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Effects of Weight Loss on Lean Mass, Strength, Bone, and Aerobic Capacity

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Abstract

Purpose—To evaluate the hypothesis that exercise attenuates the reductions in lean mass, muscle strength, BMD, and VO₂max that accompany modest weight loss induced by calorie restriction.

Methods—Overweight, sedentary women and men (n=52, 45–65y) were randomized to 6–8% weight loss by using calorie restriction (CR), endurance exercise (EX), or both (CREX). The CR and CREX groups underwent counseling to reduce energy intake by 20% and 10%, respectively. The EX and CREX groups exercised 7.4±0.5 and 4.4±0.5 hr/wk, respectively. Before and after 16.8±1.1 weeks of weight loss, lean mass and BMD were measured with dual-energy X-ray absorptiometry, strength was measured with dynamometry, and aerobic capacity (VO₂max) was measured with indirect calorimetry during maximal-intensity treadmill exercise.

Results—Weight loss was ~7% in all groups. Decreases in whole body (~2%, p=0.003) and lower extremity (~4%, p<0.0001) lean mass occurred in the CR group (both p<0.05). Despite similar weight loss, these reductions were attenuated in the CREX group (~1%, p=0.44 and ~2%, p=0.05, respectively) and absent in the EX group. Absolute aerobic capacity decreased ~6% in the CR group (p=0.04), was unchanged in the CREX group (p=0.28) and increased ~15% in the EX group (p<0.0001). No changes in muscle strength or bone were observed.

Conclusions—Modest weight loss (~7%) induced by 20% calorie restriction in overweight women and men decreases lean mass and reduces absolute VO₂max. Exercise protects against

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these effects. While the CR-induced changes might be considered physiologically appropriate for a reduced body weight, exercise preserves and/or improves these parameters during weight loss, which likely improves physical function. These findings support the notion of using exercise as an important component of weight loss programs.

Keywords

Weight management; diet modification; exercise training; maximal oxygen uptake; muscle strength; bone mineral density

INTRODUCTION

Dietary energy restriction causes weight loss and provides powerful protection against many chronic diseases. However, the catabolic state induced by calorie restriction not only affects fat tissue but it also causes undesirable catabolism of other tissues, including skeletal muscle, heart, liver, and kidney (3); many of these changes could have important functional and/or physiologic ramifications. Skeletal muscle mass decreases during weight loss from dietary restriction (2, 17), which reduces muscle strength (26) and resting metabolic rate (13). Calorie restriction causes bone loss (7, 23), which may increase fracture risk (8). Cardiac mass appears to decrease during calorie restriction (3), which may reduce maximal cardiac output and aerobic capacity.

Exercise is an important adjunct to calorie restriction for weight loss. It contributes to the energy deficit and may also promote long-term weight maintenance after weight loss (5). Exercise may also attenuate some of the negative consequences of weight loss on lean mass (4, 22), bone (24, 32), and aerobic capacity (20). We previously reported that modest weight loss (~9%) induced by 1 year of 20% calorie restriction decreased muscle mass and strength, absolute aerobic capacity, and bone mineral density, while full preservation of these outcomes occurred during a similar magnitude weight loss induced by endurance exercise training (33, 36). However, in the absence of diet modification, the amount of exercise required to produce meaningful weight loss is substantial (~1 hr daily) (16), especially for overweight and obese individuals who may have limited success in adhering to exercise programs. Therefore, it may be prudent to use more modest amounts of exercise in combination with calorie restriction. However, it is not clear if more modest amounts of exercise (e.g. ~30–40 min/day), when used in combination with calorie restriction to promote weight loss, are effective for preserving lean mass, muscle strength, bone, and aerobic capacity.

The purpose of the present study was to evaluate the effects of matched, modest (~7%) weight loss, induced by calorie restriction (CR), endurance exercise training (EX), or both (CREX) on lean mass, muscle strength, bone, and aerobic capacity. We hypothesized that the lesser amount of exercise used in the CREX intervention would be sufficient to prevent some, but not all of the losses induced by CR alone. While in contrast, full preservation of lean mass, bone, and aerobic capacity would occur in response to the same magnitude of weight loss when induced by EX alone. This study is unique from most previous studies in that the energy deficit and weight loss were partially (CREX group) or fully (EX group)

induced by exercise. In most previous studies, the exercise interventions did not contribute meaningfully to the weight loss, which was mainly induced by CR. Furthermore, the present study included a group that underwent weight loss solely by using exercise, which is rare in the existing scientific literature but is representative of many individuals in the population who maintain healthy body weight by performing large volumes of exercise without restricting energy intake. The data in this report were from a trial in which insulin sensitivity and related outcomes were primary outcomes. The primary outcomes have been published previously (35) and the data in the present report reflect secondary outcomes.

METHODS

Study participants

Nonsmoking, overweight (BMI 25.0–29.9 kg/m²), middle-aged (45–65 yr) men and postmenopausal women were recruited from the Saint Louis Missouri metropolitan area. Participants were required to be weight stable (<3% change in body weight) and non-exercisers (<20 min/session and <3 d/wk) for at least 6 months prior to enrollment. A medical evaluation and diagnostic ECG stress test were used to identify and exclude individuals with major chronic diseases and/or conditions for which exercise is contraindicated, such as coronary artery disease, diabetes, and musculoskeletal problems. For medications, stable dosages were required for 6 months prior to baseline testing and the participants were advised to maintain stable dosages throughout the study. Participants provided informed written consent to participate in the study, which was reviewed and approved by the Institutional Review Boards at Saint Louis University and Washington University. The study was registered at ClinicalTrials.gov (registry ID: NCT00777621).

Study Design and Randomization

After baseline testing, participants were randomly assigned to CR, EX, or CREX. The randomization sequence was generated by using www.randomization.com and included multiple block sizes and stratification for sex. The allocation ratio was initially 1:1:1 and was later revised to 2:2:1 to account for greater drop-out rates in the CR and EX groups. The study statistician generated the randomization sequence, the research coordinators enrolled participants, and personnel who were not otherwise involved in the study used the allocation sequence to assign participants to the study groups. Outcomes were assessed at baseline and again after a 2-week weight stability period which followed the active weight loss portion of the intervention (see Figure, Supplemental Digital Content 1, study timeline for weight loss interventions, weight stabilization, and outcomes testing).

Interventions

The interventions were designed to create a 20% energy deficit, with the goal of reducing body weight by 6–8% over 12–14 weeks (see Figure, Supplemental Digital Content 1, study timeline for weight loss interventions, weight stabilization, and outcomes testing). The duration of the intervention was adjusted as needed to allow subjects to reach the weight loss goal. The initial prescribed energy deficit was calculated as 20% of baseline total energy expenditure and energy intake, as described previously (35). The CR and EX prescriptions were adjusted each week as needed to yield the targeted rate of weight loss. After the weight

loss goal was attained, the prescriptions were adjusted so that body weight remained stable (0.5 kg variation based on 3-day rolling average) for at least 2 weeks before follow-up testing commenced (see Figure, Supplemental Digital Content 1, study timeline for weight loss interventions, weight stabilization, and outcomes testing). Participants measured and recorded fasted morning body weight at home each day for monitoring of weight loss progress during the intervention (weight as a study outcome was measured in the laboratory as described below); they also visited our facility weekly to turn in home weight logs and for other study requirements, as described below.

