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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 life style modification program

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Abstract

Objectives—To evaluate the determinants of change in () insulin sensitivity in overweight coronary artery disease (CAD) male patients without diabetes after an intensive lifestyle intervention (ILI).

Materials/methods—All patients received nutritional counseling and performed 4-months of exercise training (ET) according to one of 2 protocols; aerobic ET (65–70% of peak VO_2) 25–40 minutes 3 times/week (N=30), or walking (50–60% of peak VO_2) 45–60 minutes 5 times/week (N=30). Data from participants of both ET groups were pooled and post ILI results were compared to baseline data. The primary outcome was insulin sensitivity (m-value) assessed by the gold standard technique, the euglycemic hyperinsulinemic clamp. Changes in weight, BMI, total and % fat mass (by DEXA-scan), waist circumference (WC), total abdominal and visceral fat (by CT-scan), hs-CRP, peak VO_2 , daily energy intake (EI) and physical activity energy expenditure (PAEE) (by doubly labeled water technique) were also assessed.

Results—Daily EI decreased by 335 Kcal, and PAEE increased by 482 Kcal/day (all $p < 0.0001$). The mean weight loss was 6.4 Kg and the mean improvement in m-value was 1.6 mg/KgFFM /

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min. Univariate determinants of β -value were low baseline PAEE, walking protocol, weight, BMI, total and % fat mass, WC, total abdominal and visceral fat, and PAEE (all $p < 0.05$). In multivariate analysis the only significant determinant of β -value was PAEE ($p < 0.02$).

Conclusions—In this analysis, the most powerful determinant of improved insulin sensitivity in overweight CAD patients is the change in PAEE.

Keywords

Exercise; Diet; Weight; Waist circumference; Insulin Sensitivity; Cardiac rehabilitation

Introduction

Type 2 diabetes 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 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 (BMI ≥ 30 Kg/m²) increased from 33% to 44% in ten years and over 80% of CR participants are now overweight (BMI ≥ 25 Kg/m²). [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, 14% of whom had a history of cardiovascular disease at baseline. [16] Preliminary results have shown that, after one year, body weight was reduced among the active group compared to usual-care patients, with favorable effects on fasting glucose and Hb A1C, 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.

Methods

Study design and patient characteristics

The present analysis is a sub-study 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 >27 kg/m² and a waist circumference (WC) >102 cm for men (or >88 cm for women) were considered for participation. Diabetes patients (i.e. on hypoglycemic medication or fasting glucose > 126 mg/dL) were excluded since medication doses were susceptible to require adjustment after ILI. We also excluded subjects with severe deconditioning (peak aerobic capacity of <14 ml/Kg/min), as in a preliminary nonrandomized trial such subjects were unable to increase their exercise-related caloric expenditure and were less successful at accomplishing weight loss.[24] 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 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 to failure to comply). For the current sub-study, we used only male results due to the limited number of women in the trial, precluding a stratified analysis by gender, and the potential gender differences in metabolic response to weight loss and exercise training.[19–20] 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 two 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 to 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 gold standard technique.[18, 21–23]

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 they were 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).

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 < 1Kg 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/session), lower intensity (50–60% vs. 65–70% peak VO_2) and more frequent (5–7 vs. 3 times/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 2–4 sessions/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 1–3 sessions/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 Kcal/day vs. 1457 ± 670 Kcal/day, for standard CR vs. the high caloric expenditure walking protocol respectively). The behavioral weight loss program included 16 weekly one-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).

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, hs-CRP, a marker of inflammation, and aerobic capacity. Insulin sensitivity was determined after an over-night fast using euglycemic hyperinsulinemic clamp technique.[18, 21–23] During this procedure, artificial hyperinsulinemia is induced by infusing insulin at a constant rate of 240 pmol/m²/min (to attain postprandial peripheral insulin levels and suppress hepatic glucose output), while blood glucose is monitored every 5 min and euglycemia is maintained throughout the clamp by infusing 20% dextrose at variable rates to keep glucose levels steady. 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 200–250 grams of carbohydrate and 12 grams of fiber per 1000 Kcal/day. Results are expressed in mg of glucose relative to fat-free mass per minute (mg/KgFFM/min). Indices of general obesity consisted of body weight, BMI, total fat mass and percent body fat [measured by dual energy x-ray absorptiometry (DEXA)-scan (GE Lunar Prodigy, Madison, WI)]. Indices of abdominal obesity included WC, and total abdominal fat area and visceral fat area [measured by CT scanning (GE Medical Systems, Milwaukee, WI, Philips Electronics N.V., Eindhoven, the Netherlands)].[27] High sensitivity C-reactive protein (hs-CRP) was used as inflammatory marker, and measured using a colorimetric ELISA.[28] Peak aerobic capacity (peak VO_2) was measured during a symptom-limited treadmill test using a graded modified-Balke protocol until volitional fatigue, cardiovascular symptoms, or 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 mL/min. 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 two stable isotopes, deuterium (^2H) and oxygen-18 (^{18}O), and then averaged daily. The test measures the subject's carbon dioxide (CO_2) production, which is converted to total energy expenditure (Kcal/d) 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, 22, 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 one-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.

