2013

The Clinical Application of Periodized Resistance Training during a 12-Week Hypocaloric Treatment for Obesity: A Joint Retrospective and Prospective Single-Center Study

Edward Jo
THE CLINICAL APPLICATION OF PERIODIZED RESISTANCE TRAINING DURING A 12-WEEK HYPOCALORIC TREATMENT FOR OBESITY: A JOINT RETROSPECTIVE AND PROSPECTIVE SINGLE-CENTER STUDY

By

EDWARD JO

A Dissertation submitted to the Department of Nutrition, Food and Exercise Sciences in partial fulfillment of the requirements for the degree of Doctor of Philosophy

Degree Awarded:
Fall Semester, 2013
Edward Jo defended this dissertation on November 1, 2013.
The members of the supervisory committee were:

Jeong-Su Kim
Professor Directing Dissertation

Cathy W. Levenson
University Representative

Bahram H. Arjmandi
Committee Member

Michael J. Ormsbee
Committee Member

Carla M. Prado
Committee Member

The Graduate School has verified and approved the above-named committee members, and certifies that the dissertation has been approved in accordance with university requirements.
TABLE OF CONTENTS

List of Tables ........................................................................................................................................ vi
List of Figures ...................................................................................................................................... vii
List of Abbreviations ............................................................................................................................ x
Operational Definitions ........................................................................................................................... xii
Abstract .................................................................................................................................................. xiv

1. INTRODUCTION .............................................................................................................................1
   1.1 Background ..................................................................................................................................1
   1.2 Main Objective, Central Hypothesis, and Significance ...............................................................3
   1.3 Specific Aims and Working Hypotheses ......................................................................................4
      1.3.1 Specific Aim 1 (Retrospective analysis) .............................................................................4
      1.3.2 Hypothesis for Specific Aim 1 .........................................................................................4
      1.3.3 Specific Aim 2 (Prospective analysis) ...............................................................................4
      1.3.4 Hypothesis for Specific Aim 2 .........................................................................................5
   1.4 Assumptions ...............................................................................................................................5
   1.5 Delimitations ..............................................................................................................................5
   1.6 Limitations ..................................................................................................................................6

2. REVIEW OF LITERATURE .............................................................................................................7
   2.1 Definition, Classifications, and Epidemiology of Obesity .........................................................7
   2.2 Public Health Relevance of Obesity ..........................................................................................8
      2.2.1 Quality of Life and Physical Function ..............................................................................8
      2.2.2 Mortality Risk .................................................................................................................11
      2.2.3 Disease Burden ..............................................................................................................12
      2.2.4 Economic Burden ............................................................................................................14
   2.3 Current Dietary Approach in Obesity Therapeutics .....................................................................15
      2.3.1 Overview .........................................................................................................................15
      2.3.2 Treatment of Obesity through Proprietary Hypocaloric Diets .......................................16
      2.3.3 Efficacy for Acute Weight-Loss and Long-Term Maintenance ....................................17
      2.3.4 Hypocaloric Diets and Body Composition: Outcomes for Lean Tissue .....................19
      2.3.5 Metabolic and Functional Consequences of Rapid Weight-Loss ..................................20
      2.3.6 Physiological Basis for Lean Tissue Loss during Energy Restriction ............................23
   2.4 Exercise Training Application in Hypocaloric Weight-Loss Treatments ....................................30
      2.4.1 Overview .........................................................................................................................30
      2.4.2 Specificity of Training Adaptation in Muscle: Rationale for Resistance Exercise ..........30
      2.4.3 Effects of Resistance Training on Weight-Loss Composition, Metabolic Rate and Function during VLCD Treatment .................................................................34
      2.4.4 Research Limitations to be Addressed ............................................................................37
   2.5 Summary and Implications for Future Research ......................................................................37
3. METHODS ............................................................................................................................39

3.1 Specific Aim 1 (Retrospective Study) ..............................................................................39
3.1.1 Experimental Design ................................................................................................. 39
3.1.2 Description of Dietary Treatment Program ................................................................ 39
3.1.3 Anthropometry and Body Composition ................................................................. 40
3.1.4 Estimated Resting Metabolic Rate ........................................................................... 40
3.1.5 Lipid and Metabolic Panels ...................................................................................... 40
3.1.6 Exercise History and Attitude Questionnaire ......................................................... 41
3.1.7 Analysis of Data ....................................................................................................... 41

3.2 Specific Aim 2 (Prospective Study) ................................................................................41
3.2.1 Participants ............................................................................................................... 41
3.2.2 Experimental Design .............................................................................................. 42
3.2.3 Control Dietary Condition ........................................................................................ 44
  3.2.3.1 Modified VLCD with whey protein supplementation ......................................... 44
3.2.4 Strength Testing and Control and Experimental Exercise Protocols ....................... 45
  3.2.4.1 Familiarization and strength testing ..................................................................... 45
  3.2.4.2 Standard treatment control condition .............................................................. 47
  3.2.4.3 Periodized resistance training condition ............................................................ 47
3.2.5 Weekly Clinical Visit ............................................................................................... 49
  3.2.5.1 Assessment procedures for weekly clinical visit ................................................... 50
3.2.6 Laboratory Testing Procedures ................................................................................ 51
  3.2.6.1 Resting metabolic rate and fat oxidation ............................................................ 51
  3.2.6.2 Total and regional body composition ................................................................... 52
  3.2.6.3 Biochemical markers ......................................................................................... 52
  3.2.6.4 Dynamic and static contractile kinetics ............................................................. 53
3.2.7 Analysis of Data ....................................................................................................... 54

4. RESULTS ..............................................................................................................................55

4.1 Specific Aim 1 (Retrospective Study) ..............................................................................55
4.1.1 Descriptive Variables ............................................................................................... 55
4.1.2 Weekly Weight-Loss Trajectory .............................................................................. 56
4.1.3 Pre- and Post-Treatment Body Composition, Anthropometric, and RMR Measures ..............................................................59
  4.1.3.1 Total sample ....................................................................................................... 59
  4.1.3.2 Gender and age cohorts ..................................................................................... 59
4.1.4 Relative Weight-Loss Composition ........................................................................... 63
4.1.5 Blood Lipid and Metabolic Profile .......................................................................... 64
4.1.6 Correlations ............................................................................................................. 67
4.1.7 Descriptive Analysis of Exercise History and Attitude Questionnaire ....................... 68

4.2 Specific Aim 2 (Prospective Study) ................................................................................70
4.2.1 Descriptive and Control Variables .......................................................................... 70
4.2.2 Weekly Weight-Loss and Bi-Weekly RMR Trajectory ................................................. 72
4.2.3 Body Composition (DXA) and Anthropometric Measures at Pre, Mid, and Post ..............................................................75
  4.2.3.1 Total body mass ................................................................................................. 75
4.2.3.2 Total and regional fat mass and body fat percentage ........................................75
4.2.3.3 Total lean body mass, appendicular skeletal muscle mass index, and
LBM percentage ............................................................................................................76
4.2.3.4 Weight-loss composition ....................................................................................78
4.2.4 Resting Metabolism and Fat Oxidation Rate at Pre, Mid, and Post .................79
4.2.4.1 Resting metabolic rate .....................................................................................79
4.2.4.2 Fat oxidation rate .........................................................................................81
4.2.5 Skeletal Muscle Contractile Kinetics at Pre, Mid, and Post ...............................81
4.2.5.1 Isokinetic contraction .....................................................................................82
4.2.5.2 Isometric contraction ....................................................................................82
4.2.6 Upper and Lower Body Isotonic Strength at Pre, Mid, and Post .....................84
4.2.6.1 Upper body 1RM ........................................................................................84
4.2.6.2 Lower body 1RM .........................................................................................86
4.2.7 Biochemical Responses at Pre, Mid, and Post ..................................................87
4.2.7.1 Biomarkers for fat metabolism .................................................................87
4.2.7.2 Hormonal and growth factor responses .....................................................89
4.2.8 Correlation ..........................................................................................................92

5. DISCUSSION ................................................................................................................93
5.1 Specific Aim 1: Systematic Evaluation of a Proprietary VLCD Treatment for
Obesity .............................................................................................................................93
5.1.1 Treatment Outcomes for Overall Patient Cohort ..............................................93
5.1.2 Gender-Specific Responses .............................................................................96
5.1.3 Age-Specific Responses and Gender by Age Interactions ..............................97
5.1.4 Implications for Clinical Practice and Research ..............................................99
5.2 Specific Aim 2: Periodized Resistance Training Intervention .............................101
5.2.1 Outcomes for Body Composition, Energy Metabolism, and Function ..........101
5.2.2 Application to Clinical Practice and Future Research Implications ...............108

APPENDICES ................................................................................................................110
A. The Florida State University Institutional Review Board Approval of Study
Protocol ............................................................................................................................110
B. Tallahassee Memorial Healthcare Institutional Review Board Approval of Study
Protocol ............................................................................................................................111
C. Informed Consent Form .........................................................................................112
D. Strength Test Data Sheet .......................................................................................122
E. Laboratory Test Data Sheet ...................................................................................124
F. Clinical Visit Data Sheet .......................................................................................126
G. Daily Activity Log .................................................................................................127
H. Resistance Exercise Log .......................................................................................128
I. Exercise History and Attitude Questionnaire .......................................................129

REFERENCES ............................................................................................................131

BIOGRAPHICAL SKETCH .........................................................................................154
LIST OF TABLES

Table 3.1. Daily meal configuration and macronutrient composition for control dietary condition .................................................................................................................................................................................................45

Table 3.2. Timetable and periodization format of resistance training protocol from experimental weeks 1-12 .................................................................................................................................................................49

Table 4.1. Mean values for descriptive variables for total, gender, and age cohorts..............55

Table 4.2. Weekly mean values for bodyweight (BW), absolute change (Δ) from initial BW for total and gender cohorts, and body mass index (BMI) .........................................................................................................................................................56

Table 4.3. Pre- and post-treatment means for body composition and anthropometric measures as well as estimated resting metabolic rate (RMR_{estimate}) for total sample ........................................................................................................................................59

Table 4.4. Gender-specific pre- and post-intervention means for body composition and anthropometric measures as well as estimated RMR (RMR_{estimate}). ........................................................................................................60

Table 4.5. Age-group-specific pre- and post-intervention means for body composition and anthropometric measures as well as estimated RMR (RMR_{estimate}). ........................................................................................................61

Table 4.6. Pre- and post-treatment hemoglobin A1c (HbA1c), fasting glucose, and lipid levels for total sample ......................................................................................................................................................................................65

Table 4.7. Baseline comparisons of descriptive measures between cohorts of Specific Aim 1 and Specific Aim 2 .............................................................................................................................................................................71

Table 4.8. Baseline comparisons of descriptive measures between CON and RT ..................71

Table 4.9. Body composition and anthropometric measures at pre-, mid-, and post-intervention 77

Table 4.10. RMR and fat oxidation at pre-, mid-, and post-intervention ................................80

Table 4.11. Skeletal muscle contractile kinetics at pre-, mid-, and post-intervention .............81
LIST OF FIGURES

Figure 2.1. Molecular rationale for muscle atrophy with negative energy balance ...................27
Figure 2.2. Skeletal muscle signaling pathways regulated by differentiated exercise ..............33
Figure 3.1. Timeline of 14-week experimental period .................................................................43
Figure 4.1. Weekly bodyweight measurements for total sample ..............................................57
Figure 4.2. Weekly bodyweight-change from pre-treatment for males and females ..................57
Figure 4.3. Weekly bodyweight-change from pre-treatment for age-groups ..............................58
Figure 4.4. Weekly body mass index (BMI) for total sample ....................................................58
Figure 4.5. Change from pre- to post-treatment in total bodyweight (BW), fat free mass (FFM), and fat mass measured by bioelectrical impedance analysis (FM_{BIA}) for total sample, gender, and age-group ..............................................................62
Figure 4.6. Gender by age interaction for pre-to-post change in total body weight (BW), fat free mass (FFM), and fat mass measured by bioelectrical impedance analysis (FM_{BIA}) ....................62
Figure 4.7. Relative contribution of fat free mass (FFM)- and fat mass (FM)-loss to total weight-loss in total sample and gender and age cohorts .................................................................63
Figure 4.8. Gender by age interaction for relative contribution of fat free mass (FFM)- and fat mass (FM)-loss to total weight-loss .................................................................64
Figure 4.9. Pre- to post-treatment fasting glucose and lipid levels .............................................65
Figure 4.10. Pre- to post-treatment hemoglobin A1c (HbA1c) .....................................................66
Figure 4.11. Relative change in hemoglobin A1c (HbA1c) from pre- to post-treatment for males and females ...........................................................................................................66
Figure 4.12. Relationship between fat free mass (FFM) and estimated resting metabolic rate (RMR_{estimate}) before treatment and their relationship after treatment .........................67
Figure 4.13. Relationship between change in fat free mass (FFM) and change in estimated resting metabolic rate (RMR_{estimate}) .........................................................................................67
Figure 4.14. Relationship between pre-treatment estimated resting metabolic rate (RMR_{estimate}) and the change in fat mass measured by bioelectrical impedance (FM_{BIA}) ..................68
Figure 4.15. Self-reported time spent daily for specific activities ..............................................69
Figure 4.16. Self-reported evaluation of general walking function ...............................................69

Figure 4.17. Relative level of interest for specific exercise-related activities among total sample ............................................................................................................................................70

Figure 4.18. Weekly bodyweight-change from pre-intervention for CON and RT .......................72

Figure 4.19. Weekly body mass index (BMI)-change from pre-intervention for CON and RT .......73

Figure 4.20. Weekly waist circumference-change from pre-intervention for CON and RT ........74

Figure 4.21. Bi-weekly resting metabolic rate (RMR_{\text{clinic}})-change from pre-intervention for CON and RT ............................................................................................................................................74

Figure 4.22. Change in total body mass (TBM) from pre-intervention for CON and RT ............76

Figure 4.23. Change in fat mass (FM) and lean body mass (LBM) from pre-intervention for CON and RT ............................................................................................................................................77

Figure 4.24. Relative contribution of fat mass (FM)- and lean body mass (LBM)-loss to changes in total body mass (TBM) at mid- and post-intervention ..............................................................................................78

Figure 4.25. Change in resting metabolic rate (RMR) from pre-intervention for CON and RT ...79

Figure 4.26. Change in fat oxidation rate (FO) from pre-intervention for CON and RT ............80

Figure 4.27. Pre- to post-change in contractile kinetics for CON and RT ........................................83

Figure 4.28. Change in relative isometric peak extension and flexion torque (Nm/ kg LBM) from pre-intervention for CON and RT ............................................................................................................................................84

Figure 4.29. Change in upper body one-repetition maximum (1RM) from pre-intervention for CON and RT ............................................................................................................................................85

Figure 4.30. Pre-, mid-, and post-intervention upper body one-repetition maximum (1RM) after adjusting for total body mass (TBM) and lean body mass (LBM) ................................................................................85

Figure 4.31. Change in lower body one-repetition maximum (1RM) from pre-intervention for CON and RT ............................................................................................................................................86

Figure 4.32. Pre-, mid-, and post-intervention lower body one-repetition maximum (1RM) after adjusting for total body mass (TBM) and lean body mass (LBM) ................................................................................87

Figure 4.33. Change in serum free fatty acid (FFA) level from pre-intervention for CON and RT ............................................................................................................................................88
Figure 4.34. Change in serum free glycerol level from pre-intervention for CON and RT ........88

Figure 4.35. Change in serum beta-hydroxybutyrate (β-HB) level from pre-intervention for CON and RT .............................................................................................................................................89

Figure 4.36. Change in serum cortisol from pre-intervention for CON and RT .........................90

Figure 4.37. Change in serum insulin-like growth factor-1 (IGF-1) level from pre-intervention for CON and RT .............................................................................................................................................90

Figure 4.38. Change in serum insulin-like growth factor-1 binding protein-3 (IGFBP-3) level from pre-intervention for CON and RT .............................................................................................................................................91

Figure 4.39. Change in insulin-like growth factor-1 (IGF-1): insulin-like growth factor-1 binding protein-3 (IGFBP-3) from pre-intervention for CON and RT .............................................................................................................................................91

Figure 4.40. Relationship between the pre to post changes for lean body mass (LBM) and resting metabolic rate (RMR) .............................................................................................................................................92
LIST OF ABBREVIATIONS

β-HB= Beta-Hydroxybutyrate
4E-BP1= Eukaryotic initiation factor 4E binding protein
Akt= Protein kinase B
AMP= Adenosine monophosphate
AMPK= Adenosine monophosphate-activated protein kinase
ASM= Appendicular skeletal muscle mass
ATP= Adenosine triphosphate
BCAA= Branched chain amino acid
BF%= Body fat percentage
BIA= Bioelectrical impedance analysis
BMC= Bone mineral content
BMD= Bone mineral density
BMI= Body mass index
BW= Total body weight
CDC= Centers for Disease Control and Prevention
CON= Standard treatment control group
CVD= Cardiovascular disease
DM= Diabetes mellitus
DXA= Dual-energy x-ray absorptiometry
FFM= Fat free mass
FFM%= Fat free mass percentage
FM= Fat mass
FM_BIA= Fat mass as measured via BIA
FO= Fat oxidation
FoxO= Forkhead box
HbA1c= Hemoglobin A1c
HDL= high density lipoprotein
HRQOL= Health-related quality of life
IGF-1= Insulin like growth factor-1
IGFBP-3= Insulin like growth factor-1 binding protein-3
IWQOL= Impact of weight on quality of life
LBM= Lean body mass
LBM%= Lean body mass percentage
LDL= low density lipoprotein
mTOR= Mammalian target of rapamycin
MuRF1= Muscle ring finger1
NHANES= National Health and Nutrition Examination Survey
p70S6K= p70 ribosomal protein S6 kinase
QALY= Quality-adjusted life-years
RDA= Recommended Daily Allowance
LCD= Low calorie diet
RM= Repetition maximum
RMR= Resting metabolic rate
RMR_clinic= Clinic-based assessment of resting metabolic rate
$RMR_{estimate} =$ Estimated resting metabolic rate
$ROI =$ Regions of interest
$rpS6 =$ Ribosomal protein S6
$RQ =$ Respiratory Quotient
$RT =$ Resistance training group
$TBM =$ Total body mass
$TMH =$ Tallahassee Memorial Healthcare
$TSC2 =$ Tuberous sclerosis complex 2
$UbP =$ Ubiquitin proteasome pathway
$VCO_2 =$ Carbon dioxide output
$VLCD =$ Very low calorie diet
$VLDL =$ very low density lipoprotein
$VO_2 =$ Oxygen uptake
$WC =$ Waist circumference
$WHO =$ World Health Organization
OPERATIONAL DEFINITIONS

*Total Body Mass* - The sum of total tissue mass as determined by dual energy x-ray absorptiometry

*Total Body Weight* - The scale weight of a person

*Lean Body Mass* - The non-fat and non-bone mineral content compartments of total tissue mass as measured by dual energy x-ray absorptiometry.

