Clinical Nutrition 38 (2019) 372–382

Contents lists available at ScienceDirect

Clinical Nutrition

journal homepage: http://www.elsevier.com/locate/clnu

Original article

Resistance training during a 12-week protein supplemented VLCD treatment enhances weight-loss outcomes in obese patients

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ARTICLE INFO

Article history:
Received 1 August 2017
Accepted 15 December 2017

Keywords:
Weight-loss
Body composition
Caloric restriction
Resistance exercise
Skeletal muscle

SUMMARY

Background: This investigation evaluated the efficacy by which resistance training enhances body composition, metabolic, and functional outcomes for obese patients undergoing a 12-week medically supervised hypocaloric treatment.

Methods: This was a single-blind, randomized, parallel-group prospective trial. Morbidly obese patients were prescribed a 12-week proprietary very low calorie diet (VLCD) treatment (Optifast®) with supplemental protein (1120 kcals/day) and were placed in one of two groups for 14 weeks: 1) Standard Treatment Control (CON) ($n = 5$) or 2) Resistance Training (RT) ($n = 6$). Both groups underwent a pedometer-based walking program; however only RT performed resistance training 3 days/week for 12 weeks. Body composition, resting energy expenditure (REE), neuromuscular function, and serum biomarkers were measured at weeks 0, 6, and 13.

Results: Both groups exhibited a significant loss of total body mass (TBM) (CON: -19.4 ± 2.3 kg, $p = 0.0009$ vs. RT: -15.8 ± 1.5 kg, $p = 0.0002$) and fat mass (FM) (CON: -14.7 ± 1.8 kg, $p = 0.0002$ vs. RT: -15.1 ± 2.1 kg, $p = 0.0002$) with no group differences. CON lost 4.6 ± 0.8 kg ($p = 0.004$) of lean mass (LM) while RT demonstrated no changes. Group differences were found for the relative proportion of total weight-loss due to FM-loss (CON: $75.6 \pm 3.4\%$ vs. RT: $96.0 \pm 6.0\%$, $p = 0.03$) and LM-loss (CON: $24.4 \pm 3.2\%$ vs. RT: $4.0 \pm 6.5\%$, $p = 0.03$). CON demonstrated a 328.6 ± 72.7 kcal/day ($-14.3 \pm 2.4\%$) ($p = 0.02$) decrease in REE while RT exhibited a non-significant decrease of $4.6 \pm 1.6\%$ ($p = 0.78$). RT demonstrated greater improvements in all measures of contractile function and strength when compared to CON ($p < 0.05$). At post-treatment, RT exhibited greater serum free fatty acids ($p = 0.01$), glycerol ($p = 0.003$), and β-hydroxybutyrate ($p = 0.005$) than CON.

Conclusion: Resistance training was advantageous for weight-loss composition by preservation of LM without compromising overall weight- or fat-loss in morbidly obese men and women undergoing a protein supplemented VLCD. These changes accompanied positive adaptations for resting metabolism and muscular function.

1. Introduction

Epidemiological findings from the National Health and Nutrition Examination Survey (NHANES 2011–2014) reported that just over 36% of U.S. adults are currently classified as obese, while 16%

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https://doi.org/10.1016/j.clnu.2017.12.015
0261-5614/

represent incidences of severe cases [1]. Obesity reflects a prevalence rate far exceeding the threshold of 15% set by the World Health Organization for epidemics needing intervention [1]. Hence, national health initiatives have prompted the urgency for effective clinical treatments to reconcile the global spread of obesity and subdue the heightened socioeconomic burdens directly attributable to this epidemic. Despite the technical advancements in treatment options, such as surgical- or pharmacological-based approaches, medically supervised weight-loss programs incorporating hypocaloric dietary modifications have remained an ongoing and widely prescribed treatment for obesity [2]. Amongst hypocaloric treatment programs, proprietary Very Low Calorie Diets (VLCD) (~800 kcal/day), e.g. Optifast® (Nestlé HealthCare Nutrition), have been medically prescribed as a viable option for high-risk patients whose body mass index (BMI) exceeds 35 kg/m^2, exhibit critical mortality risk, or have failed to respond favorably to conventional and unmonitored weight-loss programs.

VLCD prescriptions, which are based largely on liquid meal replacement formulas, have been consistent with outcomes of revitalized health with significant body weight reductions ranging between 15 and 27% in obese subjects [2,3]. This loss in total body mass (TBM), however, cannot be solely accounted for by reduced adiposity, but also significant deficits in lean mass (LM) or skeletal muscle [4–6]. With respect to these frequently reported weight-loss patterns, the potential for optimum weight-loss (i.e. weight-loss quality) as well as sustainable weight-maintenance is adversely affected on multiple levels. Lowered resting energy expenditure (REE), neuromuscular declines, undue fatigue, poor physical functioning, and increased risk for musculoskeletal injury have been reported to occur as a result of reduced LM [2,7]. Any of these factors taken together with the loss of LM would be conducive to impeded fat reduction, weight-regain, and relapses of prior health complications [8].

While large-scale weight-loss yields important clinical benefits for the morbidly obese, the rate of recidivism remains inordinately high with contemporary VLCD programs. In fact, significant weight-regain has been reported in 77%–100% of subjects who underwent a VLCD-based weight-loss intervention [3,9]. Accordingly, previous findings indicated that VLCD-treated subjects initially lost 19.6% (−21.4 kg) of their entry weight; however, maintained only 4.3% (−5.1 kg) after 4.5 years [2,10]. Thus, a positive prognosis for acute and prolonged treatment success remains, at present, marginally supported with current VLCD-based therapies. When considering the public health relevance of these corollaries, a major unmet clinical need is a strategy that can be practically applied to current VLCD programs in efforts to optimize weight-loss composition/quality while enhancing metabolic and functional outcomes. To address the burden imposed by severe hypocaloric diets on lean tissue morphology, energy metabolism, and perhaps physical function, the integration of exercise countermeasures has been examined extensively [4,11–14]. However, an equivocal body of pertinent data has likely precluded the sophisticated integration of exercise training into clinical weight-management prescriptions using a VLCD system.

As a potent anabolic stimulus for skeletal muscle, resistance training would appear as the ideal countermeasure to losses in LM during caloric restriction; yet, most studies have employed relatively low-force activities in the form of aerobic exercise training [13,15,16]. On the basis of previous whole-body outcomes [14,16] and molecular rationale [17], aerobic training may be an ineffective strategy for LM retention during severe hypocaloric conditions. In fact, aerobic training has even demonstrated to extend LM loss beyond the degree induced by caloric restriction alone, suggesting that prolonged, low-force activity can exacerbate the catabolic nature of energy deficiency in muscle [14,16,18,19]. Because it is well established that high-force and high-load bearing activities function favorably to improve skeletal muscle mass and performance, resistance training may be the most effective means of optimizing VLCD treatments towards enhanced weight-loss composition, resting metabolism, and muscular function [20]. Of the limited pool of available evidence comparing modes of exercise during VLCD-induced weight-loss, resistance training demonstrated similar effects on fat reduction but greater efficiency in maintaining LM and REE [4]. Unfortunately, these previous attempts using resistance training to moderate the burden of severe hypocaloric diets lack sufficient support to be systematically integrated into current therapeutic procedures. This likely is attributable to the paucity of applicable clinical data that can properly guide medical weight-management programs towards an optimized hypocaloric treatment through a resistance exercise prescription. Thus, the purpose of this study was to evaluate the efficacy by which resistance training enhances body composition, REE, and muscular function in obese patients undergoing a 12-week medically supervised protein-supplemented VLCD. The central hypothesis was that integration of resistance training during the 12-week high-protein hypocaloric intervention would elicit superior weight-loss composition, resting metabolism, and muscular function than the standard clinical treatment.

