessed by the euglycemic-hyperinsulinemic clamp, the criterion standard technique [18,22-24].

The study protocol was approved by the University of Vermont Committee on Human Research and was registered as a clinical trial (NCT00628277). After having understood and signed an informed consent, each patient underwent a clinical evaluation to ascertain that he or she was on current recommended evidence-based therapies for secondary prevention of CAD [25]. Testing was completed at the University of Vermont General Clinical Research Center (RR-109).

2.2. Exercise training and behavioral weight loss program

Subjects underwent a 4-month intervention of exercise training and behavioral weight loss counseling. After the 4-month intervention, patients entered a 1-month weight stabilization phase, in which they continued their exercise protocol but maintained their body weight at less than 1-kg variation from the 4-month value. The standard CR protocol included 25 minutes of treadmill walking and 8 minutes on 2 of 3 ergometers: arm, rowing, or cycling. The walking protocol emphasized longer duration (45-60 vs 25-40 minutes per session), lower intensity (50%-60% vs 65%-70% peak VO_2), and more frequent (5-7 vs 3 times a week) exercise than the standard CR group [18]. Essentially, it corresponded to a "walk

daily and walk far" recommendation. After performing all sessions on-site for 2 weeks, subjects in the walking protocol performed 2 to 4 sessions a week in their home environment using a heart rate monitor, from which the information was subsequently downloaded at the CR center to ascertain duration of exercise. Both groups eventually performed 1 to 3 sessions a week on-site with home exercise logs. Exercise logs were reviewed weekly with the exercise physiologist to estimate caloric expenditure and ascertain compliance. Overall, a wide range of PAEE was accomplished in both groups (1261 ± 526 vs 1457 ± 670 kcal/d for standard CR vs the high–caloric expenditure walking protocol, respectively). The behavioral weight loss program included 16 weekly 1-hour group counseling sessions led by a dietician emphasizing dietary records, itemization of food, and caloric content. The daily caloric goal was 500 kcal less than predicted maintenance calories [26]. There were no specific recommendations regarding type of macronutrient intake. Features of behavior modification included self-monitoring, stimulus control, problem solving, social assertion, goal setting, feedback, relapse prevention, and family involvement. Preventive cardiovascular medications were kept steady throughout the study period (98 % of patients were receiving aspirin; 83 %, statins; 70%, β-blockers; 35 %, angiotensin-converting enzyme-inhibitors or angiotensin receptor blockers; and 28 %, clopidogrel).

2.3. *Data collection*

Prospective data collection was identical at baseline and follow-up. Exercise was restricted for a minimum of 36 hours preceding assessment of insulin sensitivity; indices of general and abdominal obesity; high-sensitivity C-reactive protein (hs-CRP), a marker of inflammation; and VO_2. Insulin sensitivity was determined after an overnight fast using euglycemic-hyperinsulinemic clamp technique [18,22-24]. During this procedure, artificial hyperinsulinemia is induced by infusing insulin at a constant rate of 240 pmol/(m^2 min) (to attain postprandial peripheral insulin levels and suppress hepatic glucose output), whereas blood glucose is monitored every 5 minutes; and euglycemia is maintained throughout the clamp by infusing 20% dextrose at variable rates to keep glucose levels steady. The *m*-value represents the average dextrose infusion rate during the final 30 minutes of the 3-hour clamp. The procedure was preceded by 3 days of standardized meals consisting of 200 to 250 g of carbohydrate and 12 g of fiber per 1000 kcal per day. Results are expressed in milligrams of glucose relative to fat-free mass per minute (mg/[kg FFM min]). Indices of general obesity consisted of body weight, BMI, total fat mass, and percentage body fat (measured by dual-energy x-ray absorptiometry scan; GE Lunar Prodigy, Madison, WI). Indices of abdominal obesity included WC, and total abdominal fat area and visceral fat area (measured by computed tomographic scanning; GE Medical Systems, Milwaukee, WI; Philips Electronics, Eindhoven, the Netherlands)] [27]. High-sensitivity CRP was used as inflammatory marker and measured using a colorimetric enzyme-linked immunosorbent assay [28]. Peak VO_2 was measured during a symptom-limited treadmill test using a graded modified Balke protocol until volitional fatigue, cardiovascular symptoms, or greater than or equal to 2-mm electrocardiographic ST-segment depression. Expired gas was analyzed using a SensorMedics Vmax 29c (Yorba Linda, CA) with measurement of absolute peak VO_2 in milliliters per minute. Daily energy intake was estimated using 3-day dietary diaries and analyzed with the Food Intake Analysis System (FIAS, Houston, TX). Total energy expenditure was assessed over a 7-day period by the doubly labeled water technique using 2 stable isotopes, deuterium and oxygen-18, and then averaged daily. The test measures the subject's carbon dioxide production, which is converted to total energy expenditure (kilocalories per day) using the Weir formula [29]. Resting metabolic rate and thermal effect of a meal were obtained by indirect calorimetry using the ventilated hood technique [18,23,29,30]. Daily PAEE was derived after subtracting resting metabolic rate and thermal effect of a meal from total energy expenditure. All measures were taken at baseline and repeated after the 1-month weight-stabilization phase (5-month follow-up), with the exception of the daily energy intake estimate and PAEE, which were repeated during week 15 of the diet and exercise program.