*Fat Free Mass* - The non-fat compartment of total body weight as measured by the following equation: FFM = total body weight – total body fat assessed through bioelectrical impedance analysis.

*Programmed Resistance Training* - A long-term exercise program consisting of repeated bouts of resistance exercise with training variables applied in a systematic manner over the designated training period. The term “periodized” is synonymous with the term “programmed” within the context of exercise training.

*Periodization* - The systematic variation of exercise training variables, e.g. intensity and volume, within a given training period.

*One-repetition Maximum (1RM)* - The greatest load that can be moved through the entire range of motion properly for no more than 1 complete repetition for a given exercise.

*Intensity* - The resistance or load that is counteracted by a given muscle group during resistance exercise. Intensity, herein, is measured as a percentage of 1RM for a given exercise.

*Volume* - The mathematical product of sets and repetitions (sets x repetitions) for a given exercise.

*Very-Low Calorie Diet (VLCD)* - A dietary program that provides approximately 800 kcals per day. Typical VLCD programs are administered by way of proprietary meal-replacement formulas that control for daily nutrient and caloric intake and is medically supervised.

*Maximal Voluntary Isokinetic Contraction* - The torque produced by a muscle group in a maximal effort muscle action (concentric and/or eccentric) through a specified range of movement at a constant angular velocity of movement. As angular velocity is constrained, torque is the variable that changes.
**Maximal Voluntary Isometric Contraction**- The torque produced by a muscle group in a maximal effort concentric muscle action with a fixed muscle length (or joint angle) and zero angular velocity (i.e. static contraction)

**Isotonic Strength**- The maximum load that can be moved through the entire range of motion properly for no more than 1 complete repetition for a given exercise. Isotonic strength is measured, herein, by 1RM.
ABSTRACT

Introduction. Medically prescribed very-low calorie diet (VLCD) systems have shown efficacy in producing clinically significant weight-loss in obese patients. This loss in bodyweight (BW), however, cannot be solely accounted for by reduced adiposity, but also significant deficits in lean tissue. With respect to these frequently reported weight-loss patterns for lean body mass (LBM), the potential for optimum weight-loss as well as sustainable weight-maintenance is adversely affected on a number of levels. Lowered resting metabolic rate (RMR), neuromuscular impediments, and poor physical function have been reported to occur as a result of reduced LBM. Any of these factors taken together with a dramatic loss of lean tissue would be a condition that is conducive to impeded fat reduction, weight-regain, and relapses of prior health complications. Therefore, the main objective of this single-center clinical study was to evaluate the efficacy by which periodized resistance training enhances morphometric, metabolic, and functional outcomes for obese patients undergoing a 12-week medically supervised hypocaloric treatment. Methods. The target population was obese patients of the Tallahassee Memorial Healthcare (TMH) Bariatric Center prescribed to undergo a 12-week proprietary VLCD treatment (Optifast®). A two-pronged experimental approach was applied through the following specific aims: 1) to determine the longitudinal responses for various clinical and weight-loss parameters in patients who have fully completed the 12-week VLCD program at the TMH Bariatric Center; and 2) to determine the effects of periodized resistance training on body composition, RMR, neuromuscular function, and biochemical responses in obese participants undergoing 12 weeks of a protein-supplemented Optifast® treatment. For Specific Aim 1, data for anthropometric measures, body composition (via BIA), and lipid/metabolic profiles were acquired before and after the 12-week VLCD treatment in male (n=16) and female (n=16) patients. Gender- and age-dependent responses were examined for each variable over time. For Specific Aim 2, male and female participants were placed in one of two groups for 12 weeks: 1) Standard Treatment Control (CON) (n=4) or 2) Periodized Resistance Training (RT) (n=4). All participants consumed 1120 kcals/day by way of Optifast® products and whey protein supplementation. Both groups underwent a pedometer-based walking program; however only RT performed periodized resistance training 3 days/week for 12 weeks. Body composition (via DXA), RMR (via indirect calorimetry) and neuromuscular function (via isokinetic and isotonic
tests) were measured at pre-, mid-, and post-intervention. Serum free fatty acid (FFA), free glycerol, beta-hydroxybutyrate (β-HB), insulin-like growth factor 1 (IGF-1), IGF-1 binding protein 3 (IGFBP-3), and cortisol were analyzed (via ELISA) were analyzed for samples obtained at pre, mid, and post. **Results.** Specific Aim 1: Patients lost 22.5 kg of BW, 16.6 kg of fat mass (FM<sub>BIA</sub>), and 5.6 kg of fat free mass (FFM= BW-FM<sub>BIA</sub>) (p<0.05). The decline in FM and FFM composed 73% and 27%, respectively, of the total weight-loss. Males lost more BW than females solely due to a larger reduction in FM (p<0.05). No gender-differences were found for relative weight-loss composition. BW-loss was similar between age-groups; however the younger patients (<57yrs) lost more FM and less FFM than the older age-cohort (≥57yrs) (p<0.05). Relative weight-loss composition was significantly different between age-groups (Young: 81% FM and 19% FFM vs. Old: 65% FM and 35% FFM). Specific Aim 2: Total body mass (TBM) and FM decreased (p<0.05) pre to post in CON (-20.4 kg BW; -15.3 kg FM) and RT (-14.6 kg BW; -13.4 kg FM) with no group differences. There was a group by time interaction for LBM (LBM=TBM-FM-bone mineral content) as CON lost 5.0 kg from pre to post (p<0.05) while RT showed no significant changes. Relative weight-loss composition differed between groups (CON: 75% FM and 25% FFM vs. RT: 90% FM and 10% LBM) (p<0.05). There was a group by time interaction for RMR as CON experienced a 350.7 kcal/day decrease from pre to post (p<0.05) while RT exhibited no changes. RT demonstrated greater improvements in all measures of contractile kinetics and isotonic strength when compared to CON (p<0.05). At post-treatment, there was a significant group difference for overall change in serum FFA (CON: -40.3% vs. RT: +41.5%), glycerol (CON: -30.9% vs. RT: +30.8%) and β-HB (CON: -31.2% vs. RT: +36.6%). IGF-1 decreased (p<0.05) from pre to post for CON (-45.2%) and RT (-33.7 %), with no group differences. IGFBP-3 increased significantly from pre to post in RT (+18.9%) but not in CON. IGF-1 to IGFBP-3 ratio decreased (p<0.05) from pre to post with no group differences. Cortisol levels remained unchanged for both groups. **Conclusion.** Specific Aim 1 confirms the need to restructure current VLCD-based programs towards outcomes more conducive for long-term weight- and health-management. This led to Specific Aim 2 in which the outcomes showed resistance training to be advantageous for weight-loss composition through preserving LBM without compromising overall weight- or fat-loss. These changes corresponded to positive adaptations for energy metabolism and muscular function. Our findings offer compelling support for the clinical integration of periodized resistance training in
obesity therapeutics utilizing VLCDs with promising implications for chronic weight-management.
CHAPTER ONE

INTRODUCTION

1.1 Background

Epidemiological findings from the recent National Health and Nutrition Examination Survey (NHANES 2009-2010) reported that 36% of U.S. adults are currently classified as obese, while 16% 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\(^1,2\). 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\(^3\). Despite the methodological advancement in treatment options, such as surgical- or pharmacological-based approaches, medically supervised weight-loss programs incorporating hypocaloric dietary modifications have remained the most prudent and pragmatic intervention for clinical obesity\(^4\). Amongst hypocaloric approaches, proprietary very low calorie diet (VLCD) programs (~800 kcal/day), e.g. Optifast\(^5\) (Nestlé HealthCare Nutrition), have been medically prescribed as a viable option for high-risk patients whose body mass index (BMI) exceeds 30 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 on liquid meal replacement formulas, have been consistent with outcomes of revitalized health with significant body weight reductions ranging between 15-27% in obese subjects\(^4-7\). This loss in total body mass, however, cannot be solely accounted for by reduced adiposity, but also significant deficits in lean tissue, especially for skeletal muscle\(^7-12\). With respect to these frequently reported weight-loss patterns for lean body mass (LBM), the potential for optimum weight-loss as well as sustainable weight-maintenance is adversely affected on a number of levels. Lowered resting metabolic rate (RMR), neuromuscular deficiencies, undue fatigue, poor physical functioning, and increased risk for musculoskeletal injury have been reported to occur as a result of reduced LBM\(^4,7,13-17\). Any of these factors taken together with the dramatic loss of lean tissue would be a condition conducive to impeded fat reduction, weight-regain, and relapses of prior health complications\(^18\).

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% to 100% of subjects who underwent a VLCD-based weight-loss intervention\textsuperscript{5,19-22}. 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\textsuperscript{4,6}. Thus, a positive prognosis for acute and prolonged treatment success remains, at present, marginally supported with current VLCD-based therapeutics for obesity. 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 while enhancing metabolic and functional outcomes. To address the burden imposed by severe hypocaloric diets on lean tissue morphometry, energy metabolism, and perhaps functionality, the integration of exercise countermeasures has been examined extensively\textsuperscript{7,10,23-30}. 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 muscle, resistance training would appear as the ideal countermeasure to the loss of lean mass during caloric restriction; yet, the majority of studies have employed relatively low-force activities in the form of aerobic exercise training\textsuperscript{8,27,28}. On the basis of previous whole-body outcomes\textsuperscript{8,29-31} and molecular rationale\textsuperscript{32,33}, aerobic training may be an ineffective strategy for lean mass retention during severe hypocaloric conditions. In fact, aerobic training has even demonstrated to extend lean tissue 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\textsuperscript{8,29-31}. Because it is well established that high-force and high-load bearing activities function favorably to improve 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\textsuperscript{34-36}. 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 LBM and RMR\textsuperscript{10,37,38}. 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.

To achieve a vertical step in that regard, several important issues must be addressed. First, an empirical approach examining VLCD-treated subjects should closely represent clinical situations in which: 1) VLCDs are prescribed to high-risk patients who are severely obese and exhibit comorbidities, 2) VLCD-based treatments are medically monitored by a multidisciplinary team of physicians, dieticians, and cardiorespiratory physiologists, 3) duration of VLCD treatment is 12 weeks with regular behavioral and dietary counseling, and 4) exercise is not specifically prescribed; rather general physical activity is recommended and typically unsupervised. Secondly, an experimental resistance training intervention should be: 1) formatted based on empirical innovations in training programming, namely periodization, to optimize protocols towards enhanced lean mass and muscular strength \(^{39-45}\), 2) combined with sufficient nutrient support through high-quality protein intake for lean tissue maintenance or growth \(^{46-48}\), and 3) integrated into the standard clinical care of the VLCD-treated patient to enhance the understanding of its practical application. A clinical trial taking into account for these current limitations may be an effective means to evaluate the short-term efficacy and potential long-term value of programmed resistance training in standard VLCD-based therapeutics for obesity. An applied approach integrating sophisticated measurements of morphometric, metabolic, and functional parameters with relevant biochemical indices such as hormones, growth factors, and metabolites would be especially insightful.

### 1.2 Main Objective, Central Hypothesis, and Significance

The **main objective** of this single-center clinical trial was to evaluate the efficacy of periodized resistance training in enhancing morphometric, metabolic, and functional outcomes for obese patients undergoing a 12-week medically supervised hypocaloric intervention. The **central hypothesis** was that integration of periodized resistance training during the 12-week hypocaloric intervention would elicit superior weight-loss composition, resting metabolism, and muscular function than standard clinical treatment.

Greater knowledge regarding the resistance training-induced adaptation in lean tissue during hypocaloric conditions requires the integration of innovative and applicable training models to extend our present understanding of adaptive events that may ultimately translate to
novel clinical practices for weight-loss endeavors. The proposed investigation addresses important issues pertinent to the clinical effectiveness of current dietary- and activity-based approaches for the treatment of obesity.

1.3 Specific Aims and Working Hypotheses

The target population for the proposed clinical study was obese male and female patients prescribed a 12-week proprietary VLCD (Optifast®; Nestlé HealthCare Nutrition; Florham Park, New Jersey, USA) as part of a medical weight-management program at the Tallahassee Memorial Healthcare (TMH) Bariatric Center. A two-pronged experimental approach was applied through the following specific aims:

1.3.1 Specific Aim 1 (Retrospective analysis)

To determine the longitudinal responses for various morphometric, anthropometric, and clinical variables in patients who have fully completed the 12-week VLCD treatment program (Optifast®) at the TMH Bariatric Center.

1.3.2 Hypothesis for Specific Aim 1

In response to the 12-week VLCD treatment, obese patients will demonstrate a 15-27% decrease in body weight accounted for by both reduced body fat and LBM, which will compose 75% and 25%, respectively, of total weight-loss composition. These weight-loss patterns will be concomitant with an approximate 16% decline in RMR. A significant reduction for body mass index (BMI) and waist circumference (WC) will also be evident. Further, patients will demonstrate improved lipid and metabolic profiles following the VLCD treatment.

1.3.3 Specific Aim 2 (Prospective analysis)

a) To determine the effects of periodized resistance training on body composition, RMR, and neuromuscular function in obese participants undergoing a 12-week protein-supplemented VLCD (Optifast®) treatment.

b) To determine changes in circulating biomarkers of lean tissue anabolism [insulin-like growth factor-1 (IGF-1), and IGF binding protein-3 (IGFBP-3)], tissue catabolism (cortisol), lipolytic activity [free fatty acids (FFA) and free glycerol (FG)], and fat
oxidation [3-beta-hydroxybutyrate (β-HB)] in response to the 12-week dietary treatment with or without periodized resistance training.

1.3.4 Hypothesis for Specific Aim 2

a) Participants undergoing periodized resistance training during the 12-week modified VLCD will exhibit greater LBM, body fat loss, RMR, and neuromuscular performance than those under standard clinical treatment.

b) Periodized resistance training will present with greater alteration in systemic levels of biochemical indices to be indicative of heightened anabolic propensity and increased fat metabolism during a 12-week program when compared to standard clinical treatment.

1.4 Assumptions

The assumptions for the present investigation were as follows: 1) all laboratory equipment and techniques yielded accurate measurements over the course of repeated testing; 2) all participants adhered to the conditions outlined in the Informed Consent Form; 3) all participants performed to their utmost potential for all exercises and exercise performance assessments; and 4) all self-recorded data were of accurate reporting from each participant.

1.5 Delimitations

The retrospective study indicated in Specific Aim 1 was delimited to patients of the TMH Bariatric Center who have fully completed the 12-week Optifast® program and demonstrated the following: BMI ≥ 30 kg/m², sedentary lifestyle (based on self-reported physical activity level), and at least 18 years of age. Participation in the prospective study indicated in Specific Aim 2 was delimited also to patients of the TMH Bariatric Center who were prescribed by a physician to undergo a medically monitored dietary weight-loss program. Participation was delimitied to patients who have a BMI greater than 30 kg/m², have been physically inactive (<30 min/day of exercise) for the past 6 months, and have demonstrated 4 weeks of weight stabilization (± 2 kg of body weight) under medical supervision. Participation was denied if patients had any major chronic diseases or any physical conditions in which dietary restriction, exercise, or whey protein supplementation would be contraindicated.
1.6 Limitations

The limitations to the retrospective study indicated in Specific Aim 1 included the following: 1) data collection was restricted to the availability of medical charts filed at the TMH Bariatric Center, 2) data were collected from medical charts of patients who completed the full 12-week Optifast® program at the TMH Bariatric Center between the years 2011 and 2013, and 3) bioelectrical impedance analysis may be limited in accuracy by various factors such as hydration and tissue mass. The limitations to the prospective study indicated in Specific Aim 2 included the following: 1) the study examined the effects of a fixed resistance training program, 3) the environment in which the exercise training was administered was not completely controlled, 4) only untrained individuals were included for participation, 5) any individual under 18 years of age was excluded, and 6) dual energy x-ray absorptiometry measurements may be limited in accuracy by tissue thickness of participants.
CHAPTER TWO

REVIEW OF LITERATURE

2.1 Definition, Classifications, and Epidemiology of Obesity

Obesity is a chronic disease that is generally defined as a condition in which body fat has accumulated to an extent that health is adversely affected by comorbidities and increased risk for premature death\(^{49,50}\). However, a more standardized and clinically relevant definition of obesity operates on the basis of the body mass index (BMI). The BMI, which is calculated through dividing body mass by the square of body height (kg/m\(^2\)), serves as a heuristic proxy for human adiposity given its strong, positive correlation to both body fat percentage and total body fat\(^{51,52}\). It is a widely applied utility for weight-status classification for most epidemiologic and clinical investigations although controversial in its use as a diagnostic criterion\(^{52,53}\). The Global Database on BMI, which was generated by The World Health Organization (WHO), established the most standard weight-classification scheme called, The International Classification of Adult Underweight, Overweight, and Obesity According to BMI\(^{54,55}\). Based on these BMI-referenced classifications, WHO categorizes a BMI of less than 18.5 kg/m\(^2\) as underweight and may be indicative of health problems linked to conditions characterized by substandard body weight, e.g. malnutrition and eating disorders\(^ {54,55}\). Normal BMI ranges from 18.5 to 24.9 kg/m\(^2\), while overweightness or pre-obesity is associated with a BMI between 25.0 and 29.9 kg/m\(^2\)\(^{54}\). Adults with a BMI \(\geq 30.0\) kg/m\(^2\) are considered obese by WHO standards and can be further partitioned into several classes that correspond to the severity of disease manifestation\(^ {53,54,56}\). Obesity classes I (moderate), II (severe), and III (very severe) are associated with BMI ranges of 30.0-34.9 kg/m\(^2\), 35.0-39.9 kg/m\(^2\), and \(\geq 40.0\) kg/m\(^2\), respectively\(^ {54}\); however, these values remain disputed especially with respect to their clinical application as a diagnostic and prognostic utility\(^ {53,56}\). This BMI classification scheme for weight status\(^ {54,57}\) is fundamentally based on data obtained from large epidemiological studies that evaluated the relationship between BMI and mortality\(^ {57-60}\). For instance, adults who have a BMI \(\geq 30\) kg/m\(^2\) are considered obese because they are with greater mortality risk than those who are classified as overweight (BMI= 25.0 and 29.9 kg/m\(^2\)) or lean (BMI= 18.5 and 24.9 kg/m\(^2\))\(^ {57-60}\).
Despite the considerable public health relevance of obesity, the epidemic has drastically emerged within the past three decades. The most substantial data on the prevalence rate of obesity over time in the U.S can be derived from the National Health and Nutrition Examination Survey (NHANES). Epidemiological data from the most recent NHANES (NHANES 2009-2010) reported that 68.8% of U.S adults are overweight or obese ($\text{BMI} \geq 25 \text{ kg/m}^2$). Nearly half of this cohort have a $\text{BMI} \geq 30 \text{ kg/m}^2$, suggesting that 35.7% or nearly one-third of the U.S adult population is currently obese. Moreover, the prevalence of class II ($\text{BMI} = 35.0-39.9 \text{ kg/m}^2$) and class III ($\text{BMI} \geq 40 \text{ kg/m}^2$) obesity in the U.S is 9.1% and 6.3%, respectively, which together in itself (~15%) meet the WHO-based criteria for epidemics needing intervention. In terms of epidemiological trends, NHANES 2009-2010 data for U.S adults aged 20 and above reported a steady growth in the obese population since the late 1980s, with the age-adjusted prevalence increasing from approximately 23% in NHANES III (1988-1994) to 36% in 2009-2010. This reflects an approximate 57% increase across nearly two decades in the U.S. Recent projections based on prior NHANES reports predict that 86.3% of U.S adults will be overweight or obese (obese will account for 51.1%) by 2030 if the epidemic trend remains unresolved. Because of these projections and concern for imminent socioeconomic instability, national health initiatives, such as Healthy People 2020, have been established in part to reduce the prevalence of adulthood obesity by 10%. Achieving this agenda would be expected to alleviate the growing public health and socioeconomic burdens directly attributable to the obesity epidemic and perhaps initiate restoration of the current nationwide health status.