2. Methods

2.1. Participants

This was a 14-week, single-blind, randomized, parallel-group prospective trial and a joint effort between Florida State University and Tallahassee Memorial Healthcare (TMH). The target population were morbidly obese patients from the TMH Bariatric Center who were prescribed by a licensed bariatric physician to undergo a medically monitored VLCD-based treatment program (Optifast®; 800 kcal/day). Six male and five female participants (age = 58 ± 3 years, BW = 124.2 ± 7.5 kg, BMI = 40.8 ± 2.4 kg/m^2) were recruited through the TMH Bariatric Center. Before starting the VLCD treatment, all patients were required to undergo 4 weeks of weight stabilization under the care of the bariatric physician as part of their standard medical treatment plan. During this period, patients were recruited for the study. In addition to the criteria set forth by the bariatric physician for VLCD treatment eligibility, patients also met the following inclusion criteria to participate in this study: 1) BMI between 30 and 42 kg/m^2; 2) physically inactive (<30 min/day of exercise) for the past 6 months; and 3) at least 4 weeks of weight stabilization (±2 kg of body weight). All eligible patients underwent a comprehensive medical examination to further confirm eligibility for participation. Patients were excluded from the study if they had any medical conditions in which dietary restriction, exercise, or whey protein supplementation are contraindicated or that would confound the interpretation of results. Six participants failed to complete the treatment program and therefore, were not included in the present analysis. Patients provided investigators with informed consent prior to participation and this study was approved by the Institutional Review Boards of FSU and TMH.

2.2. Experimental protocol

Participants (N = 11) were matched for sex, body composition, and REE and randomly allocated to one of the two following groups for a 14-week study (weeks 0–13): 1) Standard Treatment Control Group (CON) (n = 5); and 2) Resistance Training Group (RT) (n = 6). All participants underwent the control dietary condition (i.e. Optifast® + whey protein supplement) from the start of week 1 to

the end of week 12 as part of a medically monitored weight-loss treatment at the TMH Bariatric Center. The control diet provided 1120 kcal/day through Optifast® meal-replacement formulas (800 kcal/day) and whey protein supplementation (320 kcal/day, 80 g/day). CON underwent a 12-week, self-paced protocol to simulate the standard clinical treatment in which exercise variables were not specifically prescribed, but rather general physical activity recommendations were provided. CON was instructed to achieve 8000–12,000 steps/day progressively through self-selected activity which was monitored weekly by daily pedometer records and exercise logs. RT underwent resistance training integrated into the standard clinical treatment. RT performed resistance exercise 3 non-consecutive days per week during the 12-week intervention period. All experimental conditions as well as the control dietary treatment began at week 1 and concluded at the end of week 12. Laboratory testing was scheduled on weeks −0 (pre-intervention), −6 (mid-intervention), and −13 (post-intervention) during which times testing procedures for REE, body composition (dual-x-ray absorptiometry [DXA]), and maximum isokinetic and isometric muscular torque were administered in addition to blood collection. Muscular strength was assessed via one-repetition maximum (1RM) testing for select exercises on experimental weeks −1, −6, and −13 at the training facility. Furthermore, participants visited the TMH Bariatric Center one time each week on the same day for the entire 12-week intervention period to meet with investigators, a bariatric physician, and/or registered dietician for body weight assessment, group- and individual-based counseling, and acquire a single week's worth of diet products. Details regarding experimental protocols and testing procedures are described below.

2.3. Control dietary condition

2.3.1. Protein supplemented VLCD

All participants underwent the control dietary condition (i.e. Optifast® + whey protein supplement) from experimental weeks 1–12 as part of a medically supervised treatment program for obese patients at the TMH Bariatric Center. The control diet was prescribed by a board certified bariatric physician and administered by way of proprietary meal-replacement formulas and whey protein supplementation. The meal-replacement formulas comprised of a powder mix, ready-to-drink blend, and instant soup, all of which contained equivalent macronutrient (35% protein, 50% carbohydrate, 15% fat) and micronutrient composition per product, equating to 160 kcals/product. Participants consumed five products a day yielding a total of 800 kcals, 70 g of protein, 100 g of carbohydrates, 15 g of fat, and 100% of the Daily Value for 24 vitamins and minerals. Also, a single 40 g serving of a whey protein supplement was consumed with meals 2 and 4. Thus, all subjects underwent a control dietary protocol that provided 1120 kcals, 150 g of protein, 100 g of carbohydrate, and 15 g of fat each day during the 12-week intervention period. Meals were separated by approximately 3 h each day with the first serving consumed within 1 h of waking and the last serving approximately 3 h prior to sleep. Participants also consumed at least 2 quarts of non-caloric liquids per day in addition to the volume consumed through the liquid-based formulas and supplements. As part of the normal clinical treatment program, patients/participants were required to attend meetings with the registered dietician and bariatric physician twice a week. During these meetings, self-recorded dietary logs and empty VLCD formula packages were collected. Also, three times per week researchers met with participants and took record of compliance via questionnaire. Although this may be an imperfect means of assessing compliance, it was deemed the most practical approach. The non-compliant drop-outs were those participants who demonstrated atypical responses to the VLCD (absence of weight-loss) or those who admitted non-compliance. Those non-compliant patients continued with their treatment program at the clinic however were excluded from the study.

2.4. Strength testing and control and experimental exercise protocols

2.4.1. Familiarization and strength testing

All familiarization, strength testing, and resistance training sessions were administered and monitored by a Certified Strength and Conditioning Specialist®. During week 1, participants attended an exercise familiarization session followed by a strength testing session 2 days later. An assessment of one-repetition maximum (1RM) was administered for two representative exercises for overall upper ($1RM_{upper}$) and lower body ($1RM_{lower}$) strength [21]. This included the chest and leg press exercises. After completion of 1RM testing, CON was excused. For RT, 1RM values obtained at pre-intervention also served as a reference to prescribe training workloads for the 2 aforementioned exercises. A 10RM strength test was performed for 8 exercises that were also administered as part of the resistance training intervention, but were not included in the assessment of muscular strength. The Baechle equation [22] was then applied to extrapolate 1RM values, which was used to prescribe resistance training intensities for the 8 exercises tested for 10RM (% predicted 1RM). The 10RM assessment was repeated at week 6 to provide an appropriate reference for load prescriptions during the last 6 weeks of resistance training. The 1RM test was repeated at weeks 6 and 13.

2.4.2. Standard treatment control condition

CON was instructed to perform general physical activity from weeks 1–12. A self-paced protocol was implemented to simulate the standard Optifast®-based treatment program in which exercise variables are not specifically programmed, but rather general physical activity is encouraged. Investigators, however, monitored participants' physical activity level each week by self-recorded daily pedometer readings (i.e. steps/day) and physical activity logs. Investigators encouraged participants to progressively yield 8000–12,000 steps/day, which are BMI-referenced cut-points established by previous data [23]. Participants were instructed to document the type and duration of physical activity as well as daily pedometer readings at the end of each day on a physical activity log.

2.4.3. Resistance training condition

Table 1 outlines the timetable and periodization of resistance training variables for each session across the experimental period. Periodized resistance training was initiated in the RT group on week 2 at the training facility. The training program was administered and monitored by a Certified Strength and Conditioning Specialist®. Participants underwent resistance training bouts integrated into the standard treatment on 3 non-consecutive days per week (on non-testing weeks) during the 12-week intervention period. A minimum of 48 h of rest separated each training session to allow adequate recovery for participants. Participants exercised at the same time of the day for each training session to control for circadian rhythm and daily hormonal fluxes. During each session, participants performed a total of 10 multi-joint exercises which included, squats, chest press, leg press, lat pulldown, leg extension, shoulder press, leg curls, back row, triceps extension, and bicep curls, in the listed order. A 1.5- to 3.0-min rest period was provided between each exercise.

Table 1
Timetable and periodization format of resistance training protocol from experimental weeks 1–12.