2.4. *Statistical analysis*

All baseline continuous variables, as well as the changes in these variables, are presented as mean ± standard deviation (SD). All data were checked for normality using the Shapiro-Wilk test. Normally distributed variables were age, *m*-value, body weight, percentage fat mass, absolute peak VO_2, Δ *m*-value, Δ body weight, Δ BMI, Δ total fat mass, Δ visceral fat, Δ hs-CRP, and Δ absolute peak VO_2. Nonnormally distributed variables were BMI, total fat mass, WC, total abdominal fat, visceral fat, hs-CRP, daily energy intake, daily PAEE, Δ percentage fat mass, Δ WC, Δ total abdominal fat, Δ daily energy intake, and Δ daily PAEE. For normally distributed variables, we used the paired *t* test to assess the difference between baseline and follow-up values; and the Wilcoxon signed rank test was used for nonnormally distributed variables. The Pearson or Spearman coefficients were used, depending on normality assessment, to evaluate the correlation between potential predictors and outcomes. To determine the independent predictors of outcomes (baseline *m*-value and change in *m*-value), we used stepwise linear regression algorithms. Nonnormally distributed variables included in the multivariate analysis models were log-transformed. To identify the independent predictors of baseline *m*-value, we adjusted for age, the indices of general obesity (body weight, BMI, total fat mass, or percentage fat mass), and abdominal obesity (WC, total abdominal fat, or visceral fat) with the highest correlation, in addition to hs-CRP, absolute peak VO_2, daily energy intake, and PAEE, if their univariate *P* value was < .15. For the primary outcome, the change in *m*-value, a similar model was created, where age, baseline *m*-value, baseline BMI, baseline WC, baseline PAEE, exercise protocol assignment, as well as the change in the indices of general obesity (Δ body weight, Δ BMI, Δ total fat mass, or Δ percentage fat mass) and abdominal obesity (Δ WC, Δ total abdominal fat, or Δ visceral fat) with the highest correlation. In addition, Δ hs-CRP, Δ absolute peak VO_2, Δ daily

energy intake, and Δ PAEE were entered into the stepwise linear regression model if their univariate *P* value was < .15. A two-sided *P* value of < .05 indicated statistical significance.

3. Results

The study population was composed of 60 patients ranging from 44 to 84 years old (mean = 63 ± 9). Two patients did not complete their interventions because of personal reasons or failure to comply; however, none of them had to discontinue because of cardiovascular health issues. Baseline, follow-up, and changes in insulin sensitivity, indices of general and abdominal obesity, inflammatory marker, VO_2, daily energy intake, and PAEE are shown in Table 1. The study population was characterized by substantial levels of generalized and abdominal obesity, with a mean BMI of 32.5, 35% body fat, and a mean WC of 112 cm. Following the ILI, the mean *m*-value increased by 24 % (1.6 mg/[kg FFM min]). All measures of obesity and hs-CRP also improved, although there was only a trend for improvement in absolute peak VO_2 at 5 months. Total weight loss was 6.4 kg (14 lb), and total fat mass loss was 4.5 kg (10 lb). Waist circumference decreased by 5%; and total abdominal fat and visceral fat decreased by 16 % and 19 %, respectively. Mean daily caloric intake decreased from 2027 kcal at baseline to 1675 kcal at follow-up, whereas baseline daily PAEE increased from 860 to 1359 kcal after the exercise and behavioral weight loss program.

Baseline body weight, BMI, total fat, and percentage fat mass were all inversely correlated in a univariate manner with baseline *m*-value (data not shown). Of all these indices of general obesity, BMI was the strongest univariate predictor ($r = -0.45$, $P = .0003$). Regarding indices of abdominal obesity, WC and total abdominal fat by computed tomographic scanning were also negatively correlated with *m*-value, whereas total abdominal fat was the strongest univariate predictor ($r = -0.38$, $P = .0029$). Visceral fat, however, was not a significant predictor of baseline *m*-value. Finally, there were no correlations between *m*-value and hs-CRP, absolute peak VO_2, daily energy intake, and PAEE at baseline. In multivariate analysis, the only significant predictor of baseline *m*-value was BMI ($P = .0004$).