Calorie restriction—The CR intervention was designed to reduce body weight by decreasing dietary energy intake while holding physical activity at baseline levels. Study dietitians counseled the participants on a weekly basis to reduce energy intake by reducing food portion sizes and by replacing energy-dense foods with those of lower energy density. Individualized guidance was based on 3-day food diaries, which were recorded weekly during the first 3 weeks of the intervention and as needed thereafter as a tool for ongoing dietary monitoring and counseling during the intervention. The intervention was also designed to keep macronutrient balance within the recommended ranges (15); this was accomplished by qualitative (and as needed, quantitative nutrient analysis) evaluation of the food diaries to identify deviations from recommendations (for example, low carbohydrate dietary patterns) and specific dietary recommendations designed to rectify problems. Participants with poor dietary compliance, as evidenced by lack of weight loss and little or no CR (based on dietary assessment), were given full food provision for 7-days at a time to improve compliance.

Exercise intervention—The exercise intervention was designed to reduce body weight by increasing exercise energy expenditure and holding energy intake constant at baseline levels. The types of exercise included cardiovascular exercise, such as brisk walking, jogging, and cycling, and functional physical activities, such as walking to work or adding yard work to the usual routine. Strength training was not included. Exercise energy expenditure prescriptions were calculated as described previously and included an adjustment to account for the energy expenditure that would have occurred in the absence of exercise (37). The participants were provided with wrist-watch type heart rate (HR) monitors (Polar, Kempele, Finland) to monitor and record exercise data (energy expenditure, HR, exercise frequency and duration); these data were recorded by study personnel during weekly meetings with the participants. To achieve the weekly exercise energy expenditure goals, the participants were encouraged to exercise ~60 min or more each day and to use moderate- to vigorous- intensity (intensity recommendations were generally based on subjective ratings of moderate or vigorous overall physical exertion during exercise but more objective guidance was provided as needed); however, beyond these general recommendations, no specific prescriptions were provided for exercise frequency, intensity, and duration. In light of the time-demands of the exercise intervention, the participants were encouraged to exercise at convenient locations such as outdoors, in a home gym, or at a conveniently located exercise facility. Free access to the University's exercise facilities was also provided.

Calorie restriction + exercise intervention—The CREX intervention included both calorie restriction and exercise, with each contributing approximately half to the total energy deficit. Therefore, the degree of calorie restriction and the exercise volume were lower than in the CR and EX interventions, respectively. Otherwise, the intervention methods were the same as those described for CR and EX.

Body weight and composition

At baseline and final testing, fasted, morning, gownned body weight was measured on two separate days and averaged. Standing height without shoes was measured to the nearest millimeter using a wall-mounted stadiometer (PORTROD, Health o meter Professional Scales, Inc., McCook, IL).

Dual-energy X-ray absorptiometry (DXA, Lunar iDXA, software version 13.31, GE Healthcare, Madison, WI) was used to measure whole body fat mass, whole body and appendicular lean mass, and whole body and regional (spine, hip, and radius) bone mineral density (BMD), and bone mineral content (BMC). Fat and lean mass data and whole-body bone data were derived from a whole-body scan. Regional scans were performed for BMD and BMC assessments of the lumbar spine (L1–L4), total hip, and wrist (distal third of the radius). Lean mass measures excluded both bone and fat mass. Upper and lower appendicular regions were automatically defined by DXA scanner's software, with manual review and adjustments made by the DXA technician, as needed. In brief, the appendicular regions were defined as the tissue distal to a line bisecting the shoulder joint for the upper appendages and bisecting the hip joint for the lower appendages. Lean mass in the appendicular regions primarily represents skeletal muscle (14). However, lean mass may also include non-muscle components (e.g. blood and some interstitial fluid) and DXA-based measures of lean mass may be susceptible to greater measurement error than more direct measures of muscle mass, such as computed tomography scans (9).

The DXA scanner was calibrated with a bone phantom every day before any scans were performed and a soft tissue calibration bar was positioned in the scan area for all whole body scans. The scans on study participants were performed in the morning after an overnight fast, and while the participant was wearing only a hospital gown and underwear. All radiopaque objects (jewelry, watches, etc.) were removed from the participant before the scan. During the scan, the DXA technician monitored the subject and scan for evidence of movement and to ensure that the appropriate region of interest was captured. Scans were repeated if needed to correct more motion or other artifacts.

Dietary intakes and physical activity levels

Energy and nutrient intakes were measured by performing computerized nutrient analyses (Food Processor SQL software, ESHA Research, Inc., Salem, OR) of 3-day food diaries, which included 2 weekdays and 1 weekend day. Estimates of calcium and vitamin D intake included supplements. Total energy expenditure was estimated as the average results from a modified Stanford 7-day physical activity recall interview (25) and accelerometry (RT3 triaxial accelerometers, StayHealthy, Inc. Monrovia, CA). Exercise energy expenditure data (EX and CREX groups only) were retrieved each week from the heart rate monitors.

Because these data reflect gross energy expenditure, net exercise energy expenditure was calculated by subtracting the energy expenditure that would have occurred in the absence of exercise, which was approximated as the product of baseline total energy expenditure in kcal/min and total exercise time. As outcomes assessments, dietary intakes and energy expenditure measures were performed once at baseline and once at the end of the active weight loss period (i.e. before weight stability). Exercise energy expenditure data from the HR monitors were collected throughout the intervention.

Muscle strength

Concentric isometric and isokinetic knee flexor and knee extensor strength was measured with as Biodex System 4 dynamometer (Shirley, NY). Prior to the tests, the participants performed light-effort cycle ergometer exercise for 5 minutes. Furthermore, immediately prior to each of the isokinetic tests described below, a test-specific warm up was performed, which consisted of 3 repetitions of alternating knee extension and flexion at 75% of maximal effort. Multiple practice sessions, which are often used in strength training studies to allow for neurologic strength gains, were not used in the present study because strength gains were not expected and the study did not involve strength training. The participants were seated with the hips flexed at 85° and the back supported, and were secured to the dynamometer with padded straps. The seat and attachment positions on the dynamometer for each participant were recorded during the baseline test and the same setup was used for the follow-up test. Prior to starting each test, the participants were given clear and standardized instructions to give maximal effort during the test and continue until the technician said stop; verbal encouragement was not given during the test. Tests were performed on the right and left legs. Results were corrected for gravity effect torque of the lower extremity. The isometric tests were performed with the knee flexed at 45° and included 3 repetitions of alternating extension and flexion. The isokinetic tests were performed at an angular velocity of 60 and 180°/s. Five repetitions of alternating extension and flexion were performed for the 60°/s tests and 30 repetitions were performed for the 180°/s tests. The peak torque value from each test was used as the measure of strength; results from tests on the right and left limbs were summed. Strength data were also reported relative to body weight and relative to appendicular and lower extremity lean mass as an index of muscle specific force. The reliability of isokinetic strength testing using similar procedures to those described above has a standard error of measure of 6–9%, with intraclass correlation coefficients of 0.90 – 0.96 (18, 29).