Day	RT variable	Experimental weeks												
		WK 1	WK 2	WK 3	WK 4	WK 5	WK 6[a]	WK 7	WK 8	WK 9	WK 10	WK 11	WK 12	WK 13
1	Sets	Familiarize	2	2	3	3	1	3	3	3	3	4	1	Post-strength
	Reps		12	12	8	8	RM	12	12	10	10	8	RM	testing
	Load (%1RM)		65	65	75	75	90	65	65	70	70	75	85	
2	Sets	No training	3	3	4	4	No training	4	4	4	4	5	1	No training
	Reps		10	10	6	6	(Lab testing)	10	10	8	8	6	RM	
	Load (%1RM)		70	70	80	80		70	70	75	75	80	90	
3	Sets	Pre-strength testing	3	3	4	4	Mid-strength	4	4	4	4	5	1	No training
	Reps		8	8	4	4	testing	8	8	6	6	4	RM	
	Load (%1RM)		75	75	85	85		75	75	80	80	85	95	
		Familiarize + Testing	Microcycle 1		Microcycle 2		Taper + Testing	Microcycle 1		Microcycle 2		Microcycle 3 + Taper		Testing
		Mesocycle 1 12-week macrocycle						Mesocycle 2						

WK = week; RT = resistance training; RM = maximum repetitions until failure.
[a] Participants underwent 1 training session on week 6 due to the subsequent laboratory and strength testing schedule. Load prescription during mesocycle 2 was relative to 1RM measures obtained from week-6 strength testing.

2.5. Laboratory testing procedures

Laboratory testing was scheduled during experimental weeks 0, 6, and 13. Participants reported to the laboratory between 6:00 am and 11:00 am following an 8-h fast and 48 h of no strenuous physical activity. Testing protocols were administered in the following order: 1) height and body weight; 2) REE; 3) body composition; 4) blood draw; and 5) dynamic and static muscular contractile function.

2.5.1. Resting energy expenditure

REE was measured using the ventilated hood and dilution technique with an open-circuit indirect calorimeter (ParvoMedics TrueOne® 2400; Salt Lake City, Utah, USA) [24]. The assessment was administered in a thermo-neutral (~24 °C), dimly lit room with the participant lying in a supine position, without speaking or sleeping and with minimal movement. For the initial 10 min, participants laid quietly in the supine position on a cushioned bed to achieve true resting conditions. Data were not collected during this time. Data acquired during the subsequent 80 min were used to compute REE according to the Weir equation and was expressed in total daily energy expenditure (kcal/day) [25].

2.5.2. Total and regional body composition

Body composition was measured by dual-energy x-ray absorptiometry (DXA) (Lunar iDXA, GE Healthcare, Madison, WI). Total body mass (TBM) was quantified through the scan. TBM, FM and LM (i.e. LM = TBM − FM − bone mineral content) were analyzed. Appendicular skeletal muscle mass (ASM) was obtained from the sum of LM in the arms and legs. ASM was then used to determine the ASM index (ASM/height in m^2), a proxy for whole-body skeletal muscle mass. The DXA machine was calibrated before each scan using a manufacturer-provided phantom, and measurements were conducted by a single certified technician who was blind to the participant's experimental treatment condition. Participants were fasted during the time of testing. Participants were also instructed to refrain from drinking fluids the morning of testing and to empty their bladder prior to the scan. Participants wore the same metal-free clothing for each scan.

2.5.3. Biochemical markers

A 10 ml sample of venous blood was drawn from the antecubital vein for the analysis of serum concentrations of insulin-like growth factor-1 (IGF-1) (Abcam®, Cambridge, MA, #ab100545), IGF binding protein-3 (IGFBP-3) (Abcam®, Cambridge, MA, #ab100541) and cortisol (Abcam®, Cambridge, MA, #ab108665) via enzyme-linked immunosorbent assay (ELISA). Also, by using commercially available colorimetric assay kits, we analyzed serum concentrations of biomarkers related to fat oxidation (3-beta-hydroxybutyrate) (BioVision Inc., Milpitas, CA, #K632-100) and lipolysis (free glycerol and free fatty acids) (BioVision Inc., Milpitas, CA, #K630-100 and K612-100). Absorbance for ELISA and colorimetric assays was analyzed by a microplate reader (Bio-Rad Model 680; Hercules, CA) using assay-specific wavelengths. All samples were assayed in duplicate.

2.5.4. Dynamic and static contractile function

Isokinetic and isometric tests were administered to evaluate maximal torque output of the knee extensors and flexors under dynamic and static conditions by using an isokinetic dynamometer (Biodex System 3 Pro; Shirley, New York, USA). Isokinetic testing was administered on the participant's dominant limb. Participants performed three trials, each including two initial practice repetitions followed by four trial repetitions. Each repetition consisted of one concentric knee extension immediately followed by one concentric knee flexion performed at a constant angular velocity of 60°/second with maximal effort. Range of motion was set between 90° and 0° with each repetition initiated from 90° of knee flexion and finished at full extension. Each trial was separated by two minutes of rest. Isometric testing was administered on the dominant limb with the dynamometer arm fixed to allow 60° of static knee flexion. Participants performed a single isometric knee extension and flexion reciprocally on three separate trials. Each trial was preceded by one practice contraction for the knee extensors and flexors. During each trial, participants were provided lay instructions to produce maximal static contractions as fast and forcefully as possible and then to maintain each contraction for five seconds. Two minutes of recovery was provided between trials.

2.5.5. Statistical analysis

All values are presented as mean ± standard error (SE). An independent T-test was used to compare mean differences between groups for all baseline descriptive measures. Data were analyzed using a 2 (group) × 3 (time) repeated measures ANOVA. In the event of a significant main effect or interaction, a Tukey *post hoc* test was performed for pairwise comparisons. All statistical analyses were performed using Statistica 12 for Windows (StatSoft; Tulsa, OK, USA) with significance set at $p < 0.05$.

3. Results

3.1. Descriptive and control variables

There were no group differences for all baseline descriptive measures obtained at pre-intervention which included age (CON: 54.6 ± 4.8 y vs. RT: 62.2 ± 2.5 y) as well as anthropometric (CON: 172.2 ± 6.5 cm, 42.7 ± 4.6 kg/m^2 vs. RT: 175.2 ± 4.3 cm, 39.2 ± 2.4 kg/m^2), body composition (Table 2), metabolic, and muscle function variables. Physical activity level, as measured by average daily steps and minutes spent on physical activity across the 12-week intervention period, was not different between groups (CON: 6235.9 ± 2102.2 steps/day, 86.5 ± 14.2 min/day vs. RT: 6166.8 ± 833.5 steps/day, 100.4 ± 13.2 min/day). There were no reported issues related to pedometer use and physical contraindications. There were no group differences for average daily caloric intake across the 12-week intervention period since all participants' dietary intake were restricted to the dietary treatment program. No critical issues relating to dietary compliance were reported across the 12-week protocol.

3.2. Body composition and anthropometric measures at pre, mid, and post

3.2.1. Total body mass

A decrease in TBM was detected over time for both CON and RT (Table 2). CON exhibited a 12.3 ± 1.2 kg (9.9 ± 0.6%) decrease in TBM from pre–mid ($p = 0.0002$) and a 7.1 ± 1.4 kg (6.5 ± 1.3%) reduction from mid–post ($p = 0.009$). The total TBM change for CON was 19.4 ± 2.3 kg (15.8 ± 1.7%) ($p = 0.0002$). RT demonstrated a 10.2 ± 1.1 kg (8.5 ± 0.4%) decline for TBM from pre–mid ($p = 0.0009$) and no change from mid–post ($p = 0.17$). The total TBM change for RT was −15.8 ± 1.5 kg (−13.2 ± 0.9%) ($p = 0.0002$). There was no group by time interaction.

3.2.2. Fat mass

A decrease in FM was identified for both CON and RT (Table 2) (Fig. 1). CON exhibited an 8.2 ± 1.2 kg (15.5 ± 3.1%) decrease in FM from pre–mid ($p = 0.004$) and a 6.5 ± 1.0 kg (15.5 ± 3.6%) reduction from mid–post ($p = 0.04$). Overall FM-change from pre–post was −14.7 ± 1.8 kg (−28.2 ± 5.4%) ($p = 0.0002$) for CON. RT demonstrated a 9.2 ± 1.7 kg (16.7 ± 2.2%) loss of FM from pre–mid ($p = 0.008$) and no change from mid–post ($p = 0.11$). The total loss of FM for RT was 15.1 ± 2.1 kg (27.6 ± 2.2%) ($p = 0.0002$). There was a decrease in android FM ($FM_{android}$), gynoid FM (FM_{gynoid}), and BF% from pre–post for CON and RT ($p < 0.05$). No group by time interactions were detected.