Univariate predictors of the change in insulin sensitivity are shown in Table 2. Decreases in body weight, BMI, total fat mass, and percentage fat mass were all significantly correlated with increased *m*-value. However, among the changes in indices of general obesity, the strongest univariate predictor was the decrease in BMI ($r = -0.40$, $P = .0023$). Of the changes in abdominal obesity measures, the strongest predictor was the decrease in WC ($r = -0.42$, $P = .0013$), although reductions in total abdominal and visceral fat were also significantly associated to increased *m*-value. There was a weak inverse

Table 2 – Predictors of improved insulin sensitivity

	R	Univariate *P* value [a]	Multivariate *P* value [b]
Δ Body weight (kg)	−0.3700	.0046	–
Δ BMI (kg/m^2)	−0.3963	.0023	NS
Δ Total fat mass (kg)	−0.3379	.0102	–
Δ Percentage fat mass (%)	−0.3627	.0056	–
Δ WC (cm)	−0.4157	.0013	NS
Δ Total abdominal fat (cm^2)	−0.3640	.0054	–
Δ Visceral fat (cm^2)	−0.3151	.0170	–
Δ hs-CRP (ng/mL)	−0.2062	.1385	NS
Δ Absolute peak VO_2 (mL/min)	−0.1331	NS	–
Δ Daily energy intake (kcal)	−0.0389	NS	–
Δ Daily PAEE (kcal)	0.4700	.0004	.0155

[a] Pearson correlation for normally distributed variables (Δ body weight, Δ BMI, Δ total fat mass, Δ visceral fat, Δ hs-CRP, and Δ absolute peak VO_2) or Spearman correlation for nonnormally distributed variables (Δ percentage fat mass, Δ WC, Δ total abdominal fat, Δ daily energy intake, Δ daily PAEE), *P* values < .15 are not shown.

[b] Linear regression algorithm adjusting for age, baseline *m*-value, baseline BMI, baseline WC, baseline PAEE, exercise protocol, Δ BMI (the strongest change in the indices of general obesity), Δ WC (the strongest change in the indices of abdominal obesity), Δ hs-CRP, and Δ daily PAEE (nonnormally distributed data were log-transformed).

Table 1 – Baseline, follow-up, and changes in insulin sensitivity, obesity indices, inflammation marker, VO_2, daily energy intake, and PAEE of study participants

	Baseline (n = 60) (mean ± SD)	5 mo (n = 58) (mean ± SD)	Changes (n = 58) (mean ± SD)	*P* value [a]
m-Value (mg/[kg FFM min])	6.60 ± 2.25	8.23 ± 2.80	+1.59 ± 2.09	<.0001
Body weight (kg)	98.01± 13.68	91.38 ± 13.90	−6.41 ± 5.41	<.0001
BMI (kg/m^2)	32.46 ± 4.10	30.26 ± 4.24	−2.12 ± 1.72	<.0001
Total fat mass (kg)	33.62 ± 8.15	28.95 ± 8.62	−4.47 ± 4.15	<.0001
Percentage fat mass (%)	35.07 ± 4.73	32.26 ± 5.78	−2.68 ± 3.50	<.0001
WC (cm)	112.19 ± 9.27	106.38 ± 9.77	−5.95 ± 5.20	<.0001
Total abdominal fat (cm^2)	579.35 ± 139.40	489.33 ± 147.73	−90.38 ± 87.22	<.0001
Visceral fat (cm^2)	246.60 ± 82.46	199.84 ± 77.15	−46.93 ± 52.36	<.0001
hs-CRP (ng/mL)	2.61 ± 2.31	2.38 ± 2.11	−0.40 ± 1.52	.0318
Absolute peak VO_2 (mL/min)	2.26 ± 0.55	2.36 ± 0.63	0.09 ± 0.36	.0612
Daily energy intake (kcal)	2026.29 ± 572.91	1674.92.14 ± 348.07	−335.1 ± 494.7	<.0001
Daily PAEE (kcal)	859.96 ± 565.64	1358.96 ± 604.98	+482.3 ± 436.1	<.0001

[a] Paired *t* test for normally distributed variables (*m*-value, body weight, percentage fat mass, and absolute peak VO_2) or Wilcoxon signed rank test for nonnormally distributed variables (BMI, total fat mass, WC, total abdominal fat, visceral fat, hs-CRP, daily energy intake, daily PAEE).

correlation between the changes in hs-CRP and *m*-value, although the *P* value did not reach statistical significance. Finally, the increase in weekly PAEE was the strongest predictor of improved insulin sensitivity in univariate analysis ($r = 0.47$, $P = .0004$).