Physiological responses to maximal-intensity exercise

The treadmill test started at 0% grade and a speed determined during a 5-minute warm-up to elicit a heart rate of ~70% of age-predicted maximal heart rate. The grade was then increased by 2 percentage points every 1 to 2 minutes until the subject could no longer continue due to fatigue. Indirect calorimetry (MedGraphics CardioO2; Graphics Corporation, St. Paul, MN) was used to continuously measure metabolic outcomes during the test, with time-averaged values being generated every 30 s. Prior to each test, the pneumotach airflow meter was calibrated with a 3 liter air syringe and the carbon dioxide and oxygen analyzers were calibrated with medical grade calibration gases. The highest 30 s average oxygen uptake was considered maximal oxygen uptake (VO₂max). The tests were

also evaluated for meeting the criteria for “true VO₂max” based meeting 2 of the following criteria: (1) maximal respiratory exchange ratio (RER_{max}) ≥ 1.10 ; (2) measured maximal heart rate (HR_{max}) $\geq$ predicted HR_{max} minus 10; and, (3) increase in oxygen uptake of ≥ 150 mL/min between the last two stages of the test. Heart rate was measured continuously by using ECG; HR_{max} was determined by manually measuring 5 normal sinus R-R intervals. Blood pressure (BP) was measured via auscultation at rest, every two minutes during the exercise test and recovery, and during maximal exercise. Maximal exercise oxygen pulse was calculated as absolute VO₂max divided by HR_{max}. Maximal exercise rate pressure product was calculated as the product of HR_{max} and maximal exercise systolic BP and was used as an index of myocardial work rate.

Statistical analyses

Analyses were performed on data from subjects who provided both baseline and follow-up data and were adherent to the intervention; lack of adherence was defined as $<1\%$ weight loss. Comparisons of baseline characteristics among groups were performed with Fisher’s exact tests and ANOVAs. Between-group comparisons of the changes in outcomes were performed with ANCOVAs in which the baseline-to-follow-up change was the dependent variable, treatment group was the independent variable; covariates included in the initial model were baseline values of the outcome, magnitude of weight loss, and sex but these were removed one at a time if they were not meaningful predictors of the outcome, based on $p \geq 0.15$. Post-hoc comparisons were performed based on the protected f-test principal and least significant difference tests. Significance of the within-group changes were based on the least squares means from the ANCOVAs. Strength data residuals were not normally distributed nor were mathematical transformations effective for normalization. Therefore, strength outcomes were analyzed by using non-parametric Kruskal-Wallis ranks sums tests for among group comparisons and Signed rank tests for within group changes. Multiple regression analyses used a stepwise selection model, with $p < 0.15$ required for entry into the model. All statistical tests were two-tailed, and significance was accepted at $P \leq 0.05$. Data from parametric tests are presented as arithmetic mean $\pm$ SE except for mean change values, which were adjusted for baseline values. Data from non-parametric tests are presented as medians and interquartile ranges except as noted. Analyses were performed using SAS for Windows (version 9.3, SAS Institute Inc., Cary, NC). Sample size calculations were based on glucoregulation outcomes which have been published previously (35).

RESULTS

Participants

Of the 69 women and men who enrolled in the study, underwent baseline testing, and were randomly allocated to study groups, 52 completed the study and were compliant with the interventions. Twelve participants dropped out before providing follow-up data and 5 participants were non-compliant as evidenced by negligible weight changes ranging from 0.5% weight loss to 1.3% weight gain. Additional details about the number of subjects recruited, screened, and enrolled are depicted in a Consort diagram in Supplemental Digital Content 2 (see Figure, Supplemental Digital Content 2, Consort diagram indicating sample

sizes) and have been presented previously (35). Participant recruitment and screening commenced in April 2008 and final data collection was completed in March 2013.

Demographic and baseline characteristics did not differ among groups (Table 1). Body fat percentage was 45% for women and 35% for men, which is well above the recommended ranges of 20–32% for women and 10–22% for men (1). Energy intake and physical activity energy expenditure were within the typical ranges for overweight inactive adults. BMD T-scores indicate that most participants were above the -1.0 threshold for osteopenia. With the exception of hip and wrist BMD in the CR group, T-scores did not differ from normal values for young sex-matched young control subjects values (i.e. T-score of zero). One participant (female, CREX group) had a diagnosis of osteoporosis prior to enrollment. Eight were on stable doses of bone-affecting medications throughout the study including thyroid medications ($n=4$), transdermal or vaginal estrogen ($n=3$), and an anti-resorptive medication ($n=1$). Baseline VO₂max was $8.2 \pm 2.8\%$ below age- and sex-specific predicted values (Table 1; $p=0.005$ vs. 100%) as expected for sedentary and overweight adults.

Dietary intakes and physical activity

Energy intake, energy expenditure, and VO₂max data have been reported previously as indicators of intervention compliance (35). Dietary intakes of energy, protein (g/day), carbohydrate, and fat decreased in the CR and CREX groups and did not change in the EX group (Table 2). When expressed relative to body mass, protein intake decreased in the CR group but did not change significantly in the CREX or EX groups. Calcium intake decreased by $\sim 11\%$ with all groups combined, with no significant difference among groups. Vitamin D decreased in the CREX group only (Table 2).

Exercise energy expenditure recorded with the HR monitors was 412 ± 26 kcal/d in the EX group and 217 ± 23 kcal/d in the CREX group (EX vs. CREX $p < 0.0001$). Respective exercise frequencies were 8 ± 1 and 6 ± 1 sessions/wk ($p=0.08$), exercise duration was 7.4 ± 0.5 and 4.4 ± 0.5 hr/week ($p=0.0002$), and exercise intensity was $77 \pm 1\%$ and $74 \pm 1\%$ of HRmax ($p=0.17$). Total energy expenditure increased in the EX (185 ± 53 kcal/d, $p=0.001$) and CREX (126 ± 48 kcal/d, $p=0.01$) groups and did not change in the CR group (-22 ± 51 kcal/d, $p=0.66$) (among-group $p=0.02$).

Body weight and lean mass

As reported previously (35), body weight decreased by $\sim 7\%$ and fat mass decreased by $\sim 15\%$ in all three groups, with no difference among groups ($p=0.56$; Table 3) as was intended by design. The average time to reach the weight loss goal was 16.8 ± 1.1 weeks. Whole body lean mass decreased in the CR group, with no change in the EX ($p=0.68$) and CREX groups ($p=0.44$) (Table 3). Lower extremity lean mass decreased by $\sim 4\%$ in the CR group and by $\sim 2\%$ in the CREX group, and did not change in the EX group ($p=0.30$). Lean mass of the upper extremities decreased by 2% with all groups combined, with no difference among groups ($p=0.29$) (Table 3). The reductions in total, appendicular, and leg lean mass in the CR group remained significant, even when the change in dietary protein intake (g/day) was included as a covariate (data not shown).