3.2.3. Lean mass

A decline in LM was detected for CON over time ($p < 0.05$); however, RT exhibited no changes from pre (Table 2) (Fig. 1). CON lost 4.1 ± 0.7 kg of LM from pre–mid (6.7 ± 1.2%) ($p = 0.004$) and no change from mid–post. The total reduction in LM from pre–post was 4.6 ± 0.8 kg (7.2 ± 1.1%) for CON ($p = 0.0008$). RT showed no changes in LM across the entire experimental period. CON lost more LM than RT from pre–post ($p = 0.04$). CON and RT exhibited a −13.6 ± 3.9% and +4.3 ± 4.5% change in ASM from pre–post, respectively; and these changes were different between groups ($p = 0.04$). There was an increase in LM% from pre–post for CON (+10.3 ± 2.4%, $p = 0.009$) and RT (+14.2 ± 2.4%, $p = 0.005$), with no group by time interaction (Fig. 1).

3.2.4. Weight-loss composition

The relative proportion of TBM-loss from FM- and LM-loss at mid and post are displayed in Fig. 2 for CON and RT. The proportion of TBM-loss due to FM- and LM-loss was similar between groups at mid. At mid, CON lost 65.6 ± 4.9% of TBM as FM and 34.4 ± 5.1% as LM while RT lost 87.4 ± 9.6% of their TBM as FM and 12.6 ± 9.2% as LM. At post, the total decrease in TBM in CON was 75.6 ± 3.4% due to FM-loss, and 24.4 ± 3.2% due to LM-loss. For RT, FM-loss and LM-loss accounted for 96.0 ± 6.0% and 4.0 ± 6.5% of total TBM-loss, respectively. The total contribution of FM and LM reductions to total weight-loss was significantly different between groups ($p = 0.03$).

3.3. Resting energy expenditure at pre, mid, and post

Changes in REE over time are displayed in Fig. 3 and Fig. 4. CON experienced a 328.6 ± 72.7 kcal/day (−14.3 ± 2.4%) decrease in REE from pre–post ($p = 0.02$) while RT demonstrated no change in REE over time (−4.6 ± 1.6%, $p = 0.78$). The overall change in REE was different between groups ($p = 0.003$). When adjusting for TBM, REE remained unchanged for CON, while RT demonstrated a 10.1 ± 2.4% ($p = 0.003$) increase from pre–post. The pre–post change in REE/TBM was greater in RT than CON ($p = 0.008$). When adjusting for LM, REE decreased by 7.7 ± 1.7% from pre- to post-intervention for CON ($p = 0.03$). RT demonstrated no change in REE when adjusted for LM (−3.6 ± 1.4%, $p = 0.70$). The pre–post change in REE/LM was significantly different between groups ($p = 0.004$).

Table 2
Body composition and anthropometric measures at weeks 0 (pre), 6 (mid), and 13 (post).

	CON (N = 5)				RT (N = 6)			
	Pre	Mid	Post	Δ (%)	Pre	Mid	Post	Δ (%)
TBM (kg)	126.1 (12.6)	113.7* (11.9)	106.6** (12.0)	−15.8 (1.7)	120.2 (10.1)	110.0* (9.2)	104.4* (11.5)	−13.2 (0.9)
FM (kg)	58.0 (9.2)	49.8* (9.3)	43.4** (9.9)	−28.2 (5.4)	53.3 (3.8)	44.1* (2.3)	38.2* (1.8)	−27.6 (3.0)
$FM_{ANDROID}$ (kg)	6.0 (0.7)	5.0 (0.7)	4.4* (0.9)	−29.5 (8.2)	5.7 (0.4)	4.6 (0.2)	3.6* (0.3)	−36.3 (6.1)
FM_{GYNOID} (kg)	8.5 (1.5)	7.2 (1.4)	6.4* (1.5)	−27.7 (5.2)	8.8 (0.7)	6.9 (0.4)	5.7* (0.6)	−33.9 (6.7)
BF% (%)	45.4 (3.8)	43.0 (4.8)	39.2* (5.4)	−15.3 (4.9)	44.8 (1.8)	40.7 (1.9)	36.6* (2.3)	−18.4 (3.5)
LM (kg)	64.9 (6.6)	60.8* (6.8)	60.3* (6.5)	−7.2^ (1.1)	63.7 (6.6)	62.8 (6.8)	63.3 (7.0)	−1.0^ (1.8)
ASM (kg/m^2)	11.0 (0.6)	9.6 (0.7)	9.5 (0.7)	−13.6^ (3.9)	9.8 (0.9)	9.8 (1.3)	10.3 (1.2)	4.3^ (4.5)
LM% (%)	52.0 (3.5)	54.1 (4.5)	57.7* (5.1)	10.3 (2.4)	52.5 (1.7)	56.4 (1.9)	59.9* (1.9)	14.2 (2.4)
BMI (kg/m^2)	42.7 (4.6)	38.0* (4.5)	36.6** (4.8)	−15.1 (1.9)	39.2 (2.4)	35.7* (2.0)	33.8* (2.0)	−13.4 (0.7)
WC (cm)	125.7 (6.1)	115.3 (6.9)	107.2* (6.9)	−15.0 (1.6)	129.4 (6.2)	116.0* (5.4)	106.3** (5.3)	−17.5 (3.5)

TBM = total body mass, FM = fat mass, $FM_{ANDROID}$ = android fat mass, FM_{GYNOID} = gynoid fat mass, BF% = body fat percentage, LM = lean mass, ASM = appendicular skeletal muscle mass index, LM% = lean mass percentage, BMI = body mass index. Δ = mean relative change from pre–post intervention. Values reported as mean (SE).
*Significantly different than Pre ($p < 0.05$).
**Significantly different than Pre and Mid ($p < 0.05$).
^Significantly different between groups ($p < 0.05$).

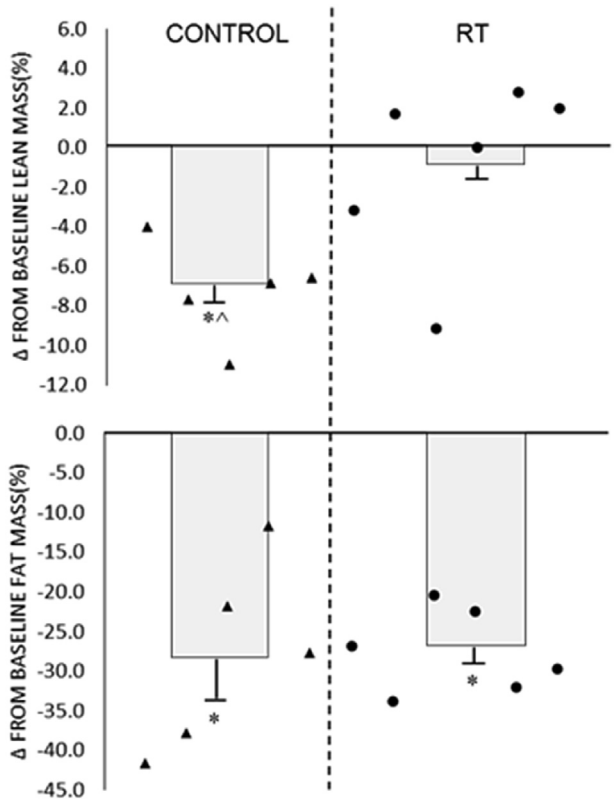

Fig. 1. Individual and group mean data for change in lean mass (top) and fat mass (bottom) from pre- to post-intervention. RT = Resistance Training Group. *Signficant change from pre- to post-intervention (p=0.0002). ^Signficantly different between groups (p=0.04).