Also shown in Table 2 are the multivariate predictors of improved insulin sensitivity. When adjusting for age, baseline *m*-value, baseline BMI, baseline WC, baseline PAEE, exercise protocol as well as Δ BMI (the strongest change in the indices of general obesity), Δ WC (the strongest change in the indices of abdominal obesity), Δ hs-CRP, and Δ daily PAEE, the only significant multivariate predictor of improved *m*-value was the increase in PAEE ($P = .0155$). Because of the high correlation between Δ BMI and Δ WC ($r = 0.8122$, $P < .0001$, data not shown) that may result in lack of statistical significance of these 2 individual independent variables, we repeated the multivariate analysis using 2 additional models. In the first one, we kept all the same variables as the above model but excluded Δ WC, whereas in the second one, we kept all variables but excluded Δ BMI instead of Δ WC. With both models, the change in PAEE remained the only significant multivariate predictor ($P < .05$) of improved insulin sensitivity.

Fig. 1 shows the results of a stratified analysis of the change in insulin sensitivity for high (≥50 percentile) vs low (<50 percentile) level of change in PAEE (independent from the exercise training protocol assignment) by level of change (high vs low) in BMI (A) and WC (B). For any level of change in BMI or WC, people with a high increase in PAEE had greater increases in *m*-value; and those with the greatest improvement in insulin sensitivity were the participants who concomitantly improved PAEE and also BMI or WC (all $P < .05$).

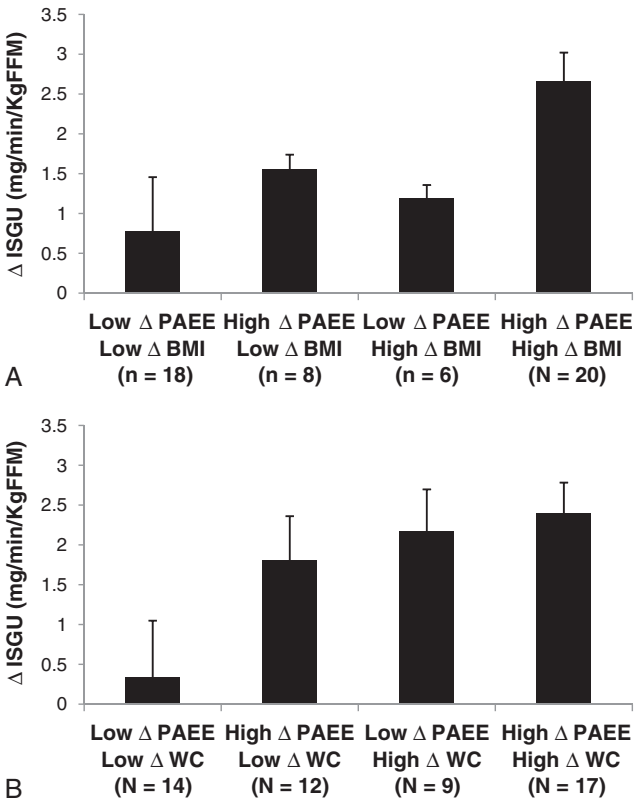

Fig. 1. Stratified analysis of the change in insulin sensitivity for . Stratified analysis of the change in insulin sensitivity for – high (≥50 percentile) vs low (<50 percentile) level of change in PAEE by level of change (high vs low) in BMI (A) and WC (B).

4. Discussion

We have recently shown that insulin sensitivity considerably improves in overweight patients with CAD after participation in a 4-month program of exercise and behaviorally oriented weight loss [18]. In the current analysis, we further sought to identify which biological and/or behavioral variables best predicted the improvement in insulin sensitivity. Our results suggest that, in overweight CAD male patients participating in an ILI that includes behavioral weight loss and exercise training, the increase in daily PAEE is the best predictor of improvement in insulin sensitivity.

The beneficial effect of exercise training on glucose metabolism and weight control is well established [15,31-45]. Our results demonstrate that, in the setting of caloric restriction and weight loss, the primary determinant of improved glucose metabolism in patients with established CAD at high risk of diabetes is the increase in PAEE. This confirms the first part of our hypothesis. We also hypothesized that the decrease in general and abdominal adiposity would be independent predictors of the improvement in *m*-value. Conversely, when controlling for the change in PAEE, we did not find an independent effect of improved BMI or WC in this population. On the other hand, this should not be interpreted to signify that improving BMI or WC is not important because we detected an additive effect of the change in these parameters and the increase in PAEE, indicating that the patients who had the greatest overall improvement in insulin sensitivity in our cohort were those who improved both their level of PAEE as well as their BMI or WC.