2.2 Public Health Relevance of Obesity

2.2.1 Quality of Life and Physical Function

The psychological and physical encumbrances imposed by excessive adiposity have consistently shown to diminish the health-related quality of life (HRQOL) in obese individuals. The concept of HRQOL and its underlying determinants encompass those aspects of overall quality of life that have direct bearing on physical or mental health. Systematic HRQOL evaluations comprise of subjective measurements of general health status indicators that typically incorporate components of human function and wellbeing. For instance, the Medical Outcomes Study 36-Item Short Form Health Survey (i.e. SF-36), is a validated questionnaire commonly used to evaluate HRQOL by assessing 8 domains: 1) physical functioning; 2) social
functioning; 3) limitations in usual-role activities; 4) bodily pain; 5) general mental health; 6) usual-role limitations due to emotional problems; 7) vitality; and 8) general health perceptions. Also, the Centers for Disease Control and Prevention (CDC) formed the CDC HRQOL-4 and -14, which are widely-used assessment tools, with good construct validity that integrate modules relevant to physical health, activity limitations, and physical symptoms. With respect to the obesity and quality of life interrelationship, cross-sectional and longitudinal studies that have applied these methods both demonstrated greater reports of reduced HRQOL as BMI increased from normal to obese classification. Accordingly, findings from the Nurses’ Health Study suggested BMI to be a direct correlate to poor physical functioning, bodily pain, and added limitations attributable to physical problems. Moreover, Kruger et al. reported that sedentary living, an established etiological factor for obesity, mutually corresponds to incidences of substandard HRQOL. Their findings suggest that one cannot attribute poor quality of life to obesity without completely considering the causative factors conducive to unhealthy weight gain, such as physical inactivity.

Kolotkin et al. designed an obesity-specific method for quality of life assessment referred to as the Impact of Weight on Quality of Life (IWQOL). This 74-item, self-reported evaluation highlights the fundamental obesity-related issues and comprises of eight interrelated elements, which include, physical health, social functioning, occupational functioning, mobility, self-esteem, sexual activity, activities of daily living, and food perception. Because of the extensive and thereby cumbersome nature of the IWQOL, the IWQOL-Lite was constructed and validated as a more abbreviated and clinically-apt assessment of HRQOL for obese individuals. In a prior study utilizing IWQOL-Lite, records of both physical and psychological elements were negatively altered as a function of elevated BMI or heavier weight status. In fact, subjects exhibiting a BMI ≥ 41 kg/m² (i.e. class III obesity) demonstrated improved scores for physical and psychological aspects of the IWQOL-Lite when active weight-loss was undertaken.

Furthermore, evidence has demonstrated the contributory nature of obesity to overt functional deficits as assessed by direct measures of whole-body and neuromuscular performance. Maffiuletti et al. evaluated neuromuscular function by way of contractile torque records from lean and obese subjects during dynamometric tests of maximal isokinetic and isometric voluntary contractions. Although absolute peak torque output of obese subjects exceeded that of their leaner counterparts, values normalized to total and lean body masses were
nearly 32% less in the former than the latter\textsuperscript{84}. Similar dynamics were also evident in a number of cross-sectional comparisons of muscular torque capacities between obese and lean subjects\textsuperscript{81-83}. When considering torque as a function of contractile velocity, i.e. muscular power, performance of obese subjects, again, were subordinate to the leaner cohort, at least when output values were normalized to body mass\textsuperscript{84}. Fatigue resistance during voluntary contractions is also an important indicator of functional status for muscle\textsuperscript{84}. Prior results from isokinetic fatigue tests of 50 consecutive maximal contractions indicated a significantly steeper decline in torque generation in obese subjects compared to the lean\textsuperscript{84}. Postural instability and poor balance are additional impediments of functionality that are evident with obesity, especially during adulthood\textsuperscript{85,86}. Such sensorimotor insufficiencies may be causal to injury while performing common tasks that incorporate some aspect of balance control and stability, e.g. picking items up from the floor, getting up from a chair, reflexively abrupt movements, etc\textsuperscript{86}. Collectively, excessive adiposity, whether directly or indirectly, imposes a negative effect on neuromuscular and sensorimotor function when cross-evaluated with healthy-weight individuals. Although the underlying mechanisms for this interrelationship remain vaguely understood, the divergent extent of functionality in obese individuals may occur in part from their presumed sedentary behaviors. This behavioral factor would conceivably impair contractile and functional capacities. In other words, the discrepancies found between obese and lean individuals with respect to physical function could be explained by differences in the level of physical activity and conditioning, i.e. obese individuals are more inactive and thereby less conditioned than leaner individuals. This leads to the contention that physical activity or level of conditioning is the primary determinant of functional deficits while unhealthy weight-status would be a subsidiary factor of causation. This reasoning is based on the paradoxical dynamic in which physically active obese individuals would likely exhibit greater functionality and strength compared to lean individuals who are sedentary and poorly conditioned. Thus, functional impediments previously demonstrated in obese subjects are likely a manifestation of physical inactivity and poor conditioning. However, a research design comparing cohorts of diverse activity level and body weight characteristics would be necessary to substantiate this assertion. Nevertheless, considering that a majority of the activities of daily living incorporate a variable degree of total body support, locomotion, balance, and coordination, impaired neuromuscular
and motor performance in obese individuals could be viewed as a major causative factor for overall functional limitations and poor quality of life.

2.2.2 Mortality Risk

In 2000, Mokdad et al.\textsuperscript{87,88} reported results from a comprehensive analysis of existing epidemiological, clinical, and CDC-derived data (1980-2002) to identify and quantitate the leading causes of mortality in the U.S. for the year 2000. Based on their findings, tobacco smoking continued to lead as the foremost cause of preventable death, contributing to approximately 435,000 or 18.1\% of all U.S. deaths in 2000\textsuperscript{87,88}. Poor diet and physical inactivity, otherwise termed overweightness\textsuperscript{57}, was estimated to have caused 365,000 deaths in 2000, which is secondary to smoking and nearly a one-third increase from a prior estimation in 1990\textsuperscript{87-89}. Within this decade, however, the disparity between deaths due to overweightness and those caused by smoking was considerably marginalized. In fact, it was projected that poor diet and physical inactivity would surpass smoking as the leading cause of preventable death by 2005 if the rising incidences of overweightness and obesity remained unresolved\textsuperscript{87,88}. In retrospect, these former projections eventually revealed itself to be rather accurate according to the most recently documented analysis of mortality caused by smoking or obesity\textsuperscript{90}. Consistent with the patterns previously noted in the leading causes of death profile\textsuperscript{87,88}, Jia et al.\textsuperscript{90} presented a trend analysis suggesting that obesity has overtaken smoking as the primary U.S. health threat in terms of mortality and disease causation. Specifically in 1993, loss of quality-adjusted life-years (QALYs) was significantly more attributable to smoking than obesity. By 2008, however, QALYs lost due to obesity had increased by an alarming 127\%, exceeding the diminishing contributions from smoking. As projected in earlier and aforementioned reports, these divergent and intersecting trend lines were resultant of a gradually rising prevalence rate for obesity between 1993 and 2008 (i.e. +85\% for obesity and -18.5\% for smoking). When interpreting this data within the context of mortality, obesity has superseded smoking as the current foremost cause of preventable death in the U.S.\textsuperscript{90}.

The Prospective Studies Collaboration evaluated the relationship between BMI and cause-specific mortality among 900,000 individuals\textsuperscript{91}. All-cause mortality was lowest within an ideal BMI range of 22.5-25.0 kg/m\textsuperscript{2}, although a more current study that controlled for smoking and preexisting cancer suggested 20.0-24.9 km/m\textsuperscript{2} to be optimum for survival\textsuperscript{56}. Findings also
indicated that a 5 kg/m² increase in BMI corresponded with a 30% greater overall mortality rate. Moreover, with a BMI of 30-35 km/m², median survival declined by 2-4 years while an 8-10 year-loss was associated with a BMI of 40-45 kg/m² (i.e. severe obesity). Accordingly, Peeters et al.92 discovered similar survival patterns among 3,457 participants of The Framingham Heart Study, a longitudinal research program providing 40 years of follow-up data for mortality93,94. Participants were 30-49 years of age at the time values used for baseline measures were acquired. Results indicated that overweight, nonsmoking females lost 3.3 years of life expectancy while males lost 3.1 years. With obesity, however, these values mounted to 7.1 years-lost for females and 5.8 years-lost for males. Given this apparent relationship between life expectancy and weight-status, it can be inferred that severe obesity would have the propensity to further reduce survival rate regardless of gender. From a practical perspective, by preventing a BMI increase from 28 kg/m² (i.e. lean) to 32 kg/m² (i.e. obese), an average middle-age adult would gain just about 2 years of life expectancy92,95. Overall, these previous results imply that BMI in itself serves as a strong predictor of all-cause mortality, lending some level of justification for the current BMI-weight classification scheme. Nevertheless, since BMI is an imperfect measure of total body fat and neglects to account for all anatomical partitions of adipose, the mortality attributable to obesity and adiposity-related factors is likely greater than what these findings suggest. It is evident that obesity has a negative bearing on the life-expectancy of those afflicted. In fact, the present obesity trends give rationale for the projection in which the current U.S generation will have a shorter life-expectancy than their parents provided that this epidemic persists without resolution96.

2.2.3 Disease Burden

The epidemic of obesity threatens to overwhelm health care resources and economic stability because of the ever-expanding sequelae of unhealthy weight status. The risk of developing medical conditions, namely type II diabetes mellitus (DM), heart disease, hypertension, and cancer are increased exponentially with excessive adiposity. The array of comorbidities associated with obesity is typically reflected in the purported metabolic syndrome49,97. This metabolic dysregulation is defined by a multiplex of interrelated risk factors for cardiovascular disease (CVD) and type II DM97-102. The core metabolic features of this condition include atherogenic dyslipidemia, insulin resistance, hypertension, systemic
inflammation, and pro-thrombotic status, while obesity has gained heightened enquiry as a critical cause and manifestation of metabolic syndrome\textsuperscript{102,103}. Although the criteria-based definition has been controversial as a utility for clinical practice, the current diagnostic standards for metabolic syndrome is that at least three of the following criteria are met\textsuperscript{102}: 1) hypertriglyceridemia: $\geq 150\text{mg/dl}$; 2) dyslipidemia: HDL $< 40\text{mg/dl}$ for male and $< 50\text{mg/dl}$ for female; 3) Hypertension: $\geq 130/85\text{mmHg}$; 4) Elevated fasting glucose: $\geq 110\text{mg/dl}$; and 5) Waist circumference: $> 102\text{cm}$ for male and $> 88\text{cm}$ for female. This widely utilized criteria, which was established by the National Cholesterol Education Program-Adult Treatment Panel III (NCEP-ATPIII), particularly focusses on waist circumference as a surrogate measure for central or abdominal obesity\textsuperscript{102}. Inclusion of this measure is justified as central obesity remains a core pathophysiological feature of metabolic syndrome and is considered a primary category of causation\textsuperscript{101}. In fact, the NCEP-ATPIII stated that the rising incidences of metabolic syndrome are vastly attributable to the obesity epidemic; a contention that is considered by most to be epidemiologically confirmed\textsuperscript{102,103}. The risk of type II DM is strongly correlated with adiposity regardless of gender or ethnicity, especially when body fat is localized to the viscera\textsuperscript{104,105}. Based on data obtained from the Nurses Health Study\textsuperscript{104}, the risk of DM was strongly correlated with BMI. In fact, a BMI of 35 kg/m$^2$ markedly increased the risk for DM by 4000%. Data from the Health Professionals Follow-Up Study\textsuperscript{105} further suggested unhealthy weight-gain to be highly causative of DM as 65% of DM cases were attributed to obesity and overweightness. When adjusted for age, a 20-kg increase in body weight was concomitant with a 15-fold greater risk for DM. Likewise, a reduction in weight has shown to be advantageous in terms of minimizing DM risk and improving insulin sensitivity. Specifically, an individual demonstrating a 5-11 kg weight-loss may reduce risk for DM by 50%, whereas a loss of 20 kg or more could eradicate the risk entirely\textsuperscript{105}. Another major comorbidity closely associated with obesity is heart disease, causing nearly 600,000 deaths in the U.S. every year\textsuperscript{106}. Manson et al.\textsuperscript{60} reported a 3.3-fold increased risk for coronary artery disease, with a BMI exceeding 29 kg/m$^2$. Fortunately, data strongly supports the potential for reversing these health risks through voluntary weight-loss\textsuperscript{107}. Although a definitive reduction of quantifiable risk has yet to be demonstrated, available data point towards a significant improvement in several clinical parameters with weight-loss that may be indicative of reduced comorbidity risk. For instance, Sjostrom et al.\textsuperscript{107} reported a highly responsive and sustained change in blood pressure and triglycerides, significantly diminishing
following a 5-10% weight-loss. Further, a reduction in total cholesterol levels appears to occur after a 20% weight-loss. Indeed, although weight-loss has shown to effectively mitigate disease risk factors, these clinical benefits are likely negated when one fails to maintain the reduced weight status. Therefore, clinical weight-loss endeavors must be accompanied by a long-term maintenance strategy to prevent relapses of prior health complications, an outcome that would conceivably reduce economic burden and reconcile healthcare resources.

2.2.4 Economic Burden

The multitude of chronic and acute health disorders linked to obesity impose significant socioeconomic constraints not only by impinging upon HRQOL, but also incurring substantial financial costs to both the afflicted individual and society as a whole. The economic impact of obesity is especially manifested in costs associated with healthcare burden and loss of productivity. The overall medical cost of obesity reflect the monetary value of healthcare resources devoted to managing obesity as well as obesity-related conditions. These include expenditures on excessive utilization of ambulatory services, hospitalization, medication, diagnostic tests, or outpatient/inpatient care. Based on one the earliest analyses of obesity-related economic spending, Wolf et al. evaluated the direct and indirect costs in the U.S for eight medical conditions closely linked to obesity: type II DM, coronary heart disease, hypertension, gallbladder disease, breast cancer, endometrial cancer, colon cancer, and osteoarthritis. Researchers estimated that the direct medical cost of obesity-related disorders in 1995 amounted to approximately $52 billion, representing 5.7% of the total annual U.S. Health Expenditure. Ensuing reports on obesity-related healthcare expenditure have exhibited a steady increase in economic costs over the subsequent years as the prevalence rate demonstrated paralleled growth.

Finkelstein and colleagues reported that medical costs related to obesity reached approximately $74 billion in 1998 based on data from the National Health Expenditure Account (NHEA). This reflects an approximate 37.4% greater mean annual medical spending compared to the amount spent by healthy-weight individuals. In 2006, estimates escalated to nearly $147 billion per year of which nearly one-half was paid by government or tax payers while the other half was financed by private insurers (i.e. Medicare and Medicaid). This suggests that the economic burden of obesity is shared amongst society as taxes and insurance premiums
finance the growing burden of medical costs associated with the management of obesity and related impediments.

Quantitating the economic burden of obesity is challenging given that costs are largely mediated by variable factors such as food systems, demographic shifts, and economic situations. The methodological approaches for the analyses of disease-specific healthcare cost are uniquely complex for obesity in that estimations are not solely based on obesity treatment per se but rather on the medical care for the many related comorbid conditions. With that said, the accuracy by which economic costs of obesity are estimated and projected remain difficult to obtain due to the constantly growing number of medical conditions being linked to obesity. Regardless, it is undoubtedly a mutually beneficial objective for society to resolve the obesity epidemic, partly to reconcile the shared financial hindrances imposed by the disease. Therefore, furthering the etiological understanding of obesity and identifying effective treatment targets and modalities would be of prime importance and urgency.

2.3 Current Dietary Approach in Obesity Therapeutics

2.3.1 Overview

As discussed earlier, the extent of morbidity and mortality related to obesity is quite substantial and has thereby imposed significant burden on the national socioeconomic status. Fortunately, there is mounting evidence that support the potential for reversing these obesity-related health risks through a range of conventional to more clinical-based weight-management strategies. Regardless of therapeutic approach, the main principle for treating obesity is to achieve weight-loss that is clinically significant. With that said, voluntary weight-loss has been consistent with reports of improved clinical health parameters, such as blood pressure, circulating lipid levels, and glucose tolerance, among overweight and obese cohorts. Because of the progressively rising prevalence of obesity and related clinical and socioeconomic liabilities, the urgency for effective treatment strategies have been of utmost priority in the medical community. When defining the efficacy of weight-loss therapeutics for clinical obesity, it is important to look beyond short-term weight-loss achievements and bear in mind the propensity for sustaining healthy-weight status and minimizing the risk for recidivism. To promote the best opportunity for long-term weight-management success, the American College of Sports Medicine, the National Heart, Lung, and Blood Institute with the National Institute of
Diabetes and Digestive and Kidney Diseases, and the Obesity Society have developed comprehensive lifestyle modules for diet, physical activity, and behavioral modifications\textsuperscript{15,36,57}. However, such a lifestyle-centric approach to weight-management may be more applicable to subclinical or post-obese populations that do not necessarily exhibit a heightened level of comorbid conditions and risk for mortality. In the case for the more high-risk patient cohort in which rapid weight-loss is of highest priority, medical-based treatment options such as bariatric surgery, pharmacotherapy, or proprietary hypocaloric diet programs have been developed and established to address the most urgent clinical cases.

2.3.2 Treatment of Obesity through Proprietary Hypocaloric Diets

Despite the methodological advancement in treatment options, such as surgical or pharmacological approaches, medically supervised weight-loss programs incorporating strict dietary modifications have remained the most prudent and pragmatic prescription for clinical obesity\textsuperscript{4}. Among the variety of dietary programs available, proprietary very low calorie diet (VLCD; 450-800 kcals/day) systems have been medically prescribed as a viable option especially for high-risk patients whose BMI exceeds 30 kg/m\textsuperscript{2}, exhibits critical mortality risk, or has failed to respond favorably to conventional and unmonitored weight-loss programs\textsuperscript{4,127,128}. VLCD-based treatments are perhaps the most utilized yet most controversial among current dietary prescriptions for the management of clinical obesity. This appears to relate primarily to concerns over their safety, cost, or long-term efficacy. In that regard, a proprietary VLCD is typically prescribed and administered under strict medical supervision by a multidisciplinary team comprised of physicians, therapists, dieticians, and exercise physiologists to especially minimize physical complications, improve compliance, and monitor clinical parameters.