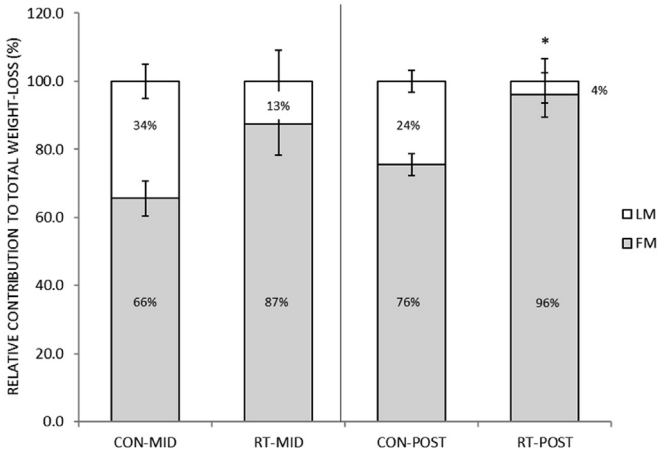

Fig. 2. Proportion of total weight-loss due to changes in fat mass (FM)- and lean mass (LM) at mid- and post-intervention. Values reported as mean ± SE. Approximate values for mean relative contributions of FM- and LM-loss are indicated in respective bars. *FM-loss and LM-loss contributions significantly different between groups (p = 0.03).

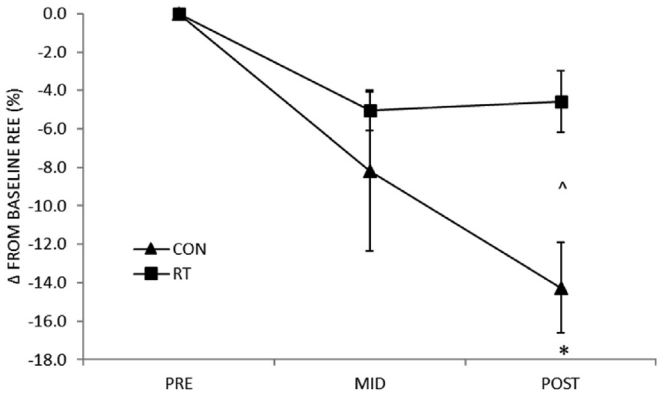

Fig. 3. Change in resting energy expenditure (REE) from pre-intervention for CON and RT. Values reported as mean ± SE. *Significantly different than Pre (p = 0.02). ^Significantly different between groups (p = 0.003).

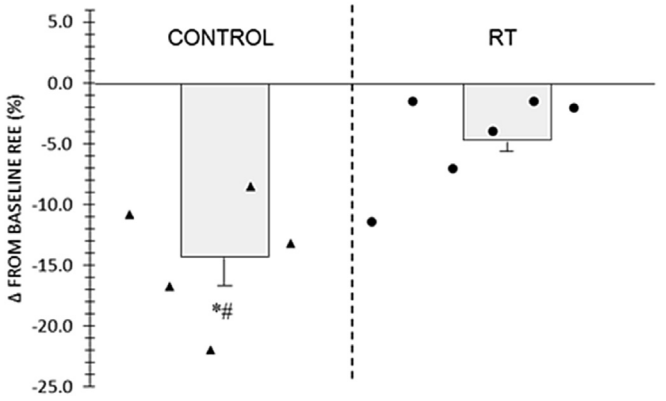

Fig. 4. Individual and group mean data for overall change in resting energy expenditure (REE) from pre-intervention. Bar values reported as mean ± SE. RT = Resistance Training Group. *Significantly different than Pre (p = 0.02). #Significantly different than RT (p = 0.003).

3.4. Muscular contractile function at pre, mid, and post

3.4.1. Isokinetic contraction

Data of contractile function measures are displayed in Fig. 5. Peak extension torque decreased from pre–post by 13.3 ± 3.2% (p = 0.004) in CON. For RT, peak extension torque increased from pre–mid (+22.7 ± 2.0%; p = 0.001) and from pre–post (+32.5 ± 3.1%; p = 0.0002). These pre–post changes for peak extension torque were different between groups (p = 0.0005). When adjusting for TBM or LM, peak extension torque remained unchanged for CON; however, RT exhibited a 52.8 ± 3.7% increase from pre–post (p = 0.0002) when adjusting for TBM and a 34.2 ± 4.7% increase (p = 0.0002) from pre–post when adjusting for LM. Pre–post changes for adjusted peak extension torque measures were greater for RT than CON (p = 0.005). CON showed an 18.8 ± 4.3% decline in average extension power from pre–post (p = 0.004) while RT demonstrated a 22.4 ± 5.1% improvement (p = 0.02). There was a group difference for these pre–post changes in average extension power (p = 0.004).

CON demonstrated a 16.2 ± 2.2% decrease in flexion peak torque from pre–post (p = 0.009) while RT exhibited a 20.6 ± 4.4% increase (p = 0.01). These pre–post changes were different between groups (p = 0.002). When adjusting for TBM or LM, CON showed no changes for peak flexion torque while RT demonstrated a 38.9 ± 4.4% pre–post increase (p = 0.0002) when adjusting for TBM and a 22.1 ± 5.6% pre–post increase (p = 0.01) when adjusting for LM. Pre–post changes for adjusted peak extension torque measures were greater for RT than CON (p = 0.002). CON showed a 17.9 ± 7.1% decline in average flexion power from pre–post (p = 0.01) while RT demonstrated a 35.8 ± 8.2% increase (p = 0.004). These pre–post changes in average flexion power were different between groups (p = 0.003).

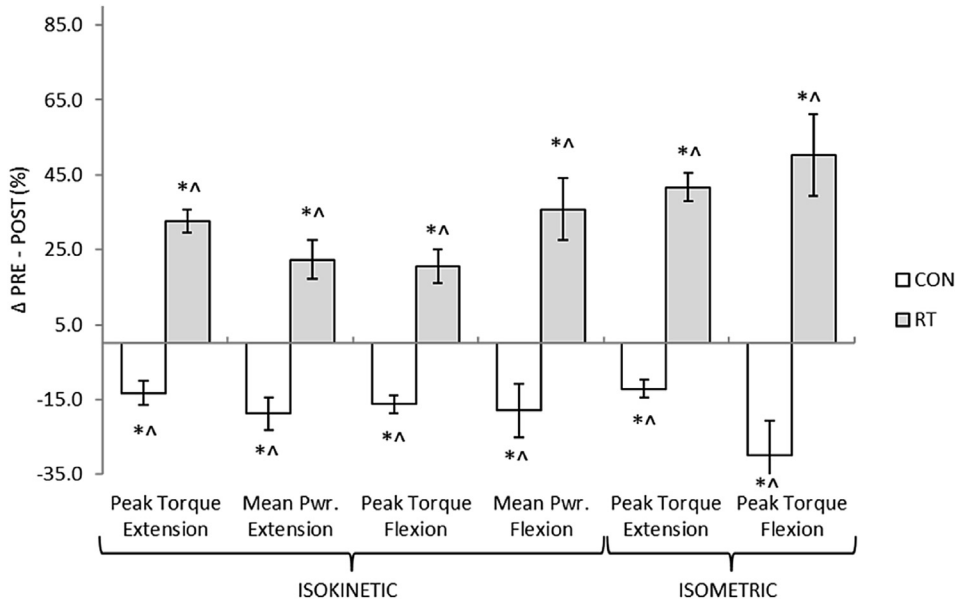

Fig. 5. Pre- to post-change in contractile function for CON and RT. Values reported as mean ± SE. Pwr. = power. *Significant pre- to post-change ($p < 0.02$). ^Significantly different between groups ($p < 0.005$).

3.4.2. Isometric contraction

Peak extension torque declined from pre–post by 12.1 ± 2.3% ($p = 0.003$) for CON while RT demonstrated a 41.7 ± 3.9% ($p = 0.0002$) increase from pre–post. Pre–post changes were significantly greater in RT compared to CON ($p = 0.002$). After adjusting for TBM or LM, peak extension torque remained unchanged over time for CON. For RT, peak extension torque increased from pre–post (+63.5%; $p = 0.0003$). Also, RT increased peak extension torque from pre–post by 43.6 ± 6.1% when adjusted for LM ($p = 0.0002$). Pre–post changes in peak torque was greater in RT than CON when adjusted for TBM or LM ($p = 0.004$).