Exercise exerts a large part of its effect by increasing the caloric deficit incurred when looking at the overall energy balance equation of energy intake vs energy expended. However, given that our multivariate analyses showed that change in PAEE was a more important predictor of change in *m*-value than were changes in general or abdominal obesity indices, a direct effect of exercise is therefore postulated. More than 30 years ago, Bjorntorp and colleagues [46] demonstrated lower insulin concentrations in response to an oral glucose tolerance test after an exercise program in 10 obese patients (of whom 8 were women), who had no clinical cardiovascular disease or other conditions that would prevent them from intensive physical training. Patients were instructed not to restrict their diet during the investigation. The results were independent of changes in body weight. In fact, weight even increased in most patients. However, the author did not measure indices of abdominal fat. It was thus not possible to conclude with certainty an independent effect of exercise alone, isolated from the change in abdominal obesity. Bogardus and colleagues [47] analyzed the effects of 12 weeks of exercise training in addition to caloric restriction compared with caloric restriction alone in 18 subjects with impaired glucose tolerance and type 2 diabetes mellitus. They

found an increase in insulin sensitivity as measured by the euglycemic clamp only in the combined interventions group; but no change occurred in the caloric restriction group despite similar changes in fat mass, fat-free mass, mean fasting levels of glucose, serum C-peptide, and insulin in both groups. Again, abdominal obesity was not measured; and the number of patients recruited was considerably smaller. Another study of 18 sedentary adults without CAD who exercised for 6 months demonstrated an increase in insulin sensitivity estimated from minimal model analysis of the frequently sampled intravenous glucose tolerance test, without a change in BMI and WC [48]. Finally, a recent study of 48 patients with type 2 diabetes mellitus found an improvement in glucose control after 12 weeks of exercise training, without any change in BMI or waist to hip ratio. However, there was no change in insulin resistance as assessed by the homeostasis model assessment index. The authors acknowledged in their discussion that the euglycemic-hyperinsulinemic clamp would have been a more sensitive technique to detect a change in insulin sensitivity [49]. Large trials of ILI with exercise and nutritional counseling have also shown a reduction in the incidence of diabetes and an improvement in insulin sensitivity in patients with impaired glucose tolerance despite minimal or no reduction in body weight or WC [50-52]. Thus, it is tenable to hypothesize that, beyond the effect of exercise on weight loss and body composition, the relationship between increase in PAEE and improvement in *m*-value in our population of obese CAD patients was explained in part by the direct effect of exercise on enhanced glucose metabolism.

The mechanisms by which exercise training increases insulin sensitivity and glucose disposal are not completely understood. As we also observed a reduction in fat-free mass following our exercise and weight loss program, it is unlikely that exercise enhanced glucose disposal by increasing the quantity of insulin-responsive tissue. A more plausible mechanism would be through the effects of exercise to enhance the metabolic efficiency of muscle by increasing muscle capillarization/blood flow, mitochondrial density, glycogen synthetic capacity, and/or key components in the intracellular signaling pathways that control glucose disposal [31,32,35,45,53-55]. In this regard, it is now recognized that upregulation of muscle GLUT-4 protein plays a major role in regulating glucose transport in muscle during exercise, although the exercise-induced signaling mechanism that leads to GLUT-4 translocation has not been elucidated [56,57]. Another explanation would be through an alteration of skeletal muscle lipid utilization and/or storage in a manner that improves insulin sensitivity [36,54,55,58]. Finally, in addition to enhancing peripheral insulin sensitivity, in populations with elevated resting hepatic glucose output (obese and with type 2 diabetes mellitus), exercise training leads to a decrease in basal glucose production and an increase in suppression of liver glucose output during insulin stimulation [32].