According to the international food standards documented by the CODEX Alimentarius\textsuperscript{129} a VLCD is defined as a hypocaloric, meal-replacement diet with a daily caloric content of 450-800 kcal\textsuperscript{130,131}. The earliest form of VLCD programs utilized a more severe energy restriction of approximately 450 kcal/day, but research has demonstrated equivalent weight-loss efficacy across 12 to 16 weeks with a VLCD providing 800 kcal/day\textsuperscript{132,133}. Thus, contemporary VLCDs are designed in reference to an 800 kcal/day diet given the greater tendency for compliance and equal effectiveness with a less severe restriction of caloric intake. It must be noted, however, that VLCDs should not be defined entirely on the basis of caloric
content. Instead, one should consider the following key features that are characteristic of most prescribed VLCD programs: 1) complete replacement of all usual food consumed through formulated products (usually liquid-based)\textsuperscript{130}; 2) hypocaloric, relatively high protein content (70-100g/day), and permits appropriate metabolic adaptations\textsuperscript{130,134}; 3) provides a full complement of the Recommended Daily Allowance (RDA) for vitamins, minerals, electrolytes, and fatty acids\textsuperscript{129,130}; and 4) total treatment duration of 12-16 weeks with a subsequent transitional period to reintroduce solid food at a more sustainable caloric intake\textsuperscript{135}.

One of the more prominent medically monitored VLCD programs prescribed today is Optifast\textsuperscript{®} (Nestlé HealthCare Nutrition), a comprehensive meal-replacement system administered through liquid-based formulas. Optifast\textsuperscript{®} is one of the few proprietary diets that mandates medical supervision and requires proper documentation to obtain products. A standard Optifast\textsuperscript{®} treatment offers a 4-phase approach to weight-loss administered in the following sequence: 1) 4 weeks of LCD (~1200-1500 kcal/day); 2) 12-week rapid weight-loss phase with full meal-replacement (~800 kcal/day); 3) 6-week transition period when solid foods are reintroduced with a more sustainable caloric intake; and 4) a variable maintenance phase to support weight-stabilization mainly through nutritional and behavioral counseling. Also, it is routine for physicians and/or clinical dieticians to circumstantially modify the patient’s VLCD program. For instance, a patient concurrently engaged in a rigorous exercise regimen or one who is of older age may be prescribed additional nutrient provision through high-quality protein supplementation.

2.3.3 Efficacy for Acute Weight-Loss and Long-Term Maintenance

In terms of the rate and amount of weight-loss achieved, a VLCD treatment that is properly administered yields outcomes superior to low calorie diets (LCD; ~1200 kcals/day; non-meal replacement), at least in theory. In support, a previously studied VLCD treatment has shown efficacy in promoting short-term weight-loss of at least 10 kg over 12 to 24 weeks in 90% of the study cohort\textsuperscript{136-138}. Contrastingly, only 60% of the subject pool exhibited a weight-loss of similar degree when utilizing a balanced LCD treatment\textsuperscript{130,139}. Moreover, a 12-week VLCD treatment resulted in a mean weight-loss of 20 kg at a rate of 1.5-2.0 kg/week for females and 2.0-2.5 kg/week for males\textsuperscript{22}; while previous LCD trials produced more moderated outcomes regardless of a longer timespan (~8.5 kg across 24 weeks at a rate of 0.4-0.5 kg/week)\textsuperscript{21,121,130,138}.
Furthermore, Tsai et al.\textsuperscript{140} recently conducted a controlled meta-analysis of six randomized trials that showed a significantly greater short-term weight loss with VLCDs (-16.1\%) versus conventional LCDs (-9.7\%). These corroborating findings were also suggested to be independent of compliance as attrition rates between VLCD and LCD treatments have shown to be comparable (i.e. 15\% vs. 20\%, respectively)\textsuperscript{130,140}. Although there is a clear consensus on the advantages of VLCDs over LCDs in the stimulation of acute rapid weight-loss, its efficacy in the context of stabilizing post-treatment weight status is of significant debate.

Indeed, weight maintenance has remained the most challenging component with all obesity therapeutics, undoubtedly perpetuating the high rate of recidivism that has been reported both anecdotally and empirically. Hence, an important question with respect to VLCD efficacy is how sustainable the outcomes are once ideal weight-loss is achieved. Deriving a firm conclusion in that regard is rather difficult given the limited availability of follow-up data in VLCD-treated subjects. However, Saris\textsuperscript{128} conducted an evaluation of weight-maintenance success following a VLCD treatment on the basis of nine randomized clinical trials. At the one-year follow-up mark, the percentage of initial weight lost that was regained demonstrated large variations ranging between -7\% to 122\%. This variation was marginalized to a range of 26\% to 121\% at a five-year follow-up time point. The Optifast\textsuperscript{\textregistered} program, as described earlier, has also demonstrated to result in a considerable rate of weight-regain following a 26-week treatment period under medical supervision\textsuperscript{6,141}. For instance, Wadden et al.\textsuperscript{141} conducted a multicenter evaluation of 517 obese patients who underwent the Optifast\textsuperscript{\textregistered} treatment program. Among the 45\% of the subject pool who completed the treatment, a weight-loss of 21.8\% of initial body weight was observed. At one-year post-treatment, patients maintained only a 9\% weight-loss from their pre-intervention weight. In a single-center evaluation of the Optifast\textsuperscript{\textregistered} program, patients lost 20\% of initial body weight after 26 weeks of treatment; however, after four years, only a 4.3\% reduction was preserved\textsuperscript{6}.

Taken together, the available body of empirical evidence point towards a more significant initial weight-loss with VLCDs compared to LCDs. However, a number of follow-up evaluations suggest long-term maintenance of weight-loss to be relatively substandard with either modes of treatment\textsuperscript{130}. Even when behavior therapy was incorporated into VLCD programs, partial to full weight-regain was evident\textsuperscript{130,138,142,143}. It can be concluded that VLCD-based weight-loss programs demonstrate some level of futility as long-term success has been
poorly supported. This suggests that practical and effective solutions to improve long-term efficacy are lacking in current VLCD-based treatment plans. Although, behavior therapy has shown some extent of effectiveness in promoting post-VLCD weight stability, it may be an insufficient approach as a high incidence of recidivism remains. With that said, an important question to probe is whether the long-term efficacy of a VLCD treatment is determined solely by behavioral factors or if the physiological adaptations to the treatment per se are causal to weight-regain. In other words, could the weight-loss patterns in body composition and metabolic adaptations acutely resulting from a VLCD treatment predispose a patient to subsequent weight-regain? Previous evidence may be suggestive of such possibilities. To address this question, the effects of VLCD or severe hypocaloric conditions on body composition, energy metabolism, and function must be explored as these factors would conceivably influence the potential for not only efficient weight-loss but also success in sustaining these outcomes.

2.3.4 Hypocaloric Diets and Body Composition: Outcomes for Lean Tissue

As aforementioned, comprehensive VLCD interventions have been consistent with outcomes of significant body weight reductions ranging between 15-27% in obese subjects\(^4-7\). This loss in total body mass, however, cannot be solely accounted for by lowered adiposity, but also significant deficits in lean tissue, especially for skeletal muscle mass\(^7-12\). Because of the clinical significance of decreased lean tissue, weight-loss treatments incorporating VLCD or other modes of severe energy restriction remain controversial. The typical weight-loss composition with VLCDs is approximately 75% fat and 25% lean mass\(^130,144\). Interestingly, these ratios are similar to those obtained with weight-loss following LCD interventions of similar dietary composition\(^130\). Chaston et al.\(^12\) conducted a broad and systematic review of various weight-loss interventions and the proportion of weight reduction attributable to decreased LBM. Lean body mass herein encompassed muscle, bone, and internal organ tissues. Among 19 trials employing severely restrictive diets for at least 9 to 16 weeks, an average of 20.6% of total weight lost was accounted for by a reduction in LBM, with the greatest contribution reported at 37.4%\(^12\). To date, a quantitative classification scheme for severity of LBM loss has yet to be devised especially in the context of voluntary weight-loss. Therefore, the measurable extent to which LBM loss is clinically relevant remains to be determined. Nevertheless, a reduction in
LBM has shown to have significant physiological consequences that may explain the relative ineffectiveness of VLCD programs with respect to long-term weight maintenance.

2.3.5 Metabolic and Functional Consequences of Rapid Weight-Loss

The significance of energy expenditure and its adaptive response to hypocaloric conditions has been somewhat confounded by issues pertaining to: 1) the methodology of normalizing data to the loss of metabolically active tissues; and 2) identifying compartments of body composition (fat, lean, or both) that are most contributory to basal energy requirements. Nevertheless, the most fundamental adaptation that can be firmly asserted is that total energy expenditure is suppressed with significant weight reduction. In support, Leibel et al. examined changes in energy expenditure and its components in response to experimental perturbations to body weight. Investigators concluded that a 10% reduction of body weight (induced by VLCD) was accompanied by a 15% decrease in 24-hour total energy expenditure. This general adaptive response has been demonstrated in a number of human and polygenic models of obesity and weight-loss. Moreover, it is suggested that all components of total energy expenditure, which include activity-related thermogenesis, postprandial thermogenesis, and RMR, are affected by weight-loss, at least to a general extent. The mechanistic underpinnings of these effects are directly associated to the loss of tissue mass, especially those with high basal energy requirements, e.g. skeletal muscle.

Weight-loss, and thereby reduced tissue mass, contributes to depressed energy expenditure through several distinct pathways. First of all, accompanying weight-loss is a reduced amount of body mass to be shifted during bodily movements, thus reducing the energy cost for any given workload of physical activity. Therefore, if the level of physical activity is unaltered pre- to post-weight-loss, activity-related thermogenesis, which accounts for 20-30% of total energy expenditure, would be conceivably lowered. Secondly, suppression of total energy expenditure during dietary restriction may occur in response to the reduced quantity of food being consumed. Resulting from decreased nutrient intake would be a blunted thermic effect of food which contributes to nearly 10% of total energy expenditure. Postprandial thermogenesis can be compartmentalized into two energy-expending components, one that is obligatory and the other, facultative. The obligatory component is simply described to be the metabolic demand, and thereby energy cost, of food digestion, which also comprises
processes of nutrient absorption and storage\textsuperscript{160}. Energy expenditure that occurs beyond these obligatory, postprandial processes is suggested to be due to heightened sympathetic nervous tone, protein turnover, and substrate cycling in response to nutrient consumption\textsuperscript{160-162}. Thus, because these processes are subdued during dietary restriction, the absolute energy expended from the thermic effect of food is diminished\textsuperscript{163}.

Lastly and perhaps most causal to the suppression of energy expenditure during weight-loss is the adaptive response for resting metabolism\textsuperscript{146}. Resting metabolism, which is typically reflected as RMR (kcals/day), accounts for approximately 60-70\% of total energy expenditure and therefore plays a significant role in the regulation of energy balance especially during weight-loss situations\textsuperscript{13,18,151}. Participants that received either a VLCD or LCD treatment exhibited a significant decrease in energy expenditure predominately through diminished resting metabolism\textsuperscript{16,27,151,153,164-166}. Total body mass appears to be a direct determinant of RMR in both healthy-weight and obese individuals, particularly the lean compartment (i.e. LBM) which comprises of more metabolically active tissues than fat, i.e. skeletal muscle\textsuperscript{14,17,145,164,167,168}. Correspondingly, LBM has been significantly correlated to not only total energy expenditure ($r^2=0.74; p<0.001$), but also RMR ($r^2=0.44; p=0.004$) among subjects studied at their initial weight and after a 10\% and 20\% weight-loss\textsuperscript{145}. In the same study cohort, obese subjects who lost 10\% of their initial weight exhibited significant declines for total energy expenditure (-17.7\%) and RMR (-14.0\%). Thus, the majority of the total energy expenditure reduced was attributable to lowered resting metabolism (~80\% accountable). These effects were also observed in parallel to a significant decrease in LBM. Therefore, deficits observed for total and resting energy expenditure, may likely be explained by the significant loss of lean tissue. Perhaps because of this relationship, rapid weight-loss situations where LBM is reduced have shown consistently to be accompanied by a decrease in RMR\textsuperscript{10,27,145,153-156,169,170}. In support, Wang et al.\textsuperscript{171} conducted an evaluation of tissue-specific metabolic rates and demonstrated 1kg of skeletal muscle to be associated with an energy expenditure of approximately 13 kcal/day while the per-kg energy cost for adipose is nearly 4.5 kcal/day. Because RMR is a major component of daily energy expenditure and therefore energy balance, maximizing resting metabolism during a rapid weight-loss scenario would be advantageous in terms of facilitating fat loss while supporting long-term weight-management. With respect to potential strategies to counter RMR suppression during severe hypocaloric conditions, maintaining lean tissue emerges as an imperative weight-loss
objective. In so doing, one may prevent the dramatic decline in energy expenditure with weight-loss. This would have significant long-term implications to weight-management as reduced energy expenditure has shown to be evidentially predictive of recidivism\textsuperscript{145,172}.

In addition to metabolic deficits, there are concerns that a reduction in LBM during weight-loss could impose negative functional consequences. This contention is partly supported by data indicating a positive correlation between LBM and functional strength in subclinical populations\textsuperscript{173-175}. Further, according to the work of Donnelly et al.\textsuperscript{7}, subjects undergoing 90 days of severe energy restriction exhibited a 13.3\% decline in absolute strength output from pre- to post-treatment while also demonstrating a significant reduction in LBM. However, muscular strength relative to LBM remained unchanged from baseline. These results suggested that the absolute loss of strength may be most accounted for by decreased lean tissue. Correspondingly, a 5-week, 800 kcal/day VLCD was shown to accompany significant declines in muscular strength relative to both body weight and LBM\textsuperscript{29}. In terms of contractile kinetics during VLCD conditions, results from Eston et al.\textsuperscript{9} and Krotkiewski et al.\textsuperscript{176} reported a significant decline in isokinetic torque output across a spectrum of constant angular velocities. In fact, the latter study suggested the changes in muscular torque production to be significantly correlated ($r=0.49; p<0.05$) to the negative changes in LBM following the VLCD. Although this does not imply causation, it can certainly support the argument that declines in muscle contractility during a VLCD is due to decreased LBM. To date, limited evidence substantiates the quantitative relationship between the changes in LBM and muscular strength especially during weight-loss conditions. Therefore, it cannot be completely ascertained whether strength loss observed during energy restriction is on the account of decreased LBM. Regardless of whether any correlation exists, hypocaloric interventions have shown to be detrimental to muscular strength. The potential clinical implications of these effects could be a reduced capacity to perform physical work and functional movements. Given that most clinically obese patients exhibit some heightened degree of functional limitations, any additional deficits to contractile force and muscular function accompanying weight-loss could be of significant disadvantage.

It can be speculated that one would be able to maintain or perhaps improve muscular strength during voluntary weight-loss even in the presence of reduced LBM. To elaborate, muscular strength is not exclusively governed by morphological phenotype but also largely through a neurological capacity to stimulate force production\textsuperscript{33}. Neural factors contributing to
force productivity include motor unit recruitment, firing frequency, and synchronization of motor unit activation. These factors are enhanced as an adaptive response to serialized neuromuscular overloading, and would result in positive strength manifestations\textsuperscript{32,33}. Therefore, strength development can be achieved independently of morphometric responses in muscle (i.e. hypertrophy or atrophy) if provided sufficient and appropriate stimuli\textsuperscript{177}. Certainly, the most potent stimulus for strength development would be persistent, mechanically-overloaded muscle contractions, which are most prudently afforded through exercise\textsuperscript{33,177}. Thus, an exercise provision that is tailored towards both lean mass and strength development may act in favor of enhanced weight-loss patterns and functional outcomes when applied to hypocaloric treatments. Considering the causative nature of LBM loss to negative metabolic and functional outcomes, evidence certainly supports the need for strategies to effectively mitigate the physiological processes that drive the loss of lean tissue during hypocaloric/energy deficient states. To identify targets for intervention, prominent pathways of lean tissue catabolism and therefore atrophy must be examined.

2.3.6 Physiological Basis for Lean Tissue Loss during Energy Restriction

The metabolism of myocellular proteins is a key determinant for the morphometric fate of skeletal muscle (i.e. hypertrophy, atrophy, or stasis) during adaptive periods. During a prolonged energy deficient state, a metabolic shift conducive to both protein catabolism and hypoanabolism drives the muscle phenotype towards the atrophic end of the adaptation continuum\textsuperscript{11,178-181}. This shift in muscle protein metabolism, often described as a negative protein turnover, reflects the body’s need to mobilize fuel substrate, such as amino acids, to contend with a deficiency in cellular energy and to reestablish energy homeostasis. Distinct molecular signaling pathways and upstream effectors, such as hormones, have been identified to delineate the mechanisms controlling the degradation and synthesis of myocellular proteins in the presence of metabolic perturbations\textsuperscript{181}. Under homeostatic conditions, regulators of protein degradation and synthesis orchestrate in a fashion that maintains muscle protein balance, and therefore, myofiber size remains relatively unchanged\textsuperscript{181}. With a negative energy balance that is sustained, protein degradation predominates while anabolic processes are repressed, ultimately coercing an adaptive response towards myocellular atrophy (Figure 2.1). This being a hallmark
of most hypocaloric weight-loss conditions, protein turnover and the mechanisms underlying hypercatabolic and hypoanabolic responses is of clinical relevance.

This adaptive response in protein metabolism is partly mediated by high circulating levels of catabolic hormones, in particular glucocorticoids. Endogenous cortisol is the most important human glucocorticoid as it is a key homeostatic regulator of systemic energy metabolism. For instance, its release from the adrenal cortex is elevated in response to hypoglycemic conditions, such as in prolonged energy restriction. In so doing, cortisol stimulates catabolism of large molecules, such as protein, to generate a substrate pool to support hepatic gluconeogenesis. It is well documented that glucocorticoids induce a catabolic response in skeletal muscle to liberate amino acids into circulation by the degradation of intact myofibril proteins, i.e. proteolysis. The catabolic signals conferred by glucocorticoids are stimulatory to the ubiquitin-proteasome pathway (UbP), one of the most prominent proteolytic mechanisms proposed to induce the atrophic phenotype in skeletal muscle. The role of UbP in skeletal muscle atrophy has been well established as so is the altered expression patterns of genes with a regulatory function in UbP-dependent proteolysis. These genes, collectively termed “atrogene”, induce two skeletal muscle-specific E3 ubiquitin ligases: muscle ring finger1 (MuRF1) and atrogin-1. Increased atrogene expression is reflective of increased protein degradation via UbP and initially requires the dephosphorylation and nuclear translocation of the forkhead box (FoxO) transcription factor. Evidence indicates that activation of FoxO by glucocorticoid administration stimulates an atrogene transcriptional program responsible for inducing UbP-proteolysis and myofiber atrophy. It is through this mechanism that cortisol disseminates its catabolic effects on skeletal muscle and may be pivotal in the loss of LBM during energy restriction.