Peak flexion torque did not change over time for CON; however, RT exhibited a 50.2 ± 10.9% improvement from pre–post ($p = 0.003$). Pre–post changes were greater in RT compared to CON ($p = 0.005$). After adjusting for TBM or LM, peak flexion torque remained unchanged over time for CON. For RT, peak flexion torque significantly increased from pre–post when adjusted for TBM (+72.8 ± 11.8%; $p = 0.0005$) and LM (+52.0 ± 11.6%; $p = 0.002$). Pre–post changes in peak torque was greater in RT than CON when adjusted for TBM or LM ($p = 0.0005$).

3.5. Upper and lower body strength at pre, mid, and post

3.5.1. Upper body 1RM

There were no changes in $1RM_{UPPER}$ over time for CON; however, RT demonstrated a 44.9 ± 7.4% ($p = 0.001$) increase from pre–post. RT demonstrated greater upper body strength gain at mid ($p = 0.003$) and post ($p = 0.004$) compared to CON. After adjusting for TBM, CON showed no changes over time, while RT exhibited an increase from pre–mid (+24.8 ± 5.2%, $p = 0.03$) and pre–post (+44.9 ± 7.4%, $p = 0.0004$). Relative $1RM_{UPPER}$ to TBM was greater in RT than CON at post ($p = 0.02$). When adjusted for LM, $1RM_{UPPER}$ was reduced from pre–post for CON (−26.1 ± 4.0%, $p = 0.046$); RT showed a 44.9 ± 7.4% improvement pre–post ($p = 0.0003$) (Fig. 6A). Relative $1RM_{UPPER}$ to LM was significantly greater in RT than CON at mid ($p = 0.04$) and post ($p = 0.006$) (Fig. 6B).

3.5.2. Lower body 1RM

There was a 23.9 ± 4.9% ($p = 0.009$) decrease in $1RM_{LOWER}$ from pre–post for CON; RT demonstrated a 41.2 ± 7.7% ($p = 0.0002$) increase from pre–post. RT demonstrated a significantly greater $1RM_{LOWER}$ gain at mid ($p = 0.01$) and post ($p = 0.0008$) compared to CON. After adjusting for TBM, CON showed a 23.9 ± 4.9% ($p = 0.01$) decrease in $1RM_{LOWER}$ from pre–post, while RT exhibited a 41.2 ± 7.7% ($p = 0.0002$) increase from pre–post (Fig. 6B). Relative $1RM_{LOWER}$ to TBM was significantly greater in RT than CON at post ($p = 0.003$). When adjusted for LM, $1RM_{LOWER}$ from pre–post decreased by 23.9 ± 4.9% ($p = 0.01$) for CON while RT experienced an increase of 41.2 ± 7.7% ($p = 0.0002$) (Fig. 6B). Relative $1RM_{LOWER}$ to LM was greater in RT than CON at post ($p = 0.003$) (Fig. 6B).

3.6. Biochemical responses at pre, mid, and post

3.6.1. Fat oxidation

For CON, there was a 21.7 ± 19.5% decrease in serum FFA level from pre–post ($p = 0.03$) and a 49.9 ± 5.5% decrease from mid–-post ($p = 0.0005$). For RT, FFA levels increased from pre–mid by 187.0 ± 60.7% ($p = 0.001$), subsequently returning to the pre-intervention level; thus, there was no change from pre–post. Pre–mid ($p = 0.0009$) and pre–post ($p = 0.01$) change in FFA level were greater in RT than CON.

Free glycerol level was elevated by 26.8 ± 7.7% ($p = 0.03$) from pre–mid for CON, subsequently returning to baseline levels at post. RT demonstrated a 99.2 ± 17.0%; increase from pre–mid ($p = 0.0009$), which then returned to baseline at post. Pre–mid ($p = 0.004$) and pre–post ($p = 0.003$) change in free glycerol level was significantly greater in RT than CON.

Serum β-HB level decreased by 25.7 ± 11.0% ($p = 0.03$) from pre–post for CON while RT showed no significant changes over time. Pre–post changes in β-HB were greater in CON than RT ($p = 0.005$).

3.6.2. Hormonal and growth factor responses

There were no significant changes in cortisol for both CON and RT over time. Serum IGF-1 level decreased by 25.9 ± 10.6% from pre–mid ($p = 0.02$) and by 40.9 ± 10.2% from pre–post ($p = 0.0007$) for CON. As for RT, IGF-1 decreased from pre–post by 24.8 ± 7.6% ($p = 0.002$). There were no significant group differences for the changes in IGF-1. Serum IGFBP-3 remained unchanged for CON, while RT demonstrated a pre–mid (+30.1 ± 7.8%, $p = 0.006$) and

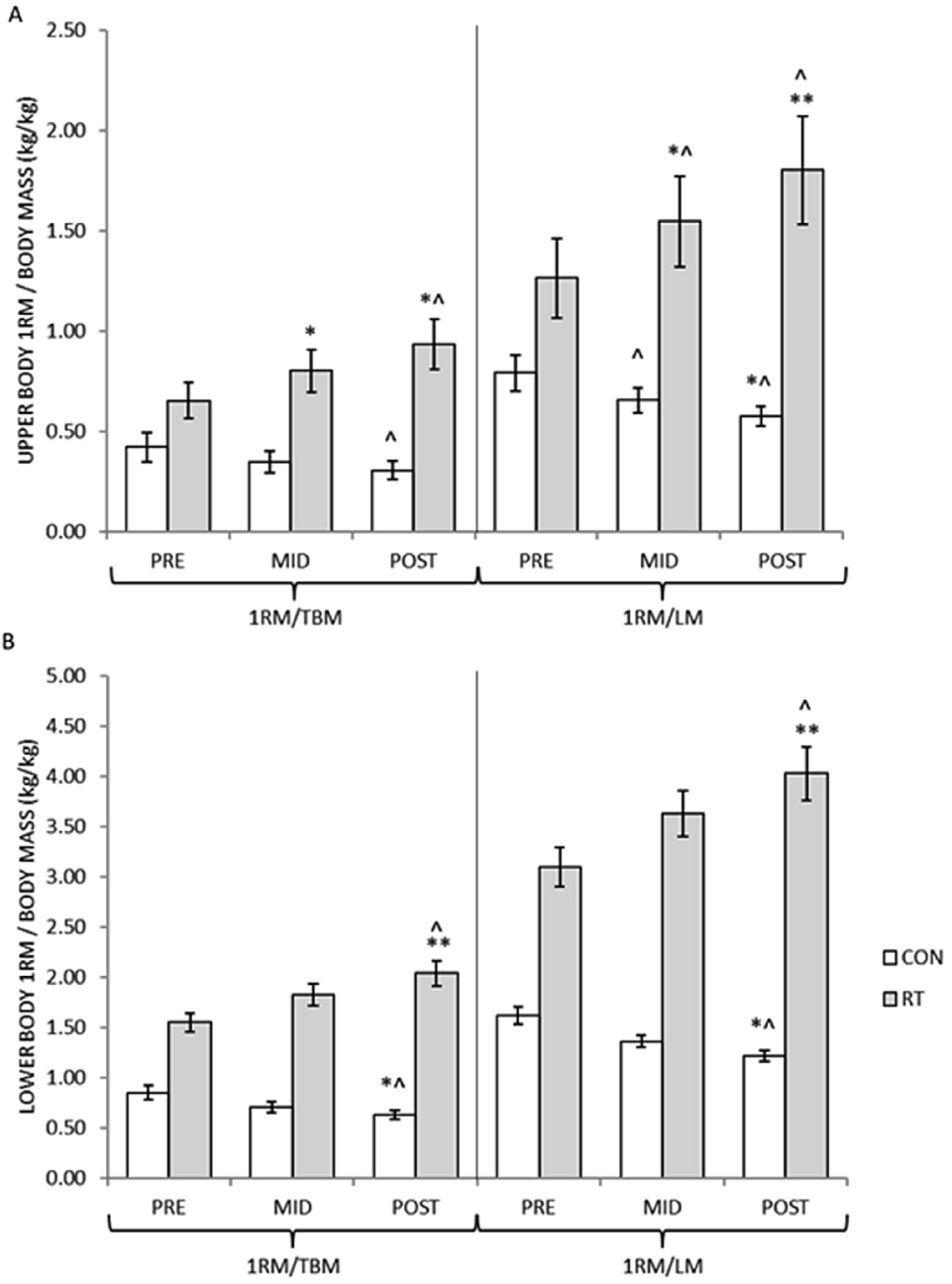

Fig. 6. Pre-, mid-, and post-intervention upper (A) and lower body (B) one-repetition maximum (1RM) after adjusting for total body mass (TBM) and lean mass (LM). Values reported as mean ± SE. *Significantly different than Pre ($p < 0.05$). **Significantly different than Pre and Mid ($p < 0.05$). ^Significantly different between groups ($p < 0.05$).