Using a stepwise multiple linear regression analysis with the change in leg lean mass as the dependent variable and the change in energy intake, change in protein intake (g/day), baseline leg lean mass, and sex as the independent variables, only the change in energy intake (20% of the variance explained, $P = 0.001$) was related to the change in leg lean mass:

$$\Delta \text{ leg lean mass (kg)} = 0.0005 (\Delta \text{ energy intake, kcal/d}) - 0.2254$$

$$F=12.05, \text{ SEE}=0.05, C_p=2.07$$

Based on this equation, a 500 kcal/d reduction in energy intake is predicted to result in a 0.5 kg (~3%) reduction in leg lean mass. Similar results were observed when changes in total or appendicular lean mass were used as the dependent variable (results not shown). None of the independent variables were significant predictors of upper extremity lean mass changes.

Muscle strength

Absolute isometric and 60°/sec isokinetic muscle strength did not change in response to weight loss in any of the three study groups (Table 4). With pooled data from all groups, marginally significant decreases in peak torque were observed for high velocity (180°/sec) isokinetic knee extension and flexion ($p=0.08$ and $p=0.02$, respectively); these changes did not differ among groups (both $p > 0.39$). When pooled strength data were reported relative to body weight, strength increased by 6% for knee flexion, by 5% for flexion and extension combined, and tended to increase for knee extension ($p=0.07$), with no difference in the magnitude of improvement among groups. Strength relative to lower extremity lean mass did not change in any group (see Figure, Supplemental Digital Content 3, absolute lower extremity strength, strength relative to body weight and strength relative to lean mass).

Bone mineral density

No changes were observed in spine, hip, or whole-body BMD in any of the study groups (Table 5). Wrist BMD decreased in the EX group but this change did not differ from the CR and CREX groups, in which no significant changes were observed. The findings were similar for bone mineral content and if changes were expressed as percentage change from baseline (data not shown). Exclusion of the 8 participants who were on stable doses of medications that affect bone did not alter these findings.

Physiological responses to maximal-intensity exercise

At baseline, 89% of the VO₂max tests met the criteria for “true VO₂max” and at follow-up, 85% of the test met the criteria. The frequency of meeting true VO₂max criteria did not differ among groups at baseline ($p=0.60$) or follow-up ($p=0.88$). Absolute VO₂max decreased by 6% in the CR group, increased by 15% in the EX group, and did not change in the CREX group (Table 6), with the magnitude of increase in VO₂max being correlated ($r=0.38$, $p=0.007$) with physical activity energy expenditure (see Figure, Supplemental Digital Content 4, for scatterplots of physical activity expenditure). Similar results were observed for VO₂max relative to lean mass. VO₂max relative to body weight was preserved in the CR group and increased by 22% in the EX group and by 13% in the CREX group (Table 6). Likewise, maximal exercise oxygen pulse did not change in response to CR but

increased in the EX (+19%) and CREX (+7%) groups. HR_{max} and RER_{max} did not change in response to any of the interventions. As reported previously (34), resting systolic blood pressure decreased in the CR (-8 ± 2 mmHg, $p=0.0002$) and CREX (-5 ± 2 mmHg, $p=0.01$) groups and did not change in the EX group (-1 ± 2 mmHg, $p=0.63$); however, the between-group comparison was not statistically significant ($p=0.07$). Resting systolic pressure decreased in all groups (CR: -3 ± 1 mmHg, $p=0.05$; EX: -3 ± 1 mmHg, $p=0.03$; CREX: -5 ± 2 mmHg, $p=0.001$), with no difference among groups ($p=0.63$). Maximal exercise systolic and diastolic blood pressures and maximal exercise rate pressure product all decreased based on all groups combined, with no differences among groups (Table 6).

DISCUSSION

Results from the present study show that modest weight loss from calorie restriction reduces total and lower extremity lean mass and absolute aerobic capacity. In contrast, the same amount of weight loss induced by exercise did not alter lower extremity lean mass and increased aerobic capacity. Although weight loss induced by calorie restriction or exercise has numerous benefits, these findings suggest that exercise may be preferable to CR, at least from the viewpoint of optimizing lean mass and VO_{2max}. However, the amount of exercise needed to cause weight loss was substantial (7.4 ± 0.5 hr/wk) and may be unrealistic for many overweight individuals with a history of being inactive. Furthermore, less exercise is required to achieve a given amount of weight loss if it is combined with calorie restriction. Therefore we sought to determine if more modest amounts of exercise (4.4 ± 0.5 hr/wk), when used in combination with CR, would prevent decreases in lean mass and aerobic capacity. Indeed, with matched weight loss, the combination of calorie restriction and exercise attenuated the reductions in lean mass and aerobic capacity that occurred with CR. The lean mass losses in the CREX group were approximately half of that observed in response to CR and reductions in VO_{2max} were fully prevented. However, as compared to the combination of CR and exercise, weight loss induced by exercise alone yielded greater benefits, as evidenced by complete preservation of lower extremity and whole body lean mass and increases in VO_{2max}. Taken together, these findings indicate that exercise protects against weight loss-induced reductions in lean mass and absolute aerobic capacity when used alone or in combination with CR.

No losses of muscle strength and bone were observed in response to weight loss in the present study. This was unexpected and prevents us from determining whether exercise has protective effects on these parameters during weight loss. The standard error of repeated isokinetic strength measures is ~ 6 – 13 Nm or 6–9% (18, 29), indicating good reliability; nonetheless, these tests may not have been sensitive enough to detect small reductions in strength that may have occurred as a consequence of the small 2–4% decrease in lower extremity lean mass. Based on a recent meta-analysis of 5 trials ($n=98$ participants), moderate calorie restriction with $6.2 \pm$ kg weight loss reduces isokinetic knee extensor strength by 5.2% ($p<0.0001$) but does not alter isokinetic knee flexor strength or handgrip strength (38). The lack of change in BMD and BMC in the CR group was also unexpected, especially in light of significant reductions in dietary protein and calcium. One explanation for this finding is that bone is slow to adapt (28) and the relatively short time frame for weight loss in the present study was not sufficient for measurable bone adaptations. A recent

meta-analysis reported that hip BMD does not decrease during 3 months of CR-induced weight loss (based on 3 studies) but does decrease by $\sim 1.0 - 1.5\%$ with interventions lasting 6 months (39). The same report indicated that spine and total body BMD do not decrease with weight loss interventions lasting up to 2 years (39). However, in our previous study of 12 months of weight loss, we observed $\sim 2\%$ reductions in hip and spine BMD and most of these changes occurred in the first 3 months with little or no change thereafter (33). This earlier study was remarkably similar to the present study in that the participants were middle-aged (57 ± 3 yr) women and men, physically inactive at baseline, and were non-obese with a similar baseline BMI (27 ± 2 kg/m²); furthermore, the degree of CR was similar to that used in the present study, with a goal of 16–20% CR during the first 3–6 months of the intervention. An alternate explanation for the lack of change in BMD in the present study is that the magnitude of weight loss ($\sim 7\%$) may have been below a critical threshold for bone loss. Accordingly, correlation data from our previous study showed that bone losses occurred only when weight loss exceeded $\sim 8-10\%$ (33).