Statistical Analysis

All baseline continuous variables, as well as the changes in these variables are presented as mean $\pm$ standard deviation (SD). All data were checked for normality using the Shapiro-Wilk test. Normally distributed variables were age, m-value, body weight, percent fat mass, absolute peak VO_2 , m-value, body weight, BMI, total fat mass, visceral fat, hs-CRP, and absolute peak VO_2 . Non-normally distributed variables were BMI, total fat mass, WC, total abdominal fat, visceral fat, hs-CRP, daily energy intake, daily PAEE, percent fat mass, WC, total abdominal fat, daily energy intake, and 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 non-normally distributed variables. The Pearson's or Spearman's 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. Non-normally 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 percent 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 < 0.15 . 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 (body weight, BMI, total fat mass, or percent fat mass) and abdominal obesity (WC, total abdominal fat, or visceral fat) with the highest correlation. Additionally hs-CRP, absolute peak VO_2 , daily energy intake, and PAEE were entered into the stepwise linear regression model if their univariate p value was < 0.15 . A two-sided p-value of < 0.05 indicated statistical significance.

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, aerobic capacity, 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/KgFFM /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 lbs) and total fat mass loss was 4.5 Kg (10 lbs). WC 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, while baseline daily PAEE increased from 860 Kcal to 1359 Kcal after the exercise and behavioral weight loss program.

Baseline body weight, BMI, total fat and % 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 ($r = -0.45$, $p = 0.0003$). Regarding indices of abdominal obesity, WC and total abdominal fat by CT scanning were also negatively correlated with m-value, while total abdominal fat was the strongest univariate predictor ($r = -0.38$, $p = 0.0029$). 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 ($p = 0.0004$).

Univariate predictors of the change in insulin sensitivity are shown in Table 2. Decreases in body weight, BMI, total fat mass, and percent 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 ($r = -0.40$, $p = 0.0023$). Of the changes in abdominal obesity measures, the strongest predictor was the decrease in WC ($r = -0.42$, $p = 0.0013$), although reduction in total abdominal and visceral fat were also significantly associated to increased m-value. There was a weak inverse 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 ($r = 0.47$, $p = 0.0004$).

Also shown in table 2 are the multivariate predictors of improved insulin sensitivity. When adjusting for age, baseline m-value, baseline BMI, baseline WC, and baseline PAEE, exercise protocol as well as BMI (the strongest change in the indices of general obesity), WC (the strongest change in the indices of abdominal obesity), hs-CRP, and daily PAEE, the only significant multivariate predictor of improved m-value was the increase in PAEE ($p = 0.0155$). Because of the high correlation between BMI and 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 WC, whereas in the second one we kept all variables but excluded BMI instead of WC. With both models, the change in PAEE remained the only significant multivariate predictor ($p < 0.05$) of improved insulin sensitivity.

Figure 1 shows the results of a stratified analysis of the change in insulin sensitivity for high (>50 percentile) versus low (<50 percentile) level of change in PAEE (independent from the exercise training protocol assignment) by level of change (high vs. low) in BMI (panel A) and WC (panel 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 $p < 0.05$).

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 since 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. Over 30 years ago Bjorntorp and colleagues 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 which would prevent them from intensive physical training.[46] 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 to an independent effect of exercise alone, isolated from the change in abdominal obesity. Bogardus and colleagues, analyzed the effects of 12 wk of exercise training in addition to caloric restriction compared to caloric restriction alone in 18 impaired glucose tolerance and type II diabetes subjects.[47] 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 change in BMI and WC.[48] Finally, a recent study of 48 type II diabetes patients found an improvement in glucose control after 12 week 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 HOMA index. The author acknowledged in their discussion that the euglycemic hyperinsulinemic clamp would have been a more sensitive technique to detect a change 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), 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. Additionally, 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=NS). 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 gender, and the potential gender differences in metabolic response to weight loss and exercise training.[19–20] We excluded diabetics 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 II 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.

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Abbreviations

MS	metabolic syndrome
CAD	coronary artery disease
CR	cardiac rehabilitation
BMI	body mass index
WC	waist circumference
ILI	intensive lifestyle intervention
PAEE	physical activity energy expenditure
DEXA	dual energy x-ray absorptiometry
hs-CRP	High sensitivity C-reactive protein

peak VO₂ Peak aerobic capacity

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Figure 1.