pre–post (+18.2 ± 6.8%, $p = 0.04$) elevation. There were no significant group differences for the changes in IGFBP-3. The IGF-1:IGFBP-3 ratio decreased from pre–post by 41.1 ± 10.4% for CON ($p = 0.01$) and by 35.4 ± 7.8% for RT ($p = 0.03$). There were no significant group differences for these changes in IGF-1: IGFBP-3.

4. Discussion

As the principal findings of this study, resistance training demonstrated a favorable impact on body composition, REE, and muscular function in severely obese men and women undergoing a protein-supplemented VLCD treatment. To our knowledge, this was the first study to implement an experimental resistance training program in morbidly obese subjects concurrently undergoing the standard medical treatment for VLCD patients. In accordance with our hypothesis, the experimental training protocol was effective in preserving LM compared to the standard control treatment (protein-supplemented Optifast® + standard exercise recommendations). When examining the longitudinal trajectory of LM, it appears that the initial six weeks of hypocaloric treatment rendered the greatest decline for both groups. Although no group difference was detected for these early LM decrements, the within-group responses from pre–mid were significant for CON, however not for RT. Moreover, CON exhibited a continual LM decline following week 6 while RT gained an average of 1 kg of LM ($p > 0.05$) from weeks 6–12 resulting in a total maintenance across the 12-week hypocaloric treatment. From a practical application perspective, it appears that our data support the use of a resistance

training span of at least 6–12 weeks for measurable maintenance or perhaps growth to occur in skeletal muscle during VLCD or other hypocaloric therapies.

There are two interlinked rationales for these outcomes for LM. First, the two most well-supported and well-known adaptations to progressive resistance training are enhanced neural activation and myofiber hypertrophy, both of which contribute to muscular function. Substantial evidence highlights the delayed manifestation of myofiber hypertrophy within a given resistance training period with neural adaptations primarily constituting the initial training responses (i.e. first 4–6 weeks) [26]. In the latter phases of a progressive resistance training regimen (i.e. ≥6 weeks), myofiber hypertrophy predominates the overall adaptive changes and is eventually reflected by a total increase in LM. The question, however, was whether these delayed hypertrophic adaptations are permitted during severe hypocaloric conditions, such as those presented during our dietary conditions. Previous research is in support of this notion as investigators reported enlarged fiber cross-sectional area following 12 weeks of resistance training under VLCD intake [12]. Results from the RT group indicate that resistance training may produce a positive trend towards LM growth following 6 weeks under severe hypocaloric intake when compared to the standard clinical treatment. Thus, it appears that the initial phase of intervention failed to elicit any marked influence on LM due to the delayed hypertrophic response in skeletal muscle to resistance training. It is conceivable through previous evidence indicated earlier and our muscular torque and strength records, that neural adaptations predominated the first mesocycle of resistance training (i.e. weeks 1–6).

A second rationale for the observed patterns for LM is derived from data indicating a reduced rate of decline following the first 6 weeks of control treatment (i.e. −6.7% from pre to mid and −0.6% from mid to post). This would imply that the supposed catabolic burden of the hypocaloric diet was less imposed on lean tissue during the latter half of the treatment period possibly due to a temporal diminishment of caloric deficit (i.e. decreased REE with same 1120 kcal/day intake). This is moderately explained by biochemical data for circulating cortisol, a major catabolic hormone shown to be a deterrent to muscular growth or maintenance especially during energy deficit [27,28]. When data were pooled, cortisol levels significantly increased in the initial half of the treatment, subsequently returning to baseline levels by week 12. Aggregated data illustrated a change in cortisol that was consistent with the responses for LM. Correspondingly, Longland et al. [28] reported a negative correlation ($r^2 = 0.11$, $p = 0.03$) between the changes in LM and changes in circulating cortisol. We speculate that the diminishing catabolic burden of the hypocaloric treatment from mid- to post-treatment eventually made conditions more permissible for an anabolic and thereby hypertrophic response to resistance training. Further, it appears that any anabolic response to support the preservation of LM in RT were independent of circulating IGF-1 levels. Our data demonstrated a temporal response in the circulating IGF-1 system consistent with reports from Henning et al. [29] who showed a decrease in serum IGF-1 and an increase in IGFBP-3 (inhibitor of IGF-1 bioactivity) during a period of caloric restriction. Although an evaluation of growth factor responses at the systemic/circulating level is an imperfect indicator of growth potential in skeletal muscle, others [30] have shown an increase in circulating IGF-1 levels to be concomitant with muscle hypertrophy in response to resistance training. From our current findings, resistance training appears to have no bearing on declining IGF-1 levels with prolonged hypocaloric treatment, suggesting that the preservation of LM by RT may have been independent of the IGF-1 system, at least at the systemic level.

With these superior LM outcomes for RT, resistance training also improved weight-loss composition when compared to control treatment. For CON, the loss of FM and LM contributed 76% and 24% towards total weight-loss, respectively, which corroborates prior reports [4,12,13]. As for RT, total weight-loss, which again was similar to CON, was 96% attributable to FM-loss and only 4% due to LM-loss. This large discrepancy in weight-loss composition provides compelling evidence supporting the application of resistance training to enhance the quality of weight-loss during a protein-supplemented VLCD treatment. These outcomes are supported by the work of Bryner et al. [4] who reported similar weight-loss composition following a 12-week resistance training intervention in VLCD-treated participants. Although, a complete comparison with this study is challenging due to divergent experimental designs, especially pertaining to training and dietary protocols as well as analytical methods. Nevertheless, it appears that both resistance training protocols, which were comparatively high in volume and frequency, produced similar weight-loss patterns. For REE and muscular function, however, our data demonstrated advantages of our training model in contrast to Bryner et al. and other non-periodized or free-living training protocols [12].

One of the tenets underlying the need to preserve LM during diet-induced weight-loss is to maintain REE at a level favorable for the continual reduction towards or maintenance of healthy weight status. CON experienced a significant 14% suppression of REE across the entire treatment period with the most dramatic decline occurring in the initial 6 weeks. RT, on the other hand, exhibited only a 5% overall decrease which was not significant. These divergent outcomes for REE may be partly driven by the treatment-specific changes in LM. This relationship is reinforced by a significant, positive correlation ($r = 0.72$, $p = 0.04$) between the change in REE and change in LM. The preservation of LM, thereby, is partly implicated as a determinant for the maintenance of REE during severe hypocaloric treatment. The practical value of mitigating the suppression of REE throughout a hypocaloric treatment is the maintenance of an adequate caloric deficit which is the hallmark requisite for continual weight-loss. In fact, when analyzing mean caloric deficit, as computed by averaging the individual differences between REE and 1120 kcals/day, RT had a greater caloric deficit than CON at post (985.5 ± 213.8 vs. 847.8 ± 245.3 kcals/day) although no significant between group difference was detected ($p = 0.69$). In addition to REE, resistance training appeared to also affect fat oxidation during the treatment period. RT demonstrated greater changes in serum FFA, glycerol, and β-HB than CON suggesting an upregulation of resting fat oxidation with resistance training during hypocaloric periods. Group differences in blood β-HB levels may be explained by a ketogenic response to the exercise intervention. The RT group demonstrated no change in β-HB across the treatment period while a 25% decrease was exhibited by CON. Interestingly, given prior evidence showing a ketogenic response to low carbohydrate intake, it was expected that β-HB levels would rise with VLCD treatment which would restrict carbohydrate intake [31]. The reduced levels of blood β-HB by CON may be indicative of an adaptive response in fat and ketone metabolism to the hypocaloric treatment. The maintenance of β-HB across the RT treatment period may reflect an increased reliance on lipid and ketone energy substrates given the volume and frequency of high intensity exercise bouts. Assuming these bouts of resistance exercise together with low carbohydrate intake challenged the maintenance of endogenous carbohydrate substrate availability (e.g. glycogen), a greater reliance on lipid and ketone substrates would be expected to increase to meet overall metabolic demands in training individuals.