Although it was not a study objective to identify causes of lean mass loss from CR, our data may provide some insights. One cause for CR-induced reductions in lean mass may be a modest disuse effect. As body weight decreases, the force generating demands on muscle for performing activities of daily living also decreases, which results in skeletal muscle atrophy. This effect would be expected in weight bearing muscles of the lower extremities, with little or no effect on upper extremity muscle. Accordingly, we observed CR-specific decreases in whole-body and lower extremity lean mass. These losses were prevented by exercise, likely because exercise put demands on muscle which compensated for the reductions in demands associated with lower body weight. Another explanation for lean mass losses in response to CR might be the decrease in dietary protein that was observed in the CR group but not in the EX or CREX groups. Dietary protein has been shown to influence lean mass losses during weight loss (11, 19). Because the anabolic effects of dietary protein are systemic (e.g. circulating factors including amino acids and IGF-1), the decreases in upper extremity lean mass would also be restricted to the CR group, which was not the case. Furthermore, the reductions in lean mass in the CR group remained significant, even when the change in dietary protein intake was included as a statistical covariate. Finally, multiple regression analyses showed that the change in energy intake, but not the change in protein intake, was a significant predictor of the lean mass losses. Taken together, these lines of evidence suggest that reductions in total energy intake were responsible for CR-induced decreases in lean mass and that the changes in protein intake had little or no effect on lean mass.

Absolute VO₂max decreased in the CR group, increased in the EX group, and remained unchanged in the CREX group. The changes were paralleled by changes in maximal exercise oxygen pulse, while HRmax was unchanged. Oxygen pulse is a function of left ventricular stroke volume (SV) and arteriovenous oxygen content difference ($a-vO_2\text{diff}$). Therefore, the observed decrease in VO₂max in the CR group and increase in the EX group was attributable to one or both of these factors. Exercise training increases VO₂max by increasing both SV and $a-vO_2\text{diff}$ (30, 31); therefore, it is likely that both contributed to the increases in VO₂max in the EX group. Because SV depends on left ventricular mass (21, 27), and because $a-vO_2\text{diff}$ depends on skeletal muscle capillary and mitochondrial density (6), the increases in VO₂max and maximal oxygen pulse in the EX group suggest that

cardiac tissue and skeletal muscle can adapt to exercise training despite the presence of a general catabolic state from weight loss. The contributions of changes in SV and a-vO₂diff to the decreases in VO₂max in the CR group are less clear but both may have been involved. Cardiac mass decreases with CR-induced weight loss (3), which might reduce left ventricular chamber size and stroke volume. Furthermore, the reductions in lean mass suggest that less muscle mass is present to extract oxygen from blood during maximal exercise, which would decrease a-vO₂diff.

A beneficial adaptation that was similar in all three groups was the decrease in maximal exercise blood pressures (based on pooled data from all three groups). Because there was no change in HR_{max}, this translated to a lower rate pressure product (12), suggesting a favorable reduction in myocardial work and oxygen consumption during intense exercise. However, in light of the decrease in VO₂max in the CR group, and based on the Fick equation (where VO₂=cardiac output × a-vO₂diff), the reduction in maximal exercise blood pressure might have resulted from a decrease in stroke volume and cardiac output during maximal exercise. In contrast, because VO₂max increased in the EX group, maximal stroke volume and cardiac output likely also increased (10). This, paired with a reduction in maximal exercise blood pressure indicates that total peripheral resistance to blood flow during maximal exercise decreased in the EX group (total peripheral resistance = mean arterial pressure ÷ cardiac output). In this context, the exercise group likely benefitted from greater improvements in maximal exercise hemodynamic function than the CR group.

This study has limitations. The short intervention duration may not have been sufficient for full adaptations to occur; this may explain the lack of change in muscle strength and bone mineral density in response to CR. Second, isometric and isokinetic strength measures may not reflect strength during functional physical activities. Furthermore, the unfamiliar nature of these tests to many study participants may contribute to measurement error, thereby increasing the risk of false-negative (type II) statistical errors. Third, circulating markers of bone turnover were not measured; because bone markers change rapidly compared to BMD, such measures might have useful for evaluating bone responses to the relatively short-duration intervention. Fourth, we used DXA-based measures of lean mass, which are not direct measures of muscle mass and may have more measurement error compared to magnetic resonance imaging- or computed tomography-based measures of muscle mass (9). Fifth, we did not measure maximal exercise cardiac output, stroke volume, and a-vO₂diff; therefore, we cannot make definitive conclusions about the mechanisms for CR- and/or EX-induced changes in VO₂max. Lastly, because the exercise prescriptions were based only on exercise energy expenditure, the frequency, intensity, and duration of exercise likely varied among subjects, which may have contributed to variability in the results.

CONCLUSIONS

Modest, calorie restriction-induced weight loss in overweight sedentary adults decreases whole body and lower extremity lean mass, suggesting skeletal muscle atrophy, and reduces absolute aerobic capacity, suggesting catabolic activity on the cardiovascular system. However, when the same amount of weight loss was induced by using exercise alone or a combination of calorie restriction and exercise, these outcomes were preserved and/or

improved. The CR-induced decreases in lean mass and aerobic capacity, are likely “physiologic” changes that are appropriate for a lighter body weight, and therefore should not be viewed as adverse effects. However, the inclusion of exercise preserves or improves lean mass and absolute aerobic capacity, while body weight decreases; this likely translates to an improvement in physical function, which is especially important in the sedentary population that was studied. Furthermore, preservation of lean mass during weight loss may help preserve resting metabolism and consequently reduce the risk of weight regain. Taken together, these findings reinforce the notion that exercise is an important component of weight loss programs, not only for contributing to an energy deficit, but also for optimizing physical function and possibly preserving metabolism.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1

Baseline characteristics of study participants.