A divergent pathway implicated as a catalyst to myocellular atrophy involves the activation of adenosine monophosphate (AMP)-activated protein kinase (AMPK), a prominent energy sensing enzyme in skeletal muscle cells. AMPK is a ubiquitously expressed protein kinase that is considered by most as the cell’s principal molecular regulator of energy homeostasis. In brief, AMPK is directly activated by elevated levels of cytosolic AMP and is accordingly sensitive to an enhanced AMP to adenosine triphosphate (ATP) ratio, a distinct mark of depleted cellular energy. Acute activation of AMPK in response to energy depriving conditions, e.g. nutrient starvation or prolonged exercise, initiates molecular events to mutually
conserve as well as generate ATP. With that regard, AMPK inhibits anabolic processes that consume cellular energy while stimulating catabolic processes that would generate energy\textsuperscript{199,202}. Protein synthesis, a major energy-costly event, is the major anabolic process inhibited upon AMPK activation\textsuperscript{199}. The mammalian target of rapamycin (mTOR) signaling pathway is central in the control of protein synthesis and is cued in response to a multiplex of anabolic stimuli, including growth factors (e.g. insulin like growth factor-1 [IGF-1]), insulin, or intramyocellular amino acids (e.g. leucine)\textsuperscript{181,203}. AMPK suppresses anabolism largely through the inhibition of mTOR signaling by two mechanisms: 1) inactivation of mTOR itself and/or 2) activation of its upstream inhibitor, tuberous sclerosis complex 2 (TSC2)\textsuperscript{204,205}. AMPK has also shown to exert catabolic effects on muscle protein in efforts to derive cellular energy, i.e. ATP, from freed amino acids. This process is regulated through a pathway similar to that involved in cortisol-induced protein degradation. Evidence reveals a link between AMPK activation and FoxO-induced transcription of atrogenes, which again is indicative of proteolysis induction and heightened atrophic potential. Romanella et al.\textsuperscript{206} investigated a model of energy deprivation in which AMPK activation led to FoxO dephosphorylation and subsequent epigenetic up-regulation of atrogin-1 and MuRF1. Activation of AMPK activity, therefore, appears to constitute changes at the protein level preceding the development of the atrophic phenotype during energy deficiency.

The loss of muscle mass induced by extended energy deficits might also involve the insulin/IGF-1 signaling pathway. This pathway incorporates many of the molecular events essential to our current understanding of protein metabolism and its regulation of morphometric adaptations in skeletal muscle. Insulin and IGF-1, in particular, are potent anabolic and anti-catabolic stimuli for skeletal muscle through distinct molecular pathways mediated by protein kinase B (Akt)\textsuperscript{207-209}. Akt is an important signaling hub activated upon growth factor ligation and has multiple substrate targets commensurate with its many molecular functions. These include those affecting protein synthesis as well as proteolysis\textsuperscript{180}. In contrast to AMPK function in protein metabolism, substantial evidence supports the role of Akt as a key activator of mTOR and therefore is highly linked to the biosynthetic pathways responsible for cellular growth\textsuperscript{207,208,210}. Akt also appears to counteract atrophic adaptations through the inhibition of FoxO translocation which in turn would suppress the expression of proteolytic atrogenes\textsuperscript{180,197}. Collectively, Akt appears to have a central function in integrating anabolic and anti-catabolic
signals derived from growth factors (i.e. IGF-1) and insulin. Hence, limiting the bioavailability of these circulating factors would conceivably preclude cellular growth potential and promote tissue catabolism.

Nutritional status is a major effector for circulating IGF-1 concentrations and may take part in the molecular events preceding the course for muscle atrophy during hypocaloric interventions. Significantly decreased serum IGF-1 was previously demonstrated during prolonged and short-term caloric restriction, delimiting the capacity for protein synthesis and muscle growth. Henning et al. characterized the temporal response of the circulating IGF-1 system to acute caloric restriction over a 48-hour period. Free IGF-1 decreased 43% with severe caloric restriction while remaining stable during a eucaloric state. Interestingly, caloric restriction yielded a dramatic 445% increase in circulating IGF-1 binding protein-3 (IGFBP-3). Because IGFBP-3 is inhibitory to the actions of free circulating IGF-1, these results suggested that severe caloric restriction obstructs ligation of IGF-1 to membrane receptors, thereby repressing downstream, Akt-mediated pathways. Consequently, both mTOR activation and FoxO/atrogene inhibition would be withdrawn.

Hypocaloric intake often deprives muscle of ample nutrient supply, which may consequently compound the catabolic effects of blunted growth factor activity. As mentioned earlier, mTOR is a key integrator of environmental cues, including nutrient availability and growth factors, and ensures that cellular growth manifests when conditions are permissible. In fact, several findings demonstrated the importance of amino acid sufficiency in mTOR signaling, as growth factors are unable to effectively activate mTOR under an inadequate amino acid reserve. Under nutrient-rich conditions in which an abundance of amino acids are present, mTOR signaling is permitted, thus allowing stimulation of biosynthetic pathways while inhibiting molecular catabolism. The fundamental role of amino acid availability in the context of muscle anabolism is to provide an ample substrate supply to support the manufacturing of myofiber proteins. However, beyond this basic function, evidence has specified unique amino acids to be stimulatory of mTOR activation and the initiation of ribosomal translation (i.e. protein synthesis). Among these amino acids, the branched chain amino acid (BCAA) leucine appears to be distinguished in the nutrient-stimulation of mTOR signaling. Atherton et al. evaluated the response of anabolic signaling mechanisms in cultured skeletal myocytes inoculated with a spectrum of amino acids, including BCAAs.
Among all amino acids administered, leucine alone stimulated a robust increase in the phosphorylation/activation of mTOR and its downstream substrate targets, including eukaryotic initiation factor 4E-binding protein (4E-BP1), p70 ribosomal protein S6 kinase (p70S6K), and ribosomal protein S6 (rpS6). Several other investigations support this distinct pro-anabolic effect of leucine in skeletal muscle by mTOR-dependent mechanisms\textsuperscript{228-231}. In the context of hypocaloric treatments, diets lacking sufficient amino acid provision would be detrimental to the retention of muscle tissue due to: 1) limited substrate pool for synthesizing new proteins, and/or 2) withdrawal of nutrient stimulation of anabolic pathways (i.e. leucine and mTOR signaling).

Figure 2.1. Molecular rationale for muscle atrophy with negative energy balance. AMP= adenosine monophosphate, ATP= adenosine triphosphate, AMPK= AMP activated protein kinase, PGC-1α= peroxisome proliferator receptor-gamma co-activator 1-alpha, IGF-1= insulin like growth factor-1, IRS-1= insulin receptor substrate-1, Akt= protein kinase b, TCS 1/2= tuberous sclerosis complex 1/2, mTOR= mammalian target of rapamycin, 4E-BP1= eukaryotic initiation factor 4e-binding protein, eIF-4E= eukaryotic initiation factor 4e, p70S6K= p70 ribosomal protein s6 kinase, rpS6= ribosomal protein s6, FoxO= forkhead box O, NF-kB= nuclear factor-kappa B, MuRF1= muscle ring finger1, ub= ubiquitin, arrows= activation, bars= inhibition.
For this reason, supplementary protein and/or amino acids have been explored as a potentially effective nutrient provision for lean mass during hypocaloric intake\textsuperscript{25,232-234}. Hypocaloric diets with relatively higher protein content (30-50\% of total kcal) have resulted in greater reduction in body weight and fat, while better preserving LBM compared to diets lower in protein content (~18\% of total kcal)\textsuperscript{24,235,236}. Therefore, when considering the importance of optimizing weight-loss patterns, a relatively high-protein hypocaloric treatment (protein accounting for ~50\% of total kcal) would be the most ideal dietary approach. A contemporary VLCD system, i.e. Optifast\textsuperscript{®}, provides a standard 800 kcals per day of which 35\%, 50\%, and 15\% derive from protein, carbohydrate, and fat, respectively. This would provide 70 g of high-quality protein daily and would elicit approximately 0.7 g/kg of bodyweight/day based on a reference bodyweight of 100 kg. In fact, the mean bodyweight at baseline for a single-center cohort of 32 patients who underwent the Optifast\textsuperscript{®} program was approximately 130 kg. Thus, the relative protein intake for this particular cohort was nearly 0.5 g/kg/day. While the RDA for protein intake is currently 0.8 g/kg/day, meta-analyses suggested that higher-protein consumption (~1.20 g/kg/day) promotes greater LBM maintenance than diets lower in protein (<0.7 g/kg/day) under weight-loss circumstances, particularly when combined with resistance training\textsuperscript{144,237}. Furthermore, Pasiakos et al.\textsuperscript{238} conducted a randomized controlled trial comparing the effects of varying levels of dietary protein (i.e. RDA vs. 2x-RDA vs. 3x-RDA) on body composition and muscle protein synthesis (MPS) during energy restriction and a subsequent weight maintenance phase. Participants, regardless of protein intake, exhibited a 3-kg weight-loss. However, weight-loss composition differed among conditions as a reduction in LBM was less and fat loss was greater in those receiving 2x-RDA and 3x-RDA compared to just the RDA treatment. Also, the post-absorptive anabolic response was blunted during energy restriction when compared to what was demonstrated within the weight-maintenance phase. Higher protein intake, however, maintained an elevated and consistent post-meal-MPS across both energy restrictive and weight maintenance phases. Thus, it remains reasonable to suggest the RDA for protein intake, and thereby customary Optifast\textsuperscript{®} protein content, to be inadequate for the preservation of LBM, especially for the average 100-130 kg patient. Based on this reference bodyweight range and the aforementioned protein recommendation (1.20 g/kg/day), approximately 150 g of protein per day would be required to facilitate the sparing of LBM during hypocaloric weight-loss treatments, especially when coupled with resistance training. From a
practical perspective, given that VLCD systems comprise of proprietary meal-replacement formulas with fixed nutrient composition, increasing protein content to 150 g/day would be most prudently achieved via addition of an 80 g/day supplement of high-quality protein, such as whey. Although additional calories would result from supplementing 80 g of protein (~320 kcal/day more), it would be clinically discouraged to substitute VLCD meal products with a protein supplement as other necessary nutrients afforded through the formulas would be compromised. Indeed, some may also be apprehensive to the idea of additional caloric intake from protein supplementation as it may be perceived to compromise the weight-loss efficacy of the VLCD program. In efforts to provide rationale for the added protein calories, Bray et al.\textsuperscript{239} concluded that excess caloric intake derived from moderate (15\% of total kcal; 1.8 g/kg/day) to high (25\% of total kcal; 3.0 g/kg/day) proportions of dietary protein leads to greater lean mass accretion while preventing further fat gain as compared to conditions in which carbohydrates and fat constituted the excess calories. Therefore, additional calories to a VLCD that is primarily derived from protein may act in favor of lean mass retention without compromising the rate of fat loss.

Undoubtedly there is much debate regarding the ideal source of supplementary protein within the context of lean tissue growth or maintenance, especially during hypocaloric weight-loss endeavors. In efforts to elucidate the optimum protein source, the role, as well as benefits, of dairy foods during energy restrictive weight-loss have been examined via meta-analysis of randomized controlled trials\textsuperscript{240}. Reports suggested that hypocaloric diets higher in dairy content result in superior weight-loss composition characterized by enhanced total weight-loss, fat loss, and LBM retention. This is most likely attributable to the type of protein that is derived from milk (i.e. whey and casein). Based on the molecular rationale presented above, a protein source rich in essential amino acids (EAA), and therefore BCAA content, and thereby leucine, would supply appropriate nutrient support for muscular growth as well as stimulation of MPS (i.e. mTOR signaling), provided that a sufficient quantity is consumed. In that specific regard, two of the most prominent supplementary forms of protein are in fact whey and casein, which comprise of an amino acid profile high in EAA, BCAA, and leucine according to the USDA Food Composition Tables. Whey may be considered as the higher-quality protein compared to casein due to its relatively greater concentration of BCAA and leucine (12\% vs. 9.3\% of total protein), which to reiterate is a unique nutrient stimulator of MPS\textsuperscript{224}. This may likely explain the reported
advantages of whey over casein supplementation in enhancing the changes in body composition and strength that accompany resistance training\textsuperscript{241}. Although very limited evidence demonstrates the role of supplementary protein in clinical VLCD interventions, whey protein supplementation, in its appropriate dosages, may be the most effective dietary means of sparing lean tissue\textsuperscript{26,241-243}.

2.4 Exercise Training Application in Hypocaloric Weight-Loss Treatments

2.4.1 Overview

An important question emerges regarding the capacity through which exercise training can elicit a hypertrophic or anti-atrophic response in muscle under the catabolic strain imposed by hypocaloric intake. This morphometric adaptation in muscle is one likely to act in favor of enhanced total LBM during energy restrictive weight-loss endeavors. With that said, it would be of significant value to further evaluate the extent to which the specific adaptations from divergent exercise modes would either protect against or facilitate lean mass reduction during rapid weight-loss. Advances in molecular physiology have considerably enhanced our understanding of the specificity of adaptations to different modes of training, i.e. endurance and resistance type, and may provide rationale for appropriate exercise programming during hypocaloric dietary treatments.

2.4.2 Specificity of Training Adaptation in Muscle: Rationale for Resistance Exercise

Many features of training adaptation in skeletal muscle are unique to the type of stimulus that is applied, namely contractile activity\textsuperscript{32,33,244}. Contractile activity can generally be defined as low muscular force development across an extended duration, or high force generation of limited duration, features characteristic of endurance and resistance exercise, respectively. Training-induced adaptations at the whole-body, cellular, and molecular levels demonstrate specificity to the mode of exercise performed\textsuperscript{245}. For instance, increased muscle cross-sectional area (hypertrophy) and enhanced motor unit recruitment patterns constitute the fundamental adaptations to repeated bouts of high-force activity, i.e. resistance exercise\textsuperscript{42,246-248}. In contrast, prolonged endurance/aerobic training elicits a variety of metabolic and morphological reformations, including enhanced maximal oxygen consumption, oxidative metabolism, and mitochondrial content concomitant with a fast-to-slow shift in muscle fiber type\textsuperscript{245,249,250}. Each mode of exercise training induces divergent signaling pathways and mechanisms that when
chronically activated, direct muscle adaptation towards either an aerobic or hypertrophic phenotype (Figure 2.2)\textsuperscript{32}.

First, myofiber hypertrophy results from proper resistance training, which provides a recurrent overloading stimulus conducive to intracellular protein synthesis and blunted proteolytic activity in muscle. Activation of signaling mechanisms associated with muscle growth have also been exhibited, composing changes at the protein level preceding the advancement towards a hypertrophic phenotype\textsuperscript{207}. For instance, the Akt-mTOR pathway has been considered by most as an integral component of the hypertrophic process since it coordinates the molecular basis for myocellular protein synthesis\textsuperscript{180,207,251,252}. Among the various stimuli that subsequently lead to Akt-mTOR activation, studies support IGF-1 as a potent anabolic agent for skeletal muscle. Resistance exercise increases circulating\textsuperscript{253,254} and muscle-derived expression\textsuperscript{255,256} of IGF-1 which may transiently increase Akt-mTOR activity and ensuing activation of translational machinery (i.e. 4E-BP1, p70S6K, and rpS6 phosphorylation)\textsuperscript{32,33}. In the context of chronic adaptations in the circulating IGF-1 system, work from Borst et al.\textsuperscript{257} and Marx et al.\textsuperscript{258} reported elevated resting concentrations of serum IGF-1 following resistance training (~25-week protocol). These systemic shifts in IGF-1 levels may explain the heightened activation of muscle-specific mTOR previously demonstrated following 8 weeks of resistance training in human subjects\textsuperscript{259}. An alternative agonist to constituents of the Akt-mTOR pathway is derived from the mechanical deformation of muscle fibers during resistance exercise, i.e. mechanotransduction. Mechanotransduction, a process converting mechanical signals from contractile activity into molecular events, plays a key role in inducing protein synthesis through an mTOR-dependent mechanism autonomous from growth factors or hormones\textsuperscript{260}. Further, while a degree of protein degradation is required for muscle remodeling during adaptive periods, resistance training may also decrease chronic activation of catabolic processes through a diminished expression of MuRF1 and atrogin-1\textsuperscript{261}. Results from others\textsuperscript{193} suggest these effects to be mediated by the actions of Akt and its inhibition of FoxO-induced modulation of atrogene transcription. Overall, resistance training induces a sequential cascade of: 1) neuromuscular activation, 2) signaling events (i.e. Akt-mTOR pathway) stemming from mechanotransduction and circulating factors (i.e. IGF-1), 3) protein synthesis due to altered gene expression and increased translation, 4) myofiber hypertrophy, and 5) muscular growth and enhanced contractile force capacity.
Indeed, it is reasonable to suggest that the specific adaptations to the diverse exercise modes demonstrate a broad degree of incompatibility, at least at the cellular and molecular levels. For instance, high-load resistance training fails to elicit any marked improvements in mitochondrial biogenesis and is therefore, a suboptimal approach to induce adaptations conducive to muscle oxidative capacity and endurance performance\textsuperscript{262}. Likewise, endurance training is an inefficient promoter of myofiber hypertrophy and may negatively affect muscle protein synthesis and turnover\textsuperscript{262,263}. Consequently, training with prolonged, low-force exercise fails to generate an adaptive response favorable for muscular growth and enhanced contractile force capacity. Endurance and resistance training, therefore, represent opposite extremes of an adaptation continuum characterized by their respective phenotypic and functional manifestations. Key regulators of muscle adaptation are continually being identified, and are likely to elucidate the specificity of training responses leading to differentiated muscle phenotypes. The work of Vissing et al.\textsuperscript{264} investigated the effects of AMPK vs. Akt-mTOR signaling mechanisms on converting divergent exercise modes into training specific adaptations in human subjects. Participants initially underwent either endurance or resistance training for 10 weeks thereby being accustomed to a distinct mode of exercise. As expected, differentiated adaptations occurred with each exercise mode as endurance training enhanced maximal oxygen uptake while resistance training increased muscle size and strength. Following the training period, data was collected before and after a single bout of exercise that was specific to the mode the subject was previously accustomed to. The results indicated that Akt-mTOR signaling is preferentially stimulated through resistance training, while AMPK was activated exclusively in endurance trained subjects. A substantial body of evidence supports the key homeostatic role of AMPK in energy metabolism during acute bouts of exercise, especially modes that deplete intracellular energy level and raise cytosolic AMP content, e.g. endurance exercise\textsuperscript{32,33,200,265}. Similar to the function of AMPK during hypocaloric conditions, its exercise-induced activation is also an effort to conserve energy by inhibiting anabolic processes, e.g. protein synthesis, while restoring ATP through catabolism of molecules, such as myofibrillar proteins. Although chronic activation of AMPK is an important component of the adaptive response in muscle to endurance training (i.e. mitochondrial biogenesis)\textsuperscript{200}, this occurs at the expense of myofiber size and muscle mass due to the continuous inhibition of anabolic pathways (i.e. mTOR) and stimulation of catabolic events (i.e. proteolysis)\textsuperscript{32,33,200,265}. 