Strengths of our study included the use of state-of-the-art techniques, such as the hyperinsulinemic-euglycemic clamp to measure insulin sensitivity, the doubly labeled water technique to measure free-living physical activity, and abdominal computed tomography scanning and dual x-ray absorptiometry to measure abdominal fat and body composition. In addition, we note that adherence to the study interventions was good in both exercise training groups, with compliance to exercise training at 87% and 84% in the walking protocol and standard CR groups, respectively (P = not significant). The study also has some limitations to acknowledge. First, a clinically important question would have been to assess the effects of ILI on CAD events in addition to insulin sensitivity. However, the size of our study population was not sufficient to evaluate CAD event rates. Moreover, women and patients with established diabetes mellitus were excluded from this analysis. We excluded women from the study analysis because of their relatively smaller number in the mother trial that would prevent a stratified analysis by sex and of the potential sex differences in metabolic response to weight loss and exercise training [20,21]. We excluded diabetic patients from the analysis because of our goal to assess insulin resistance as a primary outcome, a measure that could have been confounded by hypoglycemic drugs, particularly because medication doses were susceptible to be adjusted over the course of the study. The Look AHEAD trial has been especially designed to examine the long-term effects of ILI on CAD event rates in overweight men and women with type 2 diabetes mellitus [16].

In conclusion, we have shown that overweight and obese patients with CAD, a high-risk group, can safely exercise at an adequate intensity and volume, in an exercise- and behaviorally oriented weight loss program, to accomplish a significant improvement in insulin sensitivity. The increase in daily PAEE in the setting of ongoing behavioral weight loss intervention was the most powerful predictor of improvement in insulin sensitivity, independent of the type of exercise training prescription. The clinical implications of our findings are that weight loss accomplished by a combination of dietary caloric restriction and exercise training is likely to be superior to that induced by caloric restriction alone in terms of its ability to improve insulin resistance, and also that even with minimal changes in BMI or body composition, there is still a benefit of increased physical activity on insulin sensitivity. This information is of great importance for overweight CAD patients participating in cardiac rehabilitation who often become discouraged following an intensive lifestyle program because of their ongoing struggle to lose weight.

Funding

Supported by the National Institutes of Health grant RO1-HL72851 (Dr Ades, PI) and the General Clinical Research Center (RR-109), University of Vermont College of Medicine. Clinical Trial Registration: NCT0068277.

Acknowledgment

We are indebted to Jean-Pierre Després, PhD, for his careful review of the manuscript and helpful suggestions.

Conflict of Interest

None of the authors have any conflict of interest to disclose.

REFERENCES

[1] Miettinen H, Lehto S, Salomaa V, et al. Impact of diabetes on mortality after the first myocardial infarction. The FINMONICA Myocardial Infarction Register Study Group. Diabetes Care 1998;21:69-75.

[2] Vaccarino V, Parsons L, Every NR, et al. Impact of history of diabetes mellitus on hospital mortality in men and women with first acute myocardial infarction. The National Registry of Myocardial Infarction 2 Participants. Am J Cardiol 2000, 85: 1486-9; A1487.

[3] Mukamal KJ, Nesto RW, Cohen MC, et al. Impact of diabetes on long-term survival after acute myocardial infarction: comparability of risk with prior myocardial infarction. Diabetes Care 2001;24:1422-7.

[4] Aguilar D, Solomon SD, Kober L, et al. Newly diagnosed and previously known diabetes mellitus and 1-year outcomes of acute myocardial infarction: the VALsartan In Acute myocardial iNfarcTion (VALIANT) trial. Circulation 2004;110: 1572-8.

[5] Levantesi G, Macchia A, Marfisi R, et al. Metabolic syndrome and risk of cardiovascular events after myocardial infarction. J Am Coll Cardiol 2005;46:277-83.

[6] Bouhanick B, Cambou JP, Ferrieres J, et al. Characteristics and six-month outcomes in a cohort of 8288 diabetic and non-diabetic patients with previous history of acute coronary syndrome or stroke: the French PREVENIR 3 survey. Diabetes Metab 2006;32:460-6.

[7] Norhammar A, Lindback J, Ryden L, et al. Improved but still high short- and long-term mortality rates after myocardial infarction in patients with diabetes mellitus: a time-trend report from the Swedish Register of Information and Knowledge about Swedish Heart Intensive Care Admission. Heart 2007;93:1577-83.

[8] Daly CA, Hildebrandt P, Bertrand M, et al. Adverse prognosis associated with the metabolic syndrome in established coronary artery disease: data from the EUROPA trial. Heart 2007;93:1406-11.

[9] Audelin MC, Savage PD, Ades PA. Changing clinical profile of patients entering cardiac rehabilitation/secondary prevention programs: 1996 to 2006. J Cardiopulm Rehabil Prev 2008;28:299-306.

[10] Savage PD, Banzer JA, Balady GJ, et al. Prevalence of metabolic syndrome in cardiac rehabilitation/secondary prevention programs. Am Heart J 2005;149:627-31.

[11] Ades PA, Savage PD, Brawner CA, et al. Aerobic capacity in patients entering cardiac rehabilitation. Circulation 2006;113: 2706-12.