	All (n=52)	CR (n=17)	EX (n=16)	CREX (n=19)	Among group p-value
Sex, women	39 (75%)	13 (76%)	11 (69%)	15 (79%)	0.85
Race					
Caucasian	42 (81%)	16 (94%)	12 (75%)	14 (74%)	0.26
African-American	7 (13%)	0 (0%)	3 (19%)	4 (21%)	
Other or not specified	3 (6%)	1 (6%)	1 (6%)	1 (5%)	
Age, y	57 ± 5	57 ± 5	56 ± 6	57 ± 7	0.86
BMI, kg/m ²	27.7 ± 1.7	27.7 ± 1.7	27.0 ± 1.5	28.3 ± 1.8	0.08
Body weight, kg					
Women	75.5 ± 6.9	73.2 ± 5.1	74.2 ± 5.5	77.2 ± 8.6	0.26
Men	92.0 ± 11.5	92.4 ± 7.9	86.3 ± 11.4	98.7 ± 13.5	0.30
Body fat, % of total mass					
Women	45 ± 3	47 ± 2	43 ± 3	44 ± 4	0.26
Men	35 ± 5	33 ± 7	34 ± 5	37 ± 3	0.30
Energy intake, kcal/d	2165 ± 611	2243 ± 566	1909 ± 498	2310 ± 693	0.12
Physical activity energy expenditure, kcal/d	439 ± 177	425 ± 251	437 ± 144	452 ± 122	0.90
Spine BMD					
T-score	0.0 ± 1.4	-0.2 ± 0.8	0.2 ± 1.9	0.0 ± 1.5	0.83
Z-score	0.6 ± 1.5*	0.6 ± 1.1	0.6 ± 1.8	0.5 ± 1.5	0.97
Hip BMD					
T-score	-0.3 ± 1.0	-0.5 ± 0.7*	-0.5 ± 1.0	0.0 ± 1.0	0.23
Z-score	0.1 ± 0.9	0.1 ± 0.8	-0.2 ± 1.2	0.4 ± 0.8	0.29
Wrist BMD					
T-score	-0.4 ± 1.1	-0.7 ± 0.9*	-0.1 ± 1.0	-0.3 ± 1.4	0.32
Z-score	0.1 ± 1.0	-0.1 ± 0.9	0.3 ± 1.0	0.2 ± 1.1	0.51
VO2max, % of predicted	92 ± 20*	99 ± 24	91 ± 20	87 ± 15*	0.19

Values are means ± SD for quantitative data and counts (%) for categorical data. Among group p-values for quantitative data are from ANOVAs and for categorical data are from Fisher's Exact Tests.

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* indicates p 0.05 vs. zero for BMD T- and Z-scores and vs. 100 for predicted VO2max data. BMD, bone mineral density; T-score, number of SD above or below the average BMD values for young sex-matched adults; VO2max, maximal oxygen uptake, reported as percentage of predicted values based on sex and age (28).

Table 2

Dietary intakes in response to calorie restriction (CR), endurance exercise training (EX), or a combination of CR and EX (CREX).

	All	CR	EX	CREX	Among group p-value
Energy intake, kcal/d					
Baseline	2164 ± 85	2243 ± 137	1908 ± 125	2310 ± 159	0.16
Final	1610 ± 62	1428 ± 85	1781 ± 115	1630 ± 107	
Change	-572 ± 78	-783 ± 123 ^a	-179 ± 126 ^b	-716 ± 116 ^a	0.002
Within-group <i>P</i>	<0.0001	<0.0001	0.16	<0.0001	
Protein, g/day					
Baseline	84 ± 3	90 ± 5	73 ± 6	86 ± 6	0.09
Final	70 ± 3	65 ± 3	73 ± 7	71 ± 6	
Change	-14 ± 4	-25 ± 6 ^a	1 ± 6 ^b	-15 ± 6 ^{ab}	0.009
Within-group <i>P</i>	0.0004	<0.0001	0.90	0.01	
Protein, g/kg/d					
Baseline	1.05 ± 0.04	1.16 ± 0.06 ^a	0.93 ± 0.06 ^b	1.03 ± 0.06 ^{ab}	0.03
Final	0.94 ± 0.04	0.90 ± 0.05	1.01 ± 0.08	0.91 ± 0.05	
Change	-0.10 ± 0.05	-0.26 ± 0.07 ^a	0.08 ± 0.08 ^b	-0.12 ± 0.07 ^{ab}	0.008
Within-group <i>P</i>	0.03	0.001	0.28	0.10	
Carbohydrate, g/day					
Baseline	257 ± 12	247 ± 19 ^{ab}	223 ± 17 ^a	296 ± 26 ^b	0.05
Final	197 ± 10	168 ± 14	222 ± 19	203 ± 16	
Change	-59 ± 12	-79 ± 18 ^a	-1 ± 19 ^b	-93 ± 18 ^a	0.002
Within-group <i>P</i>	<0.0001	<0.0001	0.96	<0.0001	
Fat, g/day					
Baseline	86 ± 4	92 ± 6	80 ± 8	84 ± 9	0.50
Final	59 ± 3	52 ± 4	66 ± 4	58 ± 6	
Change	-27 ± 4	-40 ± 7 ^a	-13 ± 7 ^b	-26 ± 7 ^{ab}	0.03
Within-group <i>P</i>	<0.0001	<0.0001	0.07	0.0006	
Calcium, mg/d					
Baseline	1191 ± 96	1304 ± 180	1201 ± 202	1111 ± 130	0.73

	All	CR	EX	CREX	Among group p-value
Final	1070 ± 89	1050 ± 181	1028 ± 147	1130 ± 136	
Change	-135 ± 58	-254 ± 97	-173 ± 100	-19 ± 97	0.14
Within-group <i>P</i>	0.02	0.01	0.09	0.84	
Vitamin D, IU/d					
Baseline	353 ± 65	289 ± 106	399 ± 117	406 ± 128	0.73
Final	401 ± 66	292 ± 101	400 ± 114	511 ± 129	
Change	37 ± 16	3 ± 25	1 ± 26	105 ± 25	0.007
Within-group <i>P</i>	0.03	0.91	0.98	0.0001	

Values are arithmetic means ± SE. Among group p-values reflect the significance of the among-group differences in change values based on ANOVA. Means within each row with unlike superscripts are significantly different (*P*<0.05). For example, for the mean change in protein intake (g/day), the values for the CR group (superscript a) and the EX group (superscript b) are significantly different from each other but are not different from the mean in the CREX group (superscript ab). Calcium and vitamin D data include intakes from supplements.

Changes in lean mass and bone mineral density in response to weight loss induced by calorie restriction (CR), endurance exercise training (EX), or a combination of CR and EX (CREX).