An important factor largely neglected during hypocaloric weight-loss treatment is its detrimental effect on muscular

function. Despite evidence showing reduced physical performance in obese subjects under prolonged hypocaloric conditions [12], practical countermeasures generally lack priority as an integrative component of clinical weight-loss prescriptions. Preserving or even improving muscular function should be a key objective for obesity therapies especially given the poor existing level of function in severely obese patients as shown through prior reports [32]. In the current study, there were dramatic group-dependent responses for a spectrum of muscular performance measures, which included contractile function and whole-body isotonic strength. In the present study, we utilized knee extensor and flexor torque measures as a proxy for whole-body neuromuscular function. Corresponding to the standard treatment control, participants exhibited a decline in contractile function, reflected by significantly reduced muscular torque and power outputs. These detriments appear to occur proportionally to their observed decline in LM as peak torque values remained stable over time when adjusted for LM. Thus, in addition to maintaining REE, the maintenance of LM is also an effort to improve functional outcomes in obese patients undergoing severe caloric restriction. In so doing, it is likely that patients would achieve a better prognosis for post-treatment weight-management considering that poor functionality is likely conducive to unhealthy weight-gain or regain.

In that regard, a resistance training intervention showed to be quite advantageous during severe hypocaloric treatment as RT demonstrated significantly enhanced muscular torque, power, and strength compared to CON. For instance, peak isometric extensor torque improved nearly 42% from pre to post which was a considerable discrepancy to the 12% decrease exhibited by CON. These responses for contractile function appear to occur irrespective of LM changes in RT as isometric peak torque improved significantly from pre to post even when normalized to LM. These normalized responses were also pertinent to lower and upper isotonic strength. In more practical terms, for a given mass of lean tissue, RT was more functionally efficient as training progressed. As mentioned earlier, strength development may result from adaptations composed at the neural level independent of muscle hypertrophy, especially during the initial stages of training. In fact, despite RT losing about 1 kg of LM during the first 6 weeks of treatment, isometric peak torque was enhanced by approximately 22%. From mid- to post-intervention, during which time LM remained relatively stable, RT demonstrated continual strength development as evidenced by both isokinetic, isometric, and isotonic (1RM) measures of muscular function. This reflects the efficacy of the current resistance training program in inducing a continuous adaptive response for strength over the entire 12 weeks of severe hypocaloric intake. To our knowledge, this study was the first to demonstrate such functional adaptations to training during these specific and relatively severe weight-loss circumstances and cross-evaluated with outcomes from a standard treatment control condition.

Although our current design was not intended to examine the effects of supplementary protein on weight-loss outcomes, previous findings suggest that the custom protein composition of the Optifast® system is rather inadequate especially when combined with a resistance training intervention. For instance, without protein supplementation, our participants at a mean initial TBM of 126 kg would consume a VLCD providing only 0.6 g of protein/kg bodyweight/day. Thus, participants would have undergone a VLCD treatment with a protein content (70 g/day) below the RDA of 0.8 g/kg/day. Meta-analyses suggested that higher-protein consumption of approximately 1.2 g/kg/day promotes greater LM maintenance than diets lower in protein (<0.7 g/kg/day) under weight-loss circumstances, particularly when combined with resistance training [33,34]. In fact, Pasiakos et al. [35] showed that consuming 2–3 times above the RDA protein intake lowers the relative contribution of LM loss to the total weight reduced during energy restrictive periods. It is therefore reasonable to suggest that the RDA for protein intake, and thereby customary Optifast® protein content, remains insufficient for the preservation of LM, especially for the average 127–130 kg patient. Based on mean TBM data from the current study, in addition to the aforesaid protein recommendation (1.2 g/kg/day), approximately 150 g of protein per day would be required for the maintenance or perhaps growth of LM during a concurrent hypocaloric and resistance training intervention. Therefore, we utilized a proprietary VLCD treatment supplemented with 80 g of whey protein/day to provide a total intake of approximately 150 g/day or 1.1–1.3 g/kg/day. The relative intake also naturally increased since TBM reductions were not accompanied by a commensurate modification to protein intake. Therefore, by mid and post intervention, subjects were consuming about 1.3 and 1.5 g/kg/day perhaps contributing in part to the reduced rate of LM decline in CON and a trend towards LM growth in RT. In a recent study by Longland et al. [28], a higher protein intake of 2.4 g/kg/day compared to 1.2 g/kg/day yielded superior outcomes for LM as well as FM during an energy deficit combined with resistance training. These findings along with the present provide excellent support for the combined implementation of higher protein intake and resistance training in VLCD or hypocaloric treatment programs for obesity.

A potential limitation of the present investigation is the relatively small sample size. We encountered a relatively small pool of patients for recruitment within a 2.5-year span in addition to the drop out of 6 patients due to non-compliance to the dietary treatment. However, this may be balanced by the controlled nature of the study protocol, which to our knowledge is a unique aspect when considering the number of free-living exercise and/or dietary protocols previously implemented. Furthermore, the experimental exercise training intervention was systematic, integrative, supervised, and tested under real clinical scenarios in participants reflective of the archetype patient. Another foreseeable limitation is that the control dietary protocol utilized a standard caloric content which consequently varied the caloric deficit among participants. However, between-group analysis of energy deficit (=REE-1120 kcal/day) showed no mean differences between RT and CON at pre ($p = 0.79$), mid ($p = 0.94$), and post ($p = 0.69$) time points. Regardless, individual discrepancies in energy deficit may be viewed as a potential confounder. We opted not to implement a control dietary protocol with a constant caloric deficit to remain consistent with real-life clinical practices for VLCD treatment programs in which caloric deficits remain variable among patients. It must be noted that VLCD prescriptions are intended for the severely obese for which rapid weight-loss is of urgent necessity. Thus, the results of this study are delimited to the morbidly obese, VLCD treated population. As the next step, future investigations should expand on the current study and the work of Longland et al. [28] and compare higher vs. lower protein VLCD formulations combined with periodized resistance training in obese subjects.

Overall, our findings offer compelling support for the integration of resistance training in clinical weight-management programs utilizing VLCDs with added protein support. The preservation or improvement of LM, REE, and muscular function are key defining components of weight-loss efficacy, extending beyond former perceptions that only emphasized the total loss of body weight. The present resistance training intervention demonstrates efficacy in promoting superior body composition, metabolic, and functional outcomes during a high protein hypocaloric treatment compared to the traditional unsupervised and non-systematic exercise prescription. We provide both clinically- and scientifically-verified information to properly guide medical weight-management programs

towards a hypocaloric treatment better optimized through a resistance exercise prescription with adequate protein intake.

Conflict of interest

The results of the present study do not constitute endorsement by Clinical Nutrition and are presented clearly, honestly, and without fabrication, falsification, or inappropriate data manipulation.

Acknowledgments

This research study was partially funded by the National Strength and Conditioning Association Foundation Doctoral Grant program. The authors would like to acknowledge and thank Tallahassee Memorial Healthcare for their collaborative efforts and providing valuable resources. Finally, we acknowledge Tallahassee Gold's Gym for providing the facility for our exercise and testing protocols.

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