Stratified Analysis of the Change in Insulin Sensitivity for High (>50 percentile) versus Low (<50 percentile) Level of Change in PAEE by Level of Change (High versus Low) in BMI (panel A) and Waist Circumference (panel B)

Table 1

Baseline, Follow-up, and Changes in Insulin Sensitivity, Obesity Indices, Inflammation marker, Aerobic Capacity, Daily Energy Intake and Physical Activity Energy Expenditure of Study Participants

	Baseline (N=60) (mean $\pm$ SD)	5 Months (N=58) (mean $\pm$ SD)	Changes (N=58) (mean $\pm$ SD)	P-Value *
M-Value (mg/KgFFM /min)	6.60 $\pm$ 2.25	8.23 $\pm$ 2.80	+1.59 $\pm$ 2.09	< 0.0001
Body Weight (Kg)	98.01 $\pm$ 13.68	91.38 $\pm$ 13.90	-6.41 $\pm$ 5.41	< 0.0001
Body mass index (Kg/m ²)	32.46 $\pm$ 4.10	30.26 $\pm$ 4.24	- 2.12 $\pm$ 1.72	< 0.0001
Total Fat Mass (Kg)	33.62 $\pm$ 8.15	28.95 $\pm$ 8.62	-4.47 $\pm$ 4.15	< 0.0001
Percent Fat Mass (%)	35.07 $\pm$ 4.73	32.26 $\pm$ 5.78	- 2.68 $\pm$ 3.50	< 0.0001
Waist Circumference (cm)	112.19 $\pm$ 9.27	106.38 $\pm$ 9.77	- 5.95 $\pm$ 5.20	< 0.0001
Total Abdominal Fat (cm ²)	579.35 $\pm$ 139.40	489.33 $\pm$ 147.73	-90.38 $\pm$ 87.22	< 0.0001
Visceral Fat (cm ²)	246.60 $\pm$ 82.46	199.84 $\pm$ 77.15	-46.93 $\pm$ 52.36	< 0.0001
hs-CRP [†] (ng/mL)	2.61 $\pm$ 2.31	2.38 $\pm$ 2.11	- 0.40 $\pm$ 1.52	0.0318
Absolute Peak VO ₂ (mL/min)	2.26 $\pm$ 0.55	2.36 $\pm$ 0.63	0.09 $\pm$ 0.36	0.0612
Daily Energy Intake (Kcal)	2026.29 $\pm$ 572.91	1674.92.14 $\pm$ 348.07	- 335.1 $\pm$ 494.7	< 0.0001
Daily PAEE [‡] (Kcal)	859.96 $\pm$ 565.64	1358.96 $\pm$ 604.98	+ 482.3 $\pm$ 436.1	< 0.0001

Legend:

* Paired T-test for normally distributed variables (m-value, body weight, percent fat mass, and absolute peak VO₂) or Wilcoxon signed rank test for non-normally distributed variables (body mass index, total fat mass, waist circumference, total abdominal fat, visceral fat, hs-CRP, daily energy intake, daily PAEE)

[†] high sensitivity-C reactive protein

[‡] Physical Activity Energy Expenditure

Table 2**Predictors of Improved Insulin Sensitivity**

	R	Univariate P-Value[*]	Multivariate P-Value[†]
Body Weight (Kg)	-0.3700	0.0046	---
Body Mass Index (Kg/m ²)	-0.3963	0.0023	NS
Total Fat Mass (Kg)	-0.3379	0.0102	---
Percent Fat Mass (%)	-0.3627	0.0056	---
Waist Circumference(cm)	-0.4157	0.0013	NS
Total Abdominal Fat (cm ²)	-0.3640	0.0054	---
Visceral Fat (cm ²)	-0.3151	0.0170	---
hs-CRP [§] (ng/mL)	-0.2062	0.1385	NS
Absolute Peak VO ₂ (mL/min)	-0.1331	NS	---
Daily Energy Intake (Kcal)	-0.0389	NS	---
Daily PAEE [‡] (Kcal)	0.4700	0.0004	0.0155

Legend:

^{*} Pearson's correlation for normally distributed variables (body weight, body mass index, total fat mass, visceral fat, hs-CRP, and absolute peak VO₂) or Spearman's correlation for non-normally distributed variables (percent fat mass, waist circumference, total abdominal fat, daily energy intake, daily PAEE), p-values < 0.15 are not shown

[†] Linear regression algorithm adjusting for age, baseline m-value, baseline BMI, baseline waist circumference, baseline PAEE, exercise protocol, body mass index (the strongest change in the indices of general obesity), waist circumference (the strongest change in the indices of abdominal obesity), hs-CRP, and daily PAEE (non-normally distributed data were log-transformed)

[§] high sensitivity-C reactive protein

[‡] Physical activity energy expenditure