[12] Tuomilehto J, Lindstrom J, Eriksson JG, et al. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. N Engl J Med 2001;344:1343-50.

[13] Knowler WC, Barrett-Connor E, Fowler SE, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 2002;346:393-403.

[14] Yamaoka K, Tango T. Efficacy of lifestyle education to prevent type 2 diabetes: a meta-analysis of randomized controlled trials. Diabetes Care 2005;28:2780-6.

[15] Gillies CL, Abrams KR, Lambert PC, et al. Pharmacological and lifestyle interventions to prevent or delay type 2 diabetes in people with impaired glucose tolerance: systematic review and meta-analysis. BMJ 2007;334:299.

[16] Ryan DH, Espeland MA, Foster GD, et al. Look AHEAD (Action for Health in Diabetes): design and methods for a clinical trial of weight loss for the prevention of cardiovascular disease in type 2 diabetes. Control Clin Trials 2003;24:610-28.

[17] Pi-Sunyer X, Blackburn G, Brancati FL, et al. Reduction in weight and cardiovascular disease risk factors in individuals with type 2 diabetes: one-year results of the Look AHEAD trial. Diabetes Care 2007;30:1374-83.

[18] Ades PA, Savage PD, Toth MJ, et al. High-calorie-expenditure exercise: a new approach to cardiac rehabilitation for overweight coronary patients. Circulation 2009;119:2671-8.

[19] Savage PD, Brochu M, Poehlman ET, et al. Reduction in obesity and coronary risk factors after high caloric exercise training in overweight coronary patients. Am Heart J 2003;146:317-23.

[20] Potteiger JA, Jacobsen DJ, Donnelly JE, et al. Glucose and insulin responses following 16 months of exercise training in overweight adults: the Midwest Exercise Trial. Metabolism 2003;52:1175-81.

[21] Perreault L, Ma Y, Dagogo-Jack S, et al. Sex differences in diabetes risk and the effect of intensive lifestyle modification in the Diabetes Prevention Program. Diabetes Care 2008;31: 1416-21.

[22] DeFronzo RA, Tobin JD, Andres R. Glucose clamp technique: a method for quantifying insulin secretion and resistance. Am J Physiol 1979;237:E214-23.

[23] Ades PA, Savage PD, Toth MJ, et al. The influence of obesity and consequent insulin resistance on coronary risk factors in medically treated patients with coronary disease. Int J Obes (Lond) 2008;32:967-74.

[24] Muniyappa R, Chen H, Muzumdar RH, et al. Comparison between surrogate indexes of insulin sensitivity/resistance and hyperinsulinemic euglycemic clamp estimates in rats. Am J Physiol Endocrinol Metab 2009;297:E1023-9.

[25] Smith Jr SC, Allen J, Blair SN, et al. AHA/ACC guidelines for secondary prevention for patients with coronary and other atherosclerotic vascular disease: 2006 update: endorsed by the National Heart, Lung, and Blood Institute. Circulation 2006;113:2363-72.

[26] Harvey-Berino J. Weight loss in the clinical setting: applications for cardiac rehabilitation. Coron Artery Dis 1998;9:795-8.

[27] Toth MJ, Sites CK, Cefalu WT, et al. Determinants of insulin-stimulated glucose disposal in middle-aged, premenopausal women. Am J Physiol Endocrinol Metab 2001;281:E113-21.

[28] Macy EM, Hayes TE, Tracy RP. Variability in the measurement of C-reactive protein in healthy subjects: implications for reference intervals and epidemiological applications. Clin Chem 1997;43:52-8.

[29] Wennberg LA, Danielsson UH. A new formula for estimating metabolic rate. Eur J Appl Physiol Occup Physiol 1976;35: 231-4.

[30] Schoeller DA, Ravussin E, Schutz Y, et al. Energy expenditure by doubly labeled water: validation in humans and proposed calculation. Am J Physiol 1986;250:R823-30.

[31] Ivy JL. Role of exercise training in the prevention and treatment of insulin resistance and non-insulin-dependent diabetes mellitus. Sports Med 1997;24:321-36.

[32] Borghouts LB, Keizer HA. Exercise and insulin sensitivity: a review. Int J Sports Med 2000;21:1-12.

[33] Boule NG, Haddad E, Kenny GP, et al. Effects of exercise on glycemic control and body mass in type 2 diabetes mellitus: a meta-analysis of controlled clinical trials. JAMA 2001;286: 1218-27.

[34] Poirier P, Despres JP. Exercise in weight management of obesity. Cardiol Clin 2001;19:459-70.

[35] Hawley JA. Exercise as a therapeutic intervention for the prevention and treatment of insulin resistance. Diabetes Metab Res Rev 2004;20:383-93.