Table 3

	All	CR	EX	CREX	Among group p-value
Total body mass, kg					
Baseline	79.6 ± 1.5	77.9 ± 2.4	78.1 ± 2.3	82.4 ± 2.9	0.38
Final	73.9 ± 1.4	72.5 ± 2.3	72.6 ± 2.3	76.2 ± 2.8	
Change	5.7 ± 0.2	-5.4 ± 0.4	-5.6 ± 0.4	-6.1 ± 0.4	0.43
Within-group <i>P</i>	<0.0001	<0.0001	<0.0001	<0.0001	
Total fat mass, kg					
Baseline	32.1 ± 0.7	32.2 ± 1.1	30.4 ± 1.3	33.4 ± 1.3	0.24
Final	27.4 ± 0.7	28.1 ± 1.1	25.5 ± 1.4	28.3 ± 1.2	
Change	-4.7 ± 0.2	-4.1 ± 0.3	-4.9 ± 0.3	-5.0 ± 0.3	0.10
Within-group <i>P</i>	<0.0001	<0.0001	<0.0001	<0.0001	
Total lean mass, kg					
Baseline	44.5 ± 1.2	42.7 ± 2.5	44.7 ± 1.8	45.9 ± 2.0	0.55
Final	43.8 ± 1.2	41.8 ± 2.3	44.6 ± 1.8	45.1 ± 1.9	
Change	-0.7 ± 0.2	-0.9 ± 0.3 ^a	0.1 ± 0.3 ^b	-0.3 ± 0.3 ^b	0.03
Within-group <i>P</i>	0.0001	0.003	0.68	0.44	
Lower extremity lean mass, kg					
Baseline	14.8 ± 0.4	14.1 ± 0.9	14.9 ± 0.6	15.4 ± 0.8	0.47
Final	14.3 ± 0.4	13.5 ± 0.8	14.7 ± 0.6	14.8 ± 0.7	
Change	-0.5 ± 0.1	-0.6 ± 0.1 ^a	-0.1 ± 0.1 ^b	-0.3 ± 0.2 ^{ab}	0.06
Within-group <i>P</i>	<0.0001	<0.0001	0.30	0.05	
Upper extremity lean mass, kg					
Baseline	4.9 ± 0.2	4.7 ± 0.4	5.0 ± 0.3	5.0 ± 0.3	0.80
Final	4.8 ± 0.2	4.6 ± 0.4	4.9 ± 0.3	4.8 ± 0.3	
Change	-0.1 ± 0.03	-0.1 ± 0.1	-0.1 ± 0.1	-0.2 ± 0.1	0.29
Within-group <i>P</i>	0.0009	0.16	0.23	0.001	
Total appendicular lean mass, kg					

	All	CR	EX	CREX	Among group p-value
Baseline	19.7 ± 0.6	18.7 ± 1.3	19.9 ± 0.9	20.4 ± 1.1	0.58
Final	19.1 ± 0.6	18.1 ± 1.3	19.6 ± 0.9	19.6 ± 1.0	
Change	-0.6 ± 0.1	-0.8 ± 0.2	-0.3 ± 0.2	-0.7 ± 0.1	0.10
Within-group P	<0.0001	<0.0001	0.04	<0.0001	

Values are arithmetic means ± SE except for group-specific change values, which are least squares (adjusted) means ± SE. Among group p-values reflect the significance of the among-group differences in change values based on ANCOVA. Covariates in the initial ANCOVA model included baseline values, magnitude of weight loss, and sex but were removed from the model if they were not significant predictors of the outcome based on $p < 0.15$. Means within each row with unlike superscripts are significantly different ($p < 0.05$). For example, for the mean change in lower extremity lean mass, the values for the CR group (superscript a) and the EX group (superscript b) are significantly different from each other but are not different from the mean in the CREX group (superscript ab). Total body mass and total fat mass data have been reported previously (35).

Changes in isometric and concentric isokinetic muscle strength in response to weight loss induced by calorie restriction (CR), endurance exercise training (EX), or a combination of CR and EX (CREX).

Table 4

	All	CR	EX	CREX	Among group p-value
Knee ext. 0°/sec, NM					
Baseline	197 (157, 217)	187 (153, 205)	201 (166, 229)	197 (163, 212)	0.75
Final	193 (138, 212)	185 (160, 220)	195 (129, 213)	199 (172, 209)	
Change	-4 (-24, 12)	-2 (-18, 15)	-12 (-33, -4)	1 (-16, 17)	0.35
Within-group <i>P</i>	0.21	0.96	0.11	0.86	
Knee ext. 60°/sec, Nm					
Baseline	205 (172, 229)	200 (170, 232)	190 (160, 226)	211 (189, 219)	0.66
Final	204 (166, 249)	209 (162, 249)	197 (164, 254)	214 (171, 225)	
Change	3 (-11, 23)	2 (-9, 27)	-1 (-17, 15)	9 (-8, 25)	0.56
Within-group <i>P</i>	0.41	0.76	0.68	0.21	
Knee ext. 180°/sec, Nm					
Baseline	139 (113, 167)	134 (122, 161)	146 (114, 188)	152 (113, 169)	0.91
Final	133 (114, 160)	130 (119, 152)	146 (114, 160)	135 (113, 150)	
Change	-5 (-18, 5)	-2 (-12, 4)	-5 (-24, 16)	-9 (-19, 1)	0.53
Within-group <i>P</i>	0.08	0.58	0.50	0.08	
Knee flex. 0°/sec, Nm					
Baseline	127 (112, 160)	126 (109, 136)	152 (110, 166)	126 (115, 148)	0.68
Final	126 (106, 164)	127 (108, 152)	127 (104, 189)	125 (111, 158)	
Change	-1 (-11, 10)	0 (-5, 15)	4 (-24, 20)	-2 (-12, 2)	0.53
Within-group <i>P</i>	0.90	0.51	0.89	0.31	
Knee flex. 60°/sec, Nm					
Baseline	109 (90, 131)	109 (88, 129)	110 (96, 121)	99 (86, 132)	0.91
Final	108 (87, 135)	110 (88, 124)	106 (87, 147)	105 (86, 134)	
Change	1 (-7, 8)	4 (-6, 8)	4 (-5, 8)	0 (-8, 5)	0.87
Within-group <i>P</i>	0.69	0.70	0.59	0.90	
Knee flex. 180°/sec, Nm					

	All	CR	EX	CREX	Among group p-value
Baseline	92 (80, 116)	92 (79, 106)	97 (86, 121)	91 (71, 112)	0.79
Final	89 (75, 108)	90 (79, 105)	97 (69, 105)	87 (78, 110)	
Change	-3 (-13, 2)	-1 (-12, 6)	-7 (-16, -1)	-1 (-12, 3)	0.39
Within-group P	0.02	0.50	0.06	0.24	

Values are medians with interquartile ranges in parentheses. Non-parametric statistical analyses were performed because of non-normally distributed data (residuals). Among-group comparisons of changes in strength were performed with Kruskal-Wallis ranks sums tests. Within-group comparisons of baseline and final values were performed with Signed rank tests. Strength data were missing for 8 participants due to technical problems with equipment (n=5), knee pain (n=1), and refusal to perform the final test (n=2).

Changes bone mineral density in response to weight loss induced by calorie restriction (CR), endurance exercise training (EX), or a combination of CR and EX (CREX).