32
Since the hypercatabolic and hypoanabolic nature of endurance training parallels that of caloric restriction, such an exercise mode may be an ineffective means of preserving lean mass during energy restrictive weight-loss endeavors, despite its putative advantages for fat loss. Although resistance training appears as the ideal countermeasure to the loss of lean mass during hypocaloric intake, the question remains whether an anabolic, and thereby hypertrophic, response would manifest in muscle in a highly energy deficient state. From a clinical perspective, obese patients undergoing hypocaloric interventions, such as VLCDs, may benefit most from a resistance training prescription provided that the stimulus suffices to overcome the catabolic strain imposed by the diet and elicits an adaptive response in lean tissue concomitant with growth. Recent findings have revealed a fresh perspective on resistance training as an integrative component of dietary weight-loss treatments. When considering the major role of LBM, RMR, and physical function as key elements of successful weight-loss, it is important to
review and dissect previous experimental resistance training paradigms and its impact during hypocaloric weight-loss interventions.

2.4.3 Effects of Resistance Training on Weight-Loss Composition, Metabolic Rate and Function during VLCD Treatment

The preferred outcome for most clinical weight-loss interventions is three-fold: 1) to reduce total body adiposity to an extent that is clinically meaningful; 2) to minimize substantial declines in LBM; and 3) to maintain metabolic and functional capacities. Taken together, these factors emerge as a fundamental clinical objective which is to optimize weight-loss patterns in favor of long-term success. As outlined earlier, obesity therapeutics incorporating proprietary hypocaloric systems, such as Optifast®, have shown efficacy in clinical weight-management, however has failed to successfully resolve important issues pertaining to the maintenance of LBM, resting energy expenditure, and muscular function4-10,12. To address the burden imposed by severe hypocaloric diets on lean tissue morphometry and metabolism, the integration of exercise countermeasures has been examined extensively7,10,23-30. 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.

Based on information previously discussed, resistance training would appear as the more rational exercise provision to counteract the loss of lean mass during caloric restriction; yet, the majority of studies have employed relatively low-force activities in the form of endurance/aerobic training8,27,28. On the basis of previous whole-body outcomes8,29-31 and aforesaid molecular/cellular rationale32,33, endurance training may be an ineffective strategy for lean mass retention during severe hypocaloric conditions. In fact, endurance training has even demonstrated to extend lean tissue loss beyond the degree induced by caloric restriction alone, suggesting that prolonged, low-force activity can exacerbate the catabolic nature of VLCD treatments in muscle8,29-31. Because it is well-established that high-force and high-load bearing activities function favorably to improve muscle mass and performance, resistance training may be the most efficient means of enhancing VLCD treatments towards enhanced weight-loss composition, resting metabolism, and muscular function34-36. However, previous attempts to improve weight-loss composition with resistance training paradigms have demonstrated promising yet mixed outcomes, thereby impeding the progress towards clinical applicability.
An early investigation on obese female participants undergoing a 12-week, 800kcal/day VLCD examined the effects of resistance training on various morphometric variables\textsuperscript{7}. Based on histological analysis of quadriceps muscle fibers, resistance trained participants exhibited a significant increase in fiber cross-sectional area compared to pre-treatment measures, whereas the sedentary control group demonstrated no longitudinal changes. These results suggested that, at least on the cellular level, resistance training can produce significant muscle hypertrophy during severe hypocaloric and rapid weight-loss conditions. However, these cellular adaptations failed to manifest at the whole-body level as each group exhibited paralleled weight-loss composition from pre- to post-VLCD. Both groups, regardless of exercise, demonstrated a 16 kg weight-loss, of which 76\% was attributable to fat loss while reduced fat-free mass accounted for about 24\%. On the contrary, resistance training showed efficacy in improving muscular strength by 17.6\% and completely reversing the functional detriments evidenced in the sedentary control group. Inconsistencies in the outcomes for LBM and function, however, do not appear surprising as muscular strength gains have been well-known to precede any measurable signs of whole-muscle growth during novice resistance training\textsuperscript{246,266}. These results collectively lead to speculation that the protocols employed lacked in areas that would likely explain the failure of resistance training in maintaining lean tissue despite inducing muscle fiber hypertrophy. One possibility may be the insufficiency of the resistance training protocol in stimulating a hypertrophic response robust enough to elicit marked gains in LBM, especially when compared to a sedentary control. Exercise volume, intensity, and type performed within the allotted training period may be particular variables of interest. The employed training protocol offered limited manipulations in these exercise variables across the entire 12-week period. For instance, a change in intensity, as measured by a percentage of pre-training one-repetition maximum (1RM), was implemented once starting week 5 (i.e. 70\% 1RM from weeks 1-4 and 80\% 1RM from weeks 5-12). The issue here is that the load prescription beginning week 5 was relative to 1RM values obtained at week 1 and thus fails to account for probable strength gains achieved during the prior weeks of training (i.e. weeks 1-4). Given the dramatic overall strength improvements exhibited by the resistance trained subjects, it is reasonable to suggest that 1RM would have increased by week 5, a contention well-supported by previous literature\textsuperscript{266}. Thus, the 80\% 1RM prescription from weeks 5-12 was likely a crucial misrepresentation of “high” relative intensity and may have precluded conditions optimal for muscle growth to manifest, at least to a
measurable extent. Furthermore, training volume (i.e. sets and reps) also lacked variation across the 12-week period as the only modification employed was a 1-set addition starting week 5. Modern innovations in exercise programming illustrate the significance of training variations especially for intensity and volume\textsuperscript{39-41}. Periodization is a training concept defined as the systematic manipulation of exercise variables, e.g. intensity and volume, with the intent to avoid stagnation and promote continual adaptations/improvements\textsuperscript{39-41}. Therefore, when considering the advantages of periodization modeling in resistance training adaptations, an experimental exercise protocol should implement appropriate and timely variations while choosing proper load and volume prescriptions to produce the optimum condition for adaptation and progression. A subsequent investigation in a similar study cohort partly addressed these limitations as a more progressive training protocol was implemented\textsuperscript{10}.

A notable study by Bryner et al.\textsuperscript{10} revealed the potential therapeutic value of resistance training with respect to its application during severe hypocaloric interventions. In this study, twenty obese middle-age participants underwent 12 weeks of VLCD consisting of liquid meal-replacement formulas with a daily caloric intake of 800 kcals. During the treatment period, participants performed either a resistance or aerobic exercise regimen. One group performed resistance training 3 days/week with bouts consisting of 10 exercises performed 8-15 repetitions and gradually progressing from 2 to 4 sets across 12 weeks. A separate control group performed aerobic type exercise 1 hour/day, 4 days/week by walking, biking, or stair climbing. Results for weight-loss composition were promising with resistance training. The control group exhibited a significantly greater weight-loss than the resistance trained group (19.4% vs. 14.7%) with similar reduction in body fat, body fat percentage, and BMI. The difference in weight-loss was explained by a significant decline in LBM for the control (~-4kg) while resistance training protected against any detectable loss. In addition, resistance training preserved RMR while the control group demonstrated a significant decrease from pre- to post-treatment. Although previous results show promise for resistance training in moderating the burden of severe hypocaloric diets, they lack sufficient support to be confidently integrated into routine treatment protocols. This is likely attributed 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.
2.4.4 Research Limitations to be Addressed

To achieve a vertical step in that regard, several important issues must be addressed. First, an experimental approach examining VLCD-treated subjects should closely represent clinical situations in which: 1) VLCDs are prescribed to patients who are severely obese and exhibit comorbid conditions, 2) VLCD-based treatments are medically monitored by a multifaceted team of physicians, dieticians, and exercise physiologists, 3) duration of VLCD treatment is 12 weeks with regular behavioral counseling, and 4) exercise is not specifically prescribed; rather general physical activity is recommended and typically unsupervised.

Secondly, an experimental resistance training intervention should be: 1) formatted based on empirical innovations in training programming, i.e. periodization, to optimize protocols towards enhanced lean mass and muscular strength, 39-45, 2) combined with sufficient nutrient support through high-quality protein intake for lean tissue maintenance or growth, and 3) integrated into the standard clinical care of the VLCD-treated patient to enhance the understanding of its practical application. A trial taking into account for these limitations may be an effective means to evaluate the clinical effectiveness of resistance training in enhancing standard VLCD-based treatments towards improved weight-loss composition, metabolic rate, and muscular function. An applied approach integrating sophisticated measurements of morphometric, metabolic, and functional parameters with relevant biochemical indices such as hormones, growth factors, and metabolites would be especially insightful.

2.5 Summary and Implications for Future Research

In summary, the obesity epidemic represents an enormous challenge for the medical community to develop and implement weight-management programs that are both acutely and chronically effective. Proprietary VLCD systems have been the most prudent and pragmatic approach for urgent weight-loss circumstances due to its immediate benefits for a number of clinical parameters, i.e. blood pressure, metabolic and lipid profile, etc. However, current clinical strategies have yet to address critical issues pertaining to the long-term stability of these positive treatment outcomes. This is reflected by the extreme rate of weight recidivism that is evident within the first 4 years after completing a VLCD treatment. Beyond behavioral factors, research point towards addressing the physiological adaptations to VLCD interventions that act in favor of weight-regain. Specifically, the dramatic loss of LBM and RMR resulting from
hypocaloric treatments are conducive to the regaining of body fat and probable relapses of prior health complications. Thus, a present unmet clinical need is a practical strategy that can be applied to medical VLCD-based treatments to optimize rapid weight-loss patterns for lean tissue while enhancing RMR and physical functionality. Resistance training may be the most effective means of achieving these outcomes. Unfortunately, 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 is likely attributable to the limited availability of applicable clinical data that can efficiently guide medical weight-management programs towards an optimized hypocaloric treatment through a resistance exercise provision. To achieve progress in that regard, experimental approaches should implement a more sophisticated and systematic resistance training prescription in VLCD-treated patients under real clinical scenarios and with sufficient nutrient (i.e. protein) support. This approach coupled with the implementation of more refined analyses of body composition, energy metabolism, and neuromuscular function with relevant biochemical parameters would be of great value.
CHAPTER THREE

METHODS

3.1 Specific Aim 1 (Retrospective Study)

3.1.1 Experimental Design

This study was a single-center retrospective analysis on 32 patients (age= 58±2) of Tallahassee Memorial Healthcare (TMH) Bariatric Center who completed a 12-week medical weight-management program incorporating a proprietary VLCD (Optifast®; Nestlé HealthCare Nutrition; Florham Park, New Jersey, USA) between the years 2011 and 2013. Body composition, anthropometric, and metabolic and lipid panel data acquired during the 12-week treatment period were analyzed retrospectively from medical chart reviews of male (n=16) and female (n=16) patients. Time-dependent changes in dependent variables were compared among gender and age cohorts. Age-groups were determined by patient cohorts above and below the median age of 57 years, i.e. Young= age<57 (n=16) and Old= age≥57 (n=16). Patients included for analysis met the following criteria: 1) full completion of the 12-week Optifast® program, 2) BMI ≥ 30 kg/m², 2) sedentary (based on self-reported physical activity level), and 3) at least 18 years of age. All data sets were numerically coded with no accessible link to patient information.

3.1.2 Description of Dietary Treatment Program

The medical weight-management program of focus is administered at the TMH Bariatric Center and prescribed by a board certified bariatric physician. The program incorporates a 12-week rapid weight-loss component comprised of full meal-replacement administered through liquid-based formulas, i.e. Optifast®. A standard Optifast® treatment is implemented through a variety of products comprised of a powder mix, ready-to-drink blend, and instant soup, all of which contain equivalent macronutrient (35% protein, 50% carbohydrate, 15% fat) and micronutrient composition per product, equating to 160 kcals/product. Participants were prescribed 5 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. Participants were medically supervised and required to visit the Bariatric Center each week on a designated time and day. During each visit, participants underwent anthropometric assessments and attended a
group education class mediated by a registered dietician. The bariatric physician monitored the participant’s progress and medical condition regularly throughout the treatment period.

3.1.3 Anthropometry and Body Composition

Anthropometric parameters and body composition (two-compartment model) were measured at the TMH Bariatric Center using an FDA-approved medical body composition analyzer (Tanita TBF-310; Arlington Heights, Illinois, USA) that is equipped with a body weight scale and bioelectrical impedance analysis (BIA) capabilities. The analyzer provided computed measurements for body weight (BW), BMI, body fat percentage (BF%), fat mass (FM\textsubscript{BIA}), and fat free mass (FFM) (i.e. FFM = BW - FM\textsubscript{BIA}). Percentage of FFM of total BW (FFM%) was extrapolated from BIA data. Waist circumference (WC) was measured through a previously described protocol\textsuperscript{57}. BW and BMI were recorded each week during the 12-week treatment period. Body composition and anthropometric variables, i.e. FM\textsubscript{BIA}, FFM, BF%, FFM%, and WC, were measured and documented pre-treatment and post-treatment (13 weeks total).

3.1.4 Estimated Resting Metabolic Rate

Estimated resting metabolic rate (RMR\textsubscript{estimate}) was computed by the Tanita analyzer based on descriptive and anthropometric data. RMR\textsubscript{estimate} was calculated through gender specific predictive equations devised by The Revised Harrison and Benedict Equation\textsuperscript{267}: Male = 88.362 + (13.397 \times BW) + (4.799 \times Height) − (5.677 \times Age); female = 447.493 + (9.247 \times BW) + (3.098 \times Height) − (4.330 \times Age). RMR\textsubscript{estimate} was measured and recorded pre-treatment and post-treatment.

3.1.5 Lipid and Metabolic Panels

Lipid panels included values for total cholesterol, triglycerides, high-density lipoprotein (HDL), low-density lipoprotein (LDL) and VLDL. Metabolic parameters included fasting blood glucose levels as well as hemoglobin A1c (HbA1c) values. All measures were obtained in the 8-hour fasted state. Blood lipid and metabolic profiles were measured pre- and post-treatment.
3.1.6 Exercise History and Attitude Questionnaire

A clinic-based survey (appendix I) was administered to each participant to assess exercise/physical activity history and attitude. The questionnaire incorporated the following modules: 1) time spent daily on specific activities representative of sedentary or physically active behavior; 2) evaluation of general walking function; and 3) interest level for specific exercise-related activities. The survey was completed by each participant before the start of the 12-week treatment. Self-reported responses were quantified and interpreted for descriptive purposes.

3.1.7 Analysis of Data

All data are presented as mean ± standard error (SE). All descriptive variables were analyzed using a one-way analysis of variance (ANOVA) for baseline comparisons. Body weight and BMI were analyzed using a 2 (gender) x 2 (age-group) x 13 (time) repeated measures ANOVA. Pre- and post-treatment measurements for body composition, anthropometric, RMRestimate, and lipid and metabolic profiles were analyzed using a 2 (gender) x 2 (age-group) x 2 (time) repeated measures ANOVA. Relative and absolute change from pre to post for all dependent variables were calculated and analyzed by a 2 (gender) x 2 (age-group) factorial ANOVA. In the event of a significant main effect or interaction, a Tukey post hoc test was used for pairwise comparisons. All statistical analyses were performed using Statistica 12 for Windows (StatSoft; Tulsa, OK, USA) with significance set at p<0.05.

3.2 Specific Aim 2 (Prospective Study)

3.2.1 Participants

The target population for the proposed 12-week clinical trial was obese patients of the TMH Bariatric Center who were prescribed by the bariatric physician to undergo a medically monitored weight-management program that incorporates a proprietary hypocaloric diet (Optifast®). Eight male and/or female participants (age= 59±4 years, BW= 127.3±8.8 kg, BMI= 41.1±3.3 kg/m²) were recruited through the TMH Bariatric Center primarily by clinician referrals and announcements during weekly health education classes. Before starting the medically prescribed weight-loss diet, all patients were required to undergo 4 weeks of weight stabilization under the care of the bariatric physician as part of their medical treatment plan. During this period, patients were individually recruited for the study. In addition to the criteria set forth by
the bariatric physician for dietary treatment eligibility, patients also met the following inclusion criteria to participate in the proposed research: 1) BMI between 30 and 42 kg/m²; 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 patients who expressed interest in participating for the study and satisfied the preliminary inclusion criteria 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. These included, but were not restricted to: uncontrolled disease status, pregnancy, milk allergies, smoking, or debilitating musculoskeletal or neuromuscular impediments that would prohibit exercise. Any other medical conditions which would be contraindicated for participation were under the discretion of the physician administering the examination. Patients provided investigators with a Physician’s Approval Form signed and dated by a physician, authorizing medical clearance and full eligibility to participate in the study.

3.2.2 Experimental Design

The proposed study was a randomized clinical trial. Participants (N = 8) were matched for gender and body composition and randomly allocated to one of the two following groups for a 12-week resistance exercise training intervention study (Figure 3.1): 1) Standard Treatment Control Group (CON) (n=4); and 2) Periodized Resistance Training Group (RT) (n=4). All participants underwent the control dietary condition (i.e. Optifast® + whey protein supplement) from the start of experimental week 1 to the end of week 12 as part of a medically monitored weight-management program 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, 80g/day) (described below). CON underwent a 12-week, self-paced protocol to simulate the standard clinical treatment in which exercise variables are not specifically prescribed, but rather general physical activity recommendations are provided. CON was instructed to achieve a prescribed range of steps/day through self-selected activity which was monitored weekly by daily pedometer records and exercise logs. RT underwent a condition in which periodized resistance training was 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 experimental weeks -0 (pre-intervention), -6 (mid-intervention), and -13 (post-intervention) during which times testing procedures for RMR, body composition (dual-x-ray absorptiometry), and isokinetic and isometric muscular strength were administered in addition to blood collection. Isotonic muscular strength was assessed via one-repetition maximum (1RM) testing for select exercises on experimental weeks -1 (pre-strength test), -6 (mid-strength test), and -13 (post-strength test) at the training facility. Furthermore, participants visited the Bariatric Center on a designated time and day each week (i.e. clinical visit) for the entire 12-week intervention period to meet with investigators, a bariatric physician, and/or registered dietician for weigh-ins, clinic-based assessments for body composition and RMR, medical screening, group- and individual-based counseling, and acquire a single week’s worth of dietary products (i.e. meal-replacement formulas plus whey protein supplements). Lipid and metabolic panels were examined from medical chart reviews of pre- and post-intervention blood tests. Details regarding experimental protocols and testing procedures are described below.