[36] Bruce CR, Hawley JA. Improvements in insulin resistance with aerobic exercise training: a lipocentric approach. Med Sci Sports Exerc 2004;36:1196-201.

[37] Lakka TA, Bouchard C. Physical activity, obesity and cardiovascular diseases. Handb Exp Pharmacol 2005:137-63.

[38] Thomas DE, Elliott EJ, Naughton GA. Exercise for type 2 diabetes mellitus. Cochrane Database Syst Rev 2006;3: CD002968.
[39] Hill JO, Stuht J, Wyatt HR, et al. Physical activity in prevention and management of obesity and type-2 diabetes. Nestle Nutr Workshop Ser Clin Perform Programme 2006;11:183-91.
[40] Bell LM, Watts K, Siafarikas A, et al. Exercise alone reduces insulin resistance in obese children independently of changes in body composition. J Clin Endocrinol Metab 2007;92:4230-5.
[41] Hu G, Lakka TA, Kilpelainen TO, et al. Epidemiological studies of exercise in diabetes prevention. Appl Physiol Nutr Metab 2007;32:583-95.
[42] Jeon CY, Lokken RP, Hu FB, et al. Physical activity of moderate intensity and risk of type 2 diabetes: a systematic review. Diabetes Care 2007;30:744-52.
[43] Marwick TH, Hordern MD, Miller T, et al. Exercise training for type 2 diabetes mellitus: impact on cardiovascular risk: a scientific statement from the American Heart Association. Circulation 2009;119:3244-62.
[44] Zanuso S, Jimenez A, Pugliese G, et al. Exercise for the management of type 2 diabetes: a review of the evidence. Acta Diabetol 2010;47:15-22.
[45] Bajpeyi S, Tanner CJ, Slentz CA, et al. Effect of exercise intensity and volume on persistence of insulin sensitivity during training cessation. J Appl Physiol 2009;106: 1079-85.
[46] Bjorntorp P, De Jounge K, Sjostrom L, et al. The effect of physical training on insulin production in obesity. Metabolism 1970;19:631-8.
[47] Bogardus C, Ravussin E, Robbins DC, et al. Effects of physical training and diet therapy on carbohydrate metabolism in patients with glucose intolerance and non-insulin-dependent diabetes mellitus. Diabetes 1984;33:311-8.
[48] Duncan GE, Perri MG, Theriaque DW, et al. Exercise training, without weight loss, increases insulin sensitivity and post-heparin plasma lipase activity in previously sedentary adults. Diabetes Care 2003;26:557-62.
[49] Jorge ML, de Oliveira VN, Resende NM, et al. The effects of aerobic, resistance, and combined exercise on metabolic control, inflammatory markers, adipocytokines, and muscle insulin signaling in patients with type 2 diabetes mellitus. Metabolism 2011;60:1244-52.
[50] Pan XR, Li GW, Hu YH, et al. Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance. The Da Qing IGT and Diabetes Study. Diabetes Care 1997;20: 537-44.
[51] Hamman RF, Wing RR, Edelstein SL, et al. Effect of weight loss with lifestyle intervention on risk of diabetes. Diabetes Care 2006;29:2102-7.
[52] Ramachandran A, Snehalatha C, Mary S, et al. The Indian Diabetes Prevention Programme shows that lifestyle modification and metformin prevent type 2 diabetes in Asian Indian subjects with impaired glucose tolerance (IDPP-1). Diabetologia 2006;49:289-97.
[53] Zierath JR. Invited review: exercise training–induced changes in insulin signaling in skeletal muscle. J Appl Physiol 2002;93: 773-81.
[54] Hawley JA, Lessard SJ. Exercise training-induced improvements in insulin action. Acta Physiol (Oxf) 2008;192:127-35.
[55] Wang Y, Simar D, Fiatarone Singh MA. Adaptations to exercise training within skeletal muscle in adults with type 2 diabetes or impaired glucose tolerance: a systematic review. Diabetes Metab Res Rev 2009;25:13-40.
[56] Hayashi T, Wojtaszewski JF, Goodyear LJ. Exercise regulation of glucose transport in skeletal muscle. Am J Physiol 1997;273: E1039-51.
[57] Goodyear LJ, Kahn BB. Exercise, glucose transport, and insulin sensitivity. Annu Rev Med 1998;49:235-61.
[58] Yao-Borengasser A, Varma V, Coker RH, et al. Adipose triglyceride lipase expression in human adipose tissue and muscle. Role in insulin resistance and response to training and pioglitazone. Metabolism 2011;60:1012-20.