Table 5

	All	CR	EX	CREX	Among group p-value
Spine BMD, g/cm²					
Baseline	1.193 ± 0.025	1.172 ± 0.024	1.214 ± 0.059	1.193 ± 0.042	0.80
Final	1.194 ± 0.025	1.176 ± 0.027	1.227 ± 0.059	1.182 ± 0.042	
Change	0.001 ± 0.008	0.003 ± 0.013	0.012 ± 0.014	-0.011 ± 0.012	0.44
Within-group <i>P</i>	0.92	0.79	0.37	0.37	
Total hip BMD, g/cm²					
Baseline	0.990 ± 0.018	0.968 ± 0.023	0.972 ± 0.039	1.026 ± 0.032	0.34
Final	0.987 ± 0.019	0.965 ± 0.024	0.965 ± 0.041	1.026 ± 0.032	
Change	-0.003 ± 0.002	0.000 ± 0.004	-0.004 ± 0.004	0.003 ± 0.004	0.38
Within-group <i>P</i>	0.16	0.97	0.25	0.47	
Radius (distal 33%) BMD, g/cm²					
Baseline	0.874 ± 0.017	0.843 ± 0.025	0.906 ± 0.029	0.874 ± 0.033	0.35
Final	0.864 ± 0.018	0.841 ± 0.024	0.883 ± 0.032	0.867 ± 0.037	
Change	-0.010 ± 0.005	0.003 ± 0.009	-0.020 ± 0.009	-0.001 ± 0.008	0.11
Within-group <i>P</i>	0.04	0.72	0.02	0.86	
Whole body BMD, g/cm²					
Baseline	1.150 ± 0.017	1.127 ± 0.020	1.156 ± 0.037	1.165 ± 0.030	0.64
Final	1.148 ± 0.017	1.128 ± 0.022	1.155 ± 0.039	1.160 ± 0.030	
Change	-0.002 ± 0.003	0.005 ± 0.005	0.002 ± 0.005	0.000 ± 0.005	0.77
Within-group <i>P</i>	0.53	0.38	0.73	0.096	

Values are arithmetic means ± SE except for group-specific change values, which are least squares (adjusted) means ± SE. Among group p-values reflect the significance of the among-group differences in change values based on ANCOVA. Covariates in the initial ANCOVA model included baseline values, magnitude of weight loss, and sex but were removed from the model if they were not significant predictors of the outcome based on $p < 0.15$.

Table 6

Physiologic responses to maximal treadmill exercise in response to weight loss induced by calorie restriction (CR), endurance exercise training (EX), or a combination of CR and EX (CREX).

	All	CR	EX	CREX	Among group p-value
Absolute VO ₂ max, mL/kg					
Baseline	2000 ± 79	2112 ± 158	1985 ± 127	1914 ± 127	0.81
Final	2046 ± 88	1960 ± 177	2252 ± 148	1939 ± 131	
Change	46 ± 40	-124 ± 59 ^a	289 ± 58 ^b	64 ± 59 ^c	<0.0001
Within-group <i>P</i>	0.26	0.04	<0.0001	0.28	
VO ₂ max relative to body weight, mL/kg/min					
Baseline	24.9 ± 0.8	26.5 ± 1.6	25.4 ± 1.3	23.1 ± 1.2	0.29
Final	27.5 ± 1.0	26.5 ± 1.9	30.7 ± 1.7	25.6 ± 1.5	
Change	2.6 ± 0.5	0.4 ± 0.8 ^a	5.7 ± 0.8 ^b	3.1 ± 0.8 ^c	<0.0001
Within-group <i>P</i>	<0.0001	0.57	<0.0001	0.0003	
VO ₂ max relative to lean mass, mL/kg/min					
Baseline	45.1 ± 1.3	49.0 ± 2.1	44.3 ± 2.4		0.09
Final	46.6 ± 1.4	45.9 ± 2.4	50.5 ± 2.8	42.4 ± 1.9	
Change	1.5 ± 0.8	-2.5 ± 1.0 ^a	6.6 ± 1.0 ^b	43.7 ± 2.0	<0.0001
Within-group <i>P</i>	0.08	0.05	<0.0001	2.2 ± 1.0 ^c	
Maximal heart rate, beats/min					
Baseline	166 ± 2	165 ± 4	165 ± 3	167 ± 3	0.89
Final	163 ± 2	164 ± 4	161 ± 4	165 ± 3	0.49
Change	-2 ± 1	-1 ± 2	-5 ± 2	-1 ± 2	
Within-group <i>P</i>	0.13	0.61	0.06	0.66	
Oxygen pulse at maximal exercise, mL/beat					
Baseline	12.1 ± 0.5	12.9 ± 1.0	12.0 ± 0.7	11.5 ± 0.8	0.74
Final	12.5 ± 0.5	11.9 ± 1.0	14.0 ± 0.9	11.8 ± 0.8	<0.0001
Change	0.4 ± 0.3	-0.4 ± 0.4 ^a	2.3 ± 0.4 ^b	0.8 ± 0.4 ^c	
Within-group <i>P</i>	0.11	0.27	<0.0001	0.05	
RER at maximal exercise					

	All	CR	EX	CREX	Among group p-value
Baseline	1.22 ± 0.02	1.23 ± 0.03	1.25 ± 0.04	1.19 ± 0.01	0.38
Final	1.23 ± 0.02	1.27 ± 0.03	1.20 ± 0.03	1.22 ± 0.02	0.15
Change	0.01 ± 0.2	0.03 ± 0.03	-0.04 ± 0.03	-0.01 ± 0.2	
Within-group <i>P</i>	0.65	0.28	0.12	0.63	
Systolic BP at maximal exercise, mmHg					
Baseline	200 ± 3	197 ± 6	200 ± 6	203 ± 5	0.56
Final	194 ± 4	193 ± 6	193 ± 8	196 ± 6	0.87
Change	-6 ± 3	-4 ± 5	-6 ± 5	-8 ± 5	
Within-group <i>P</i>	0.05	0.47	0.24	0.14	
Diastolic BP at maximal exercise, mmHg					
Baseline	84 ± 1	84 ± 3	83 ± 2	84 ± 2	0.97
Final	76 ± 1	75 ± 2	76 ± 3	78 ± 2	
Change	-8 ± 2	-9 ± 2	-8 ± 2	-6 ± 2	0.64
Within-group <i>P</i>	<0.0001	0.0002	0.001	0.006	
RPP at maximal exercise, beats/min × mmHg					
Baseline	32229 ± 636	32668 ± 1380	33091 ± 836	33875 ± 1048	0.50
Final	31946 ± 793	31903 ± 1158	31368 ± 1651	32491 ± 1381	
Change	-1283 ± 636	-765 ± 1122	-1723 ± 1161	-1383 ± 1086	0.83
Within-group <i>P</i>	0.05	0.50	0.15	0.21	

Values are arithmetic means ± SE except for group-specific change values, which are least squares (adjusted) means ± SE. Among group p-values reflect the significance of the among-group differences in change values based on ANCOVA, which included baseline values, magnitude of weight loss, and sex as covariates. Means within each row with unlike superscripts are significantly different ($P < 0.05$). Data were missing for 2 participants due to refusal to perform the final test. VO₂max, maximal oxygen uptake; RER, respiratory exchange ratio; BP, blood pressure; RPP, rate pressure product.