Figure 3.1. Timeline of 14-week experimental period (1 week pre-test + 12-week intervention period + 1 week post-test). Laboratory visits were scheduled at experimental weeks 0, 6, and 13 for pre-, mid-, and post-intervention testing, respectively. 1RM tests were administered at weeks 1, 6, and 13 at the training facility. Participants were required to attend the weekly clinical visit at the Bariatric Center from experimental weeks 1-12. All participants underwent the control medical dietary treatment (i.e. Optifast® + whey protein supplement) from weeks 1-12. Also during weeks 1-12: CON underwent the standard treatment control condition and RT received the periodized resistance training intervention which was incorporated into the standard treatment.
3.2.3 Control Dietary Condition

3.2.3.1 Modified VLCD with whey protein supplementation. All participants underwent the control dietary condition (i.e. Optifast® + whey protein supplement) from experimental weeks 1-12 as part of a medically supervised weight-management program for clinically obese patients at the TMH Bariatric Center (Table 1). 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 5 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 40g 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. Justification for supplementary whey protein was three-fold: 1) as a clinical-based recommendation, whey protein supplementation was intended to provide appropriate nutrient provision for exercise during VLCD conditions; 2) to sufficiently support an anabolic response in muscle to a resistance training stimulus, previous data suggested that a dietary intake of at least 1,000-1,500 kcals/day and high protein intake (~150 g/day) would be necessary; and 3) given the known detriments of prolonged VLCD treatment to lean tissue and metabolic rate, it would have been unethical to deny high-risk patients of any treatment of potential benefit during the weight-loss program. Meals were separated by approximately 3 hours each day with the first serving consumed within 1 hour of waking. 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. During the weekly clinical visit (described below), participants’ dietary compliance was monitored and reinforced by a bariatric physician and/or registered dietician via weekly inspection of dietary records as well as group- and individual-based consultations. Adherence to the dietary program was questioned if weight-loss was less than 2 lbs (~1 kg) per week, which was a clinical standard enforced by the bariatric physician and registered dietician. At the end of each clinical visit, participants obtained a week’s worth of control diet products, which included meal-replacement formulas and whey protein supplements.
Table 3.1. Daily meal configuration and macronutrient composition for control dietary condition. All participants consumed 5 meals a day. Each meal consisted of one Optifast® meal-replacement product. Meals 2 and 4 included a 40 g serving of a pure whey protein supplement. The control dietary condition provided each day: 1120 kcals, 150 g of protein (PRO), 100 g of carbohydrate (CHO), 15 g of fat, and 100% of the Daily Value for 24 vitamins and minerals. Participants underwent the control dietary condition from experimental weeks 1-12.

<table>
<thead>
<tr>
<th>MEAL</th>
<th>DAILY DIET COMPOSITION</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>OPTIFAST</td>
</tr>
<tr>
<td>2</td>
<td>OPTIFAST</td>
</tr>
<tr>
<td>3</td>
<td>OPTIFAST</td>
</tr>
<tr>
<td>4</td>
<td>OPTIFAST</td>
</tr>
<tr>
<td>5</td>
<td>OPTIFAST</td>
</tr>
<tr>
<td></td>
<td>kcal</td>
</tr>
<tr>
<td></td>
<td>800</td>
</tr>
<tr>
<td></td>
<td>320</td>
</tr>
<tr>
<td>TOTALS</td>
<td>1120</td>
</tr>
</tbody>
</table>

3.2.4 Strength Testing and Control and Experimental Exercise Protocols

3.2.4.1 Familiarization and strength testing. All participants underwent 2 separate sessions for familiarization and pre-intervention strength testing during experimental week 1. All familiarization, strength testing, and resistance training sessions were administered and monitored by a certified strength and conditioning specialist. Immediately following pre-intervention laboratory testing at experimental week 0, participants were informed on details regarding the initial strength testing session, which included safety considerations and expected outcomes. At experimental 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 to evaluate isotonic muscular strength (appendix D) and was adapted and slightly modified from a previous protocol. One-repetition maximum was defined herein as the greatest load that can be moved through the entire range of motion properly for no more than 1 complete repetition for a given exercise. Investigators administered the 1RM test on large scaled weight-stack exercise machines that provided load increments of approximately 5 lbs. One-repetition maximum measurements were obtained from 2 representative exercises for overall upper (1RM_{upper}) and lower body (1RM_{lower}) strength. This included the chest and leg press exercises. These particular machine-based exercises were appropriate and safe to be tested on for 1RM. Participants began testing with ten minutes of self-paced walking. This was followed by an exercise-specific warm-up set of 5-10 repetitions at 40-60% of estimated 1RM. After resting 1 minute, participants completed 3-5 repetitions at 60-80% of estimated 1RM. Participants rested 1 minute and then attempted 90% of estimated 1RM as their first trial. If successful, investigators increased the load based on the participant’s perception of the previous
attempt; if unsuccessful, the last successful load defined the participant’s 1RM. Investigators determined 1RM within 3-5 trials between which participants were provided 3-5 minutes of rest. A rest period of 5 minutes was provided between 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 at least the 2 exercises aforementioned. Thus, additional strength tests were performed for 8 exercises that were also administered as part of the programmed resistance training intervention, but were not included in the assessment of isotonic muscular strength. Due to the potential risk for untrained participants to lift maximal loads on novel exercises involving small muscle groups and the use of free-weights and cables, a 10RM testing protocol was employed as a more suitable alternative to the 1RM assessment. The 10RM was defined here as the greatest load that can be moved through the entire range of motion for no more than 10 repetitions total. The 10RM was determined through the following testing protocol which was previously administered in untrained and/or obese participants$^{254,273}$: 1) Participants performed 1 set of 10 repetitions against a light load that was perceived by both the participant and investigator to permit 12-15 repetitions; 2) a second set of 10 repetitions with a slightly greater load was then administered; 3) the load was then increased to a cautious estimate of the participants’ 10RM during which time participants attempted a total of 10 repetitions as their first trial; and 4) if the trial was successful, investigators progressed the load based on the participants’ perception of the previous attempt; if unsuccessful, the last successfully executed load defined the participants’ 10RM. Investigators determined the participants’ 10RM within 3-5 trials, which was each separated by 5 minutes of rest. The Baechle equation$^{274}$ 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. It is important to note that 10RM or extrapolated 1RM values were not included for statistical analysis. These measurements exclusively served to provide reference for resistance training programming for those exercises not included in the 1RM test. The 1RM test was repeated at weeks -6 and -13 for mid- and post-intervention measures of isotonic muscular strength, respectively.
3.2.4.2 Standard treatment control condition. CON was instructed to perform general physical activity from experimental weeks 1-12. A self-paced protocol was implemented to simulate the Optifast® 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 8,000-12,000 steps/day, which are BMI-referenced cut-points established by previous data. 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. Physical activity logs were collected and evaluated by investigators during each weekly clinical visit. Participants were oriented during the initial clinical visit at the start of experimental week 1.

3.2.4.3 Periodized resistance training condition. Periodized resistance training was initiated in RT on experimental week 2 at the training facility. The proposed resistance training protocol was designed in reference to the guidelines recommended by the American College of Sports Medicine (ACSM) and National Strength and Conditioning Association (NSCA) for resistance exercise. The proposed periodization scheme was generally based on previous experimental models that showed optimal effectiveness in terms of neuromuscular adaptations to resistance training. In addition, the proposed training protocol was tailored to be specific and appropriate for the sedentary, clinically obese population to ensure foremost participant safety. Participants underwent periodized resistance training bouts integrated into the standard treatment (described in 3.11.2) on 3 non-consecutive days per week (on non-testing weeks) during the 12-week intervention period. A minimum of 48 hours of rest separated each training session to allow adequate recovery for participants. Participants were encouraged to exercise 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, each designated at individual workout stations (appendix H). Participants performed 6 upper body and 4 lower body bilateral exercises interchangeably. A 1.5- to 3.0-minute rest period was provided between each exercise during which time investigators monitored heart rate (HR) via radial artery palpation to ensure that participants were within a safe range to resume exercise. Table 2 outlines the timetable and systematic manipulations of resistance training.
variables for each session across the experimental period. The protocol incorporated programmed variations in training intensity (load) and volume (sets x repetitions) that adhered to the Linear and Daily Undulating Periodization models. The 12-week training period, i.e. macrocycle, encompassed two individual training cycles or mesocycles. The first mesocycle was administered from experimental weeks 2 through 6 after the familiarization/strength testing week. Within this first mesocycle, participants underwent two, 2-week training phases, i.e. microcycles, followed by one tapering session at the start of week 6. After the taper session in week 6, participants underwent mid-intervention 1RM strength testing two days later. The second mesocycle was applied from experimental weeks 7 through 12. Within this second mesocycle, participants underwent two 2-week microcycles, one 1-week microcycle, and one week of taper in sequential order. After this taper week at week 12, participants underwent post-intervention 1RM strength testing at the start of week 13. Within each microcycle, training intensity and volume undulated from one session to the next, reflecting the Daily Undulating Periodization format. Moreover given the length of the training period, overall intensity range progressively increased each successive microcycle, thereby integrating the Linear Periodization model into the program. Absolute training loads for any given percentage of 1RM was readjusted for the second mesocycle based on 1RM values obtained from mid-intervention strength testing at experimental week 6. Before each training session, investigators monitored blood pressure to ensure the subject was safe to commence exercise. Also, investigators took precautionary measures for blood glucose control before and after exercise according to recommendations from the subject’s physician. A standard workout log was used to document training variables by investigators during each training session and signed by participants at the completion of the bout.
3.2.5 Weekly Clinical Visit

All clinical visits were held on Monday from 4:00pm to 6:30pm each week at the TMH Bariatric Center throughout the entire 12-week intervention period. During each visit, participants underwent clinic-based assessments for anthropometric parameters, body composition, and RMR as well as evaluation of dietary and exercise logs (described below). In addition, participants attended a 1-hour group education class led by a registered dietician who reinforced dietary compliance, provided guidance, and addressed any inquiries from the participants. For the first clinical visit, participants met individually with the bariatric physician prior to class for medical screening, inspection of dietary and exercise records, individualized treatment counseling, and evaluation of treatment compliance. After the initial clinical visit, the bariatric physician met with participants every 3 weeks for the remainder of the experimental period for the same purposes aforementioned. However, the bariatric physician was available during each clinical visit to address any inquiries or concerns from participants. During each clinical visit, dietary and exercise records were collected and evaluated by the investigator. Also, starting from the first clinical visit, participants were seen by a registered nurse for

<table>
<thead>
<tr>
<th>Day</th>
<th>RT Variable</th>
<th>WK 1</th>
<th>WK 2</th>
<th>WK 3</th>
<th>WK 4</th>
<th>WK 5</th>
<th>WK 6**</th>
<th>WK 7</th>
<th>WK 8</th>
<th>WK 9</th>
<th>WK 10</th>
<th>WK 11</th>
<th>WK 12</th>
<th>WK 13</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Sets</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>3</td>
<td>1</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>4</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Reps</td>
<td>12</td>
<td>12</td>
<td>8</td>
<td>8</td>
<td>RM</td>
<td>12</td>
<td>12</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>8</td>
<td>RM</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Load (%1RM)</td>
<td>65</td>
<td>65</td>
<td>75</td>
<td>75</td>
<td>90</td>
<td>65</td>
<td>65</td>
<td>70</td>
<td>70</td>
<td>70</td>
<td>75</td>
<td>85</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Sets</td>
<td>3</td>
<td>3</td>
<td>4</td>
<td>4</td>
<td>No Training</td>
<td>No Training (Lab testing)</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>5</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Reps</td>
<td>10</td>
<td>10</td>
<td>6</td>
<td>6</td>
<td>No Training</td>
<td>No Training (Lab testing)</td>
<td>10</td>
<td>10</td>
<td>8</td>
<td>8</td>
<td>6</td>
<td>RM</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Load (%1RM)</td>
<td>70</td>
<td>70</td>
<td>80</td>
<td>80</td>
<td>No Training</td>
<td>No Training (Lab testing)</td>
<td>70</td>
<td>70</td>
<td>75</td>
<td>75</td>
<td>80</td>
<td>90</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Sets</td>
<td>3</td>
<td>3</td>
<td>4</td>
<td>4</td>
<td>Mid-Strength testing</td>
<td>Mid-Strength testing</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>5</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Reps</td>
<td>8</td>
<td>8</td>
<td>4</td>
<td>4</td>
<td>Mid-Strength testing</td>
<td>Mid-Strength testing</td>
<td>8</td>
<td>8</td>
<td>6</td>
<td>6</td>
<td>4</td>
<td>RM</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Load (%1RM)</td>
<td>75</td>
<td>75</td>
<td>85</td>
<td>85</td>
<td>Mid-Strength testing</td>
<td>Mid-Strength testing</td>
<td>75</td>
<td>75</td>
<td>80</td>
<td>80</td>
<td>85</td>
<td>95</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Familiarize + Testing</td>
<td>Microcycle 1</td>
<td>Microcycle 2</td>
<td>Taper + Testing</td>
<td>Microcycle 1</td>
<td>Microcycle 2</td>
<td>Microcycle 3</td>
<td>Taper + Testing</td>
<td>Mesocycle 1</td>
<td>Mesocycle 2</td>
<td>12-Week Macrocycle</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 3.2. Timetable and periodization format of resistance training protocol from experimental weeks 1-12. WK = week; RT = resistance training; RM = maximum repetitions until failure. ** 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.
assessment of vital signs and blood collection every other week during the experimental period. It must be noted, however, that nurse visitations were exclusive from the study and served clinical purposes only as part of the normal patient treatment at the Bariatric Center. At the end of each clinical visit, participants obtained a week’s worth of dietary products, which included Optifast® formulas and whey protein supplements.

3.2.5.1 Assessment procedures for weekly clinical visit. Data acquired from the weekly clinic-based assessments for anthropometric parameters (BW and WC), body composition, and RMR ($RMR_{clinic}$) (bi-weekly) were analyzed as secondary outcome measures to that obtained from pre-, mid-, and post-intervention laboratory tests (appendix F). Data collected from weekly assessments primarily served to longitudinally map the week-to-week course of morphometric and metabolic changes that occurred in response to the experimental conditions. The following protocols were typical clinic-based assessments during medically monitored weight-loss programs. Body composition (two-compartment model) was measured via bioelectrical impedance (BIA) using an FDA-approved medical body composition analyzer (Tanita TBF-310; Arlington Heights, Illinois, USA) which was also equipped with a bodyweight scale. This analysis provided measurements for BW, BMI, BF%, $FM_{BIA}$, FFM and FFM%. FFM was defined herein as body mass comprised of muscle, organ, and bone and was calculated as follows ($FFM=BW- FM_{BIA}$). Participants were also measured for WC using protocols previously described\textsuperscript{57}. $RMR_{clinic}$ was measured bi-weekly using an FDA-approved handheld indirect calorimeter (MedGem; Microlife Medical Home Solutions; Golden, CO, USA) through the following manufacturer-recommended procedures: 1) the participant rested for 15 minutes in the supine position in a quiet and dimly lit examination room; 2) the investigator prepared the handheld calorimeter with a new single-use mouthpiece; 3) the participants’ nostrils were sealed closed by a nose-clip; 4) the investigator started the device and then passed it to the participant while providing verbal instructions; 5) the participant inserted the mouthpiece and breathed normally while in a supine resting position for approximately 5 minutes; and 6) once the device indicated test completion, the investigator discarded the mouthpiece and recorded the RMR value (kcals) displayed on the device. Given that the device was limited to the measurement of oxygen consumption and not carbon dioxide production, no respiratory quotient (RQ) was computed. Instead, a constant RQ of 0.85 was assumed and used to derive $RMR_{clinic}$ from the
abbreviated Weir Equation: RMR= [(3.941)(VO
$_2$) + (1.106)(VO$_2$)(RQ)]$^{276}$. Previous data have been documented to show reliability and validity of this device and protocol in the measurement of RMR$^{277-279}$. Participants were instructed to abstain from exercise and eating within 4 hours of the assessments; therefore, meals and exercise were scheduled appropriately around the clinical visit (i.e. Mondays, 4:00pm-6:30pm).

3.2.6 Laboratory Testing Procedures

Laboratory testing was scheduled during experimental weeks -0 (pre-intervention), -6 (mid-intervention), and -13 (post-intervention). Participants reported to the Human Performance Laboratory at Florida State University between 6:00am and 11:00am following an 8-hour fast and 48 hours of no strenuous physical activity. Testing protocols were administered in the following order: 1) height and body weight; 2) RMR; 3) body composition; 4) blood draw; and 5) dynamic and static muscular contractile kinetics (appendix E). Participants were instructed to bring a single serving of the meal-replacement formula to ingest following blood collection and prior to isokinetic muscle testing.

3.2.6.1 Resting metabolic rate and fat oxidation. The primary measurement of RMR was acquired using the dilution technique and an open-circuit indirect calorimeter (ParvoMedics TrueOne® 2400; Salt Lake City, Utah, USA)$^{24,280}$. 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 minutes, participants laid quietly in the supine position on a cushioned bed to achieve true resting conditions. Data were not collected during this time. Subsequently, the participant’s head and upper torso was enclosed and sealed under a ventilated hood apparatus which was interfaced to the metabolic measurement system through a corrugated plastic tube. The dilution technique for RMR testing included the use of a dilution pump which mechanically drew ambient air into the ventilated hood. Ambient air then diluted expiratory air from the participant. The pump then pulled the diluted air from the hood into the mixing chamber for O$_2$ and CO$_2$ analysis. Mean oxygen uptake (VO$_2$) and carbon dioxide output (VCO$_2$) was measured for 20 minutes with the first 5 minutes of data excluded. During the initial 5 minutes, the dilution pump was adjusted to a dilution rate eliciting an expired CO$_2$ concentration of approximately 1%. Data acquired during the subsequent 15 minutes were
used to compute RMR according to the Weir equation and was expressed in total daily energy expenditure (kcal/day). Criteria for a valid RMR were a minimum of 15 minutes of steady state, determined as a <10% and <5% fluctuation in VO\(_2\) and respiratory quotient (RQ), respectively. Additional time was applied to the protocol in the event a 15-minute steady state was not observed. Based on recorded gas exchange rates (liters/min), fat oxidation (FO) was derived from the following equation with the assumption that urinary nitrogen excretion was negligible: FO (g/min) = 1.689(VO\(_2\)) – 1.689(VCO\(_2\))\(^{281}\). Prior to each test, calibration procedures were conducted for the flow meter using a 3.0 liter syringe and for the gas analyzer with verified gases of known concentrations\(^{281}\).

3.2.6.2 Total and regional body composition. Total and regional body composition was measured by dual-energy x-ray absorptiometry (DXA) (Lunar iDXA, GE Healthcare, Madison, WI) which is a safe and reliable assessment that has been previously implemented in special subject populations\(^{24,283,284}\). DXA scans were typically 7-10 minutes in duration and non-invasive with marginal radiation exposure. Total body mass (TBM) was quantified through the scan. A 3-compartment model of body composition was applied through which FM (g), LBM (i.e. LBM = TBM – FM – bone mineral content) (g), and bone mineral content (BMC) (g) was analyzed for the whole body and regions of interest (ROI). The ROI included the extremities (legs and arms), android region, gynoid region, and trunk. Data for body fat percentage (BF%) and bone-mineral density (BMD, g/cm\(^2\)) were also acquired from DXA measurements. Appendicular skeletal muscle mass (ASM) was obtained from the sum of LBM in the arms and legs. The ASM was then used to determine the ASM index (ASM / height in m\(^2\)), which has been previously applied as a proxy for whole-body skeletal muscle mass\(^{285,286}\). The DXA machine was calibrated before each scan using a manufacturer-provided phantom. All DXA measurements and analyses were conducted by a single certified technician who was blind to the participant’s experimental treatment condition.

3.2.6.3 Biochemical markers. A 10 ml sample of venous blood was drawn from the antecubital vein via sterile venipuncture techniques. For each draw, blood was collected in a serum-separating tube. Samples were allowed to clot for 30 minutes at room temperature and then centrifuged for 15 minutes at 3500 rpm to obtain serum. After separation, resultant
supernatant was aliquoted into labeled microtubes and stored at -20° C until analysis. Serum concentration 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), was analyzed via enzyme-linked immunosorbent assay (ELISA) to elucidate biochemical factors mediating any morphometric adaptations in lean tissue. 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.

3.2.6.4 Dynamic and static contractile kinetics. Isokinetic and isometric muscular 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). Knee dynamometry testing was preceded by a 5 minute warm-up activity consisting of a low-speed treadmill walk. Participants were then seated comfortably on the dynamometer chair, with the hip joint positioned at approximately 90° of flexion. The dynamometer lever arm specific for the participant’s dominant leg was attached 2-3 cm above the lateral malleolus. To minimize extraneous bodily movements during contractions and therefore to avoid contributions from non-tested muscle groups, straps were securely fastened across the participant’s chest, pelvis, and mid-thigh of the tested limb. The participant’s lateral femoral epicondyle was aligned with the center of rotation of the dynamometer attachment. Prior to each test, the dynamometer underwent auto-calibration and torque acquisition was gravity-corrected by an intrinsic device within the dynamometer. Participants performed each contraction with arms across the chest with each hand grasping the opposite shoulder. Isokinetic testing was administered on the participants’ 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. The greatest peak torque (Nm) and average power (W) values obtained from the three trials were used for further analysis for both the extensors and flexors. Isometric testing was administered on the dominant limb with the dynamometer arm fixed to allow 60° of static knee flexion, which has been shown to be the optimum joint angle for maximal isometric torque production\textsuperscript{232,292,293}. 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. The greatest isometric peak torque (Nm) value acquired from all trials for both extensors and flexors was used for analysis. Data were computed from manufacturer acquisition software and evaluated as absolute and normalized (i.e. to TBM and LM) values.

3.2.7 Analysis of Data

All values are presented as mean ± standard error (SE). A one-way ANOVA was used to compare mean differences for all baseline descriptive measures. Data collected from laboratory visits (i.e. body composition via DXA, RMR via ventilated hood technique, muscular strength, and biomarkers) were analyzed using a 2 (group) x 3 (time) repeated measures ANOVA. Relative and absolute changes over the experimental period were calculated for all dependent variables and analyzed by one-way ANOVA. Data collected during weekly clinical visits (i.e. BW, WC, and body composition via BIA) were analyzed by a 2 (group) x 13 (time) repeated measures ANOVA, while RMR\textsubscript{climic} via MedGem analysis was analyzed using a 2 (group) x 7 (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\textsuperscript{12} for Windows (StatSoft; Tulsa, OK, USA) with significance set at p<0.05.
CHAPTER FOUR

RESULTS

4.1 Specific Aim 1 (Retrospective Study)

4.1.1 Descriptive Variables

Mean values and standard errors (SE) of descriptive variables for all study cohorts (i.e. total, gender, and age-group) are reported in Table 4.1. Main gender effects indicated significantly (p<0.05) greater body weight (BW) (+24.1 kg), height (+16.4 cm), waist circumference (WC) (+13.2), fat free mass (FFM) (+23.9 kg), FFM percentage (FFM%) (+8.1%), and RMR estimate (+693.3 kcal/day) and lower body fat percentage (BF%) (-7.8 %) in males compared to females at pre-treatment. Mean age was significantly (p<0.05) different between age-groups as the young cohort was 13.4 years younger than the old. The young age-group was significantly (p<0.05) taller (+5.8 cm) and had significantly (p<0.05) less FM BIA (-11.4 kg) than the old at pre-treatment.

Table 4.1. Mean values for descriptive variables for total, gender, and age cohorts. BW= body weight, FM BIA= fat mass measured by bioelectrical impedance, FFM= fat free mass measured by bioelectrical impedance, BF%= body fat percentage, FFM%= fat free mass percentage, BMI= body mass index, WC= waist circumference, RMR estimate = estimated resting metabolic rate. Age cohort split above and below median age (57yrs), i.e. Young= age < 57; Old= age ≥57. Values reported as mean (SE).

<table>
<thead>
<tr>
<th></th>
<th>TOTAL (N=32)</th>
<th>MALE (n=16)</th>
<th>FEMALE (n=16)</th>
<th>YOUNG (n=16)</th>
<th>OLD (n=16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>58.1 (1.5)</td>
<td>58.5 (2.3)</td>
<td>57.6 (2.1)</td>
<td>51.4 (1.1)^</td>
<td>64.8 (1.6)^</td>
</tr>
<tr>
<td>BW (kg)</td>
<td>131.2 (4.2)</td>
<td>143.2 (4.2)^</td>
<td>119.1 (6.1)^</td>
<td>137.4 (5.2)</td>
<td>124.9 (6.5)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>169.0 (1.9)</td>
<td>177.2 (1.4)^</td>
<td>160.8 (2.1)^</td>
<td>171.9 (3.0)^</td>
<td>166.1 (2.2)^</td>
</tr>
<tr>
<td>BMI (kg/m^2)</td>
<td>45.8 (1.3)</td>
<td>45.6 (1.3)</td>
<td>46.1 (2.3)</td>
<td>46.6 (1.7)</td>
<td>45.1 (2.0)</td>
</tr>
<tr>
<td>WC (cm)</td>
<td>137.6 (2.6)</td>
<td>144.2 (2.7)^</td>
<td>131.0 (3.8)^</td>
<td>138.3 (3.1)</td>
<td>137.0 (4.2)</td>
</tr>
<tr>
<td>FM BIA (kg)</td>
<td>62.1 (2.7)</td>
<td>62.2 (3.4)</td>
<td>62.0 (4.3)</td>
<td>67.8 (3.4)^</td>
<td>56.4 (3.7)^</td>
</tr>
<tr>
<td>FFM (kg)</td>
<td>69.1 (2.9)</td>
<td>81.0 (3.2)^</td>
<td>57.1 (2.2)^</td>
<td>69.6 (3.5)</td>
<td>68.5 (4.6)</td>
</tr>
<tr>
<td>BF% (%)</td>
<td>47.2 (1.3)</td>
<td>43.3 (1.8)^</td>
<td>51.1 (1.4)^</td>
<td>49.4 (1.6)</td>
<td>44.9 (1.9)</td>
</tr>
<tr>
<td>FFM% (%)</td>
<td>52.7 (1.3)</td>
<td>56.8 (1.8)^</td>
<td>48.7 (1.4)^</td>
<td>50.6 (1.7)</td>
<td>54.9 (2.0)</td>
</tr>
<tr>
<td>RMR estimate (kcal/day)</td>
<td>2173.5 (76.6)</td>
<td>2520.1 (66.3)^</td>
<td>1826.8 (61.7)^</td>
<td>2282.0 (101.3)</td>
<td>2064.9 (111.3)</td>
</tr>
</tbody>
</table>
4.1.2 Weekly Weight-Loss Trajectory

For the total sample, there was a significant (p<0.05) time effect for BW (Table 4.2). Post hoc analysis revealed BW at weeks 2, 3, and 4 to be significantly (p<0.05) less than preceding weeks (Figure 4.1). For each week thereafter, BW was significantly (p<0.05) less than the previous weeks, excluding the respective week prior (e.g. week 5 significantly different from weeks 1-3 but not week 4) (Figure 4.1).

All study cohorts (i.e. total, gender, and age-group) demonstrated a significant (p<0.05) time effect for change from initial BW (BW-change) (Table 4.1). The mean BW-change across the entire treatment period was -22.5±1.4 kg (p=0.0001) for the total sample, -26.0±2.1 kg (p=0.0002) for males, -18.9±1.3 kg (p=0.0002) for females, -23.7±1.8 kg (p=0.0002) for the young age-group, and -21.2±2.2 (p=0.0002) for the old age-group. Significant (p<0.05) differences among weekly time-points for BW-change are displayed in Figure 4.2 for gender cohorts and Figure 4.3 for age cohorts. A gender by time interaction showed males exhibiting a greater BW-change from pre-treatment compared to females at weeks 12 (-24.5±1.7 vs. -17.7±1.3 kg; p=0.02) and 13(-26.0±2.1 vs. -18.9±1.3 kg; p=0.03) (Table 4.2; Figure 4.2). No significant age-group by time interaction was detected (Table 4.2; Figure 4.3) for BW-change.

Table 4.2. Weekly mean values for bodyweight (BW), absolute change (Δ) from initial BW for total and gender cohorts, and body mass index (BMI). Values reported as mean (SE).

<table>
<thead>
<tr>
<th>WEEK</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>12</th>
<th>13</th>
</tr>
</thead>
<tbody>
<tr>
<td>BW (kg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>131.2</td>
<td>127.7*</td>
<td>125.1*</td>
<td>122.4*</td>
<td>120.5*</td>
<td>118.7*</td>
<td>117.2*</td>
<td>115.8*</td>
<td>114.3*</td>
<td>113.0*</td>
<td>111.5*</td>
<td>110.1*</td>
<td>108.7*</td>
</tr>
<tr>
<td></td>
<td>(4.2)</td>
<td>(4.1)</td>
<td>(4.0)</td>
<td>(3.9)</td>
<td>(3.9)</td>
<td>(3.9)</td>
<td>(3.9)</td>
<td>(3.8)</td>
<td>(3.9)</td>
<td>(3.8)</td>
<td>(3.9)</td>
<td>(3.9)</td>
<td>(3.9)</td>
</tr>
<tr>
<td>Δ BW -Total (kg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.0</td>
<td>-3.5*</td>
<td>-6.1*</td>
<td>-8.7*</td>
<td>-10.7*</td>
<td>-12.4*</td>
<td>-14.0*</td>
<td>-15.4*</td>
<td>-16.9*</td>
<td>-18.2*</td>
<td>-19.7*</td>
<td>-21.1*</td>
<td>-22.5*</td>
</tr>
<tr>
<td></td>
<td>(0.0)</td>
<td>(0.4)</td>
<td>(0.5)</td>
<td>(0.6)</td>
<td>(0.7)</td>
<td>(0.8)</td>
<td>(0.9)</td>
<td>(1.0)</td>
<td>(1.1)</td>
<td>(1.1)</td>
<td>(1.2)</td>
<td>(1.2)</td>
<td>(1.4)</td>
</tr>
<tr>
<td>Δ BW -Male (kg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.0</td>
<td>-4.2*</td>
<td>-7.1*</td>
<td>-10.2*</td>
<td>-12.5*</td>
<td>-14.5*</td>
<td>-16.3*</td>
<td>-18.1*</td>
<td>-20.0*</td>
<td>-21.3*</td>
<td>-22.9*</td>
<td>-24.5*</td>
<td>-26.0*</td>
</tr>
<tr>
<td></td>
<td>(0.0)</td>
<td>(0.6)</td>
<td>(0.9)</td>
<td>(0.8)</td>
<td>(0.9)</td>
<td>(1.1)</td>
<td>(1.3)</td>
<td>(1.3)</td>
<td>(1.5)</td>
<td>(1.5)</td>
<td>(1.7)</td>
<td>(1.7)</td>
<td>(2.1)</td>
</tr>
<tr>
<td>Δ BW -Female (kg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.0</td>
<td>-2.7*</td>
<td>-5.1*</td>
<td>-7.3*</td>
<td>-8.8*</td>
<td>-10.3*</td>
<td>-11.7*</td>
<td>-12.6*</td>
<td>-13.8*</td>
<td>-14.7*</td>
<td>-16.4*</td>
<td>-17.8*</td>
<td>-18.9*</td>
</tr>
<tr>
<td></td>
<td>(0.0)</td>
<td>(0.4)</td>
<td>(0.5)</td>
<td>(0.7)</td>
<td>(0.8)</td>
<td>(0.9)</td>
<td>(1.0)</td>
<td>(1.0)</td>
<td>(1.1)</td>
<td>(1.1)</td>
<td>(1.2)</td>
<td>(1.3)</td>
<td>(1.3)</td>
</tr>
<tr>
<td>Δ BW -Young (kg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.0</td>
<td>-3.6*</td>
<td>-6.8*</td>
<td>-9.5*</td>
<td>-11.8*</td>
<td>-13.7*</td>
<td>-15.6*</td>
<td>-17.0*</td>
<td>-18.5*</td>
<td>-19.8*</td>
<td>-21.2*</td>
<td>-22.5*</td>
<td>-23.7*</td>
</tr>
<tr>
<td></td>
<td>(0.0)</td>
<td>(0.4)</td>
<td>(0.7)</td>
<td>(0.8)</td>
<td>(0.9)</td>
<td>(1.0)</td>
<td>(1.2)</td>
<td>(1.4)</td>
<td>(1.5)</td>
<td>(1.5)</td>
<td>(1.6)</td>
<td>(1.7)</td>
<td>(1.8)</td>
</tr>
<tr>
<td>Δ BW -Old (kg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.0</td>
<td>-3.3*</td>
<td>-5.4*</td>
<td>-7.9*</td>
<td>-9.5*</td>
<td>-11.1*</td>
<td>-12.4*</td>
<td>-13.7*</td>
<td>-15.3*</td>
<td>-16.8*</td>
<td>-18.1*</td>
<td>-19.7*</td>
<td>-21.2*</td>
</tr>
<tr>
<td></td>
<td>(0.0)</td>
<td>(0.7)</td>
<td>(0.8)</td>
<td>(0.9)</td>
<td>(1.0)</td>
<td>(1.1)</td>
<td>(1.3)</td>
<td>(1.3)</td>
<td>(1.5)</td>
<td>(1.5)</td>
<td>(1.7)</td>
<td>(1.8)</td>
<td>(2.2)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>45.8</td>
<td>44.6*</td>
<td>43.7*</td>
<td>42.8*</td>
<td>42.1*</td>
<td>41.6*</td>
<td>41.0*</td>
<td>40.5*</td>
<td>40.0*</td>
<td>39.5*</td>
<td>39.0*</td>
<td>38.5*</td>
<td>38.1*</td>
</tr>
<tr>
<td></td>
<td>(1.27)</td>
<td>(1.25)</td>
<td>(1.23)</td>
<td>(1.22)</td>
<td>(1.22)</td>
<td>(1.23)</td>
<td>(1.24)</td>
<td>(1.25)</td>
<td>(1.25)</td>
<td>(1.3)</td>
<td>(1.3)</td>
<td>(1.3)</td>
<td>(1.3)</td>
</tr>
</tbody>
</table>
Figure 4.1. Weekly bodyweight measurements for total sample. Values reported as mean ± SE. Numerical ranges indicate prior weekly time-points in which mean bodyweight was significantly different (p<0.05).

Figure 4.2. Weekly bodyweight-change from pre-treatment for males and females. Values are reported as mean ± SE. Numerical ranges indicate prior weekly time-points in which BW-change from pre-treatment was significantly different (p<0.05).
* Significant gender by time interaction (p<0.05)
Figure 4.3. Weekly bodyweight-change from pre-treatment for age-groups. Values are reported as mean ± SE. Numerical ranges indicate prior weekly time-points in which BW-change from pre-treatment was significantly different (p<0.05).

Figure 4.4. Weekly body mass index (BMI) for total sample. Values are reported as mean ± SE. Numerical ranges indicate prior weekly time-points in which BMI was significantly different (p<0.05).
There was a significant (p<0.05) time effect for BMI in all study cohorts with no significant time interactions detected for gender or age-group (Table 4.2). Post hoc comparisons of weekly time-points demonstrating a main effect (p<0.05) for BMI are displayed in Figure 4.4.

4.1.3 Pre- and Post-Treatment Body Composition, Anthropometric, and RMR Measures

4.1.3.1 Total sample. There was a significant (p<0.05) time effect for all body composition and anthropometric variables as well as RMRestimate (Table 4.3). Participants exhibited a significant (p=0.0001) decrease in BW (-22.2±1.4 kg), FM_{BIA} (-16.6±1.4 kg), FFM (-5.6±0.9 kg), BF% (-6.0±0.9 %), BMI (-7.7±0.5 kg/m^2), WC (-18.4±1.3 cm), and RMRestimate (-269.6±22.5 kcal/day) from pre- to post-treatment. There was a significant (p=0.0001) increase in FFM% (+6.1±0.9 %).

<table>
<thead>
<tr>
<th>Table 4.3. Pre- and post-treatment means for body composition and anthropometric measures as well as estimated resting metabolic rate (RMRestimate) for total sample. BW= body weight, FM_{BIA}= fat mass measured by bioelectrical impedance, FFM= fat free mass measured by bioelectrical impedance, BF%= body fat percentage, FFM%= fat free mass percentage, BMI= body mass index, WC= waist circumference. ∆= mean absolute change from pre- to post-intervention. Values reported as mean (SE). * Significantly different than Pre (p&lt;0.05)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TOTAL (N= 32) Pre</td>
</tr>
<tr>
<td>BW (kg)</td>
</tr>
<tr>
<td>FM_{BIA} (kg)</td>
</tr>
<tr>
<td>FFM (kg)</td>
</tr>
<tr>
<td>BF% (%)</td>
</tr>
<tr>
<td>FFM% (%)</td>
</tr>
<tr>
<td>BMI (kg/m^2)</td>
</tr>
<tr>
<td>WC (cm)</td>
</tr>
<tr>
<td>RMRestimate (kcal/day)</td>
</tr>
</tbody>
</table>

4.1.3.2 Gender and age cohorts. Both males and females demonstrated a significant (p<0.05) time effect for all body composition and anthropometric variables as well as RMRestimate (Table 4.4). Males exhibited a significant (p=0.0002) decrease in BW (-25.5±2.3 kg), FM_{BIA} (-19.5±2.2 kg), FFM (-6.0±1.7 kg), BF% (-7.5±1.3%), BMI (-8.1±0.7 kg/m^2), WC (-18.1±1.8 cm), and RMRestimate (-353.1±31.5 kcal/day) with a significant (p=0.0002) increase in FFM%
(+7.4±1.3%) from pre- to post-treatment. Females demonstrated a significant (p<0.05) decrease in BW (-18.8±1.4 kg; p=0.0002), FM_{BIA} (-13.6±1.4 kg; p=0.0001), FFM (-5.1±0.5 kg; 
p=0.0004), BF% (-4.5±1.0%; p=0.001), BMI (-7.4±0.6 kg/m^2; p=0.0002), WC (-18.8±2.0 cm; 
p=0.0002) and RMR_{estimate} (-185.9±13.0 kcal/day) with a significant (p<0.05) increase in FFM% 
(+4.8±1.0%; p=0.0008) from pre- to post-treatment. Males exhibited a significantly greater 
decrease in BW (-25.5±2.3 kg vs. -18.8±1.4 kg; p=0.02), FM_{BIA} (-19.5±2.2 kg vs. -13.6±1.4 kg; 
p=0.02), and RMR_{estimate} (-353.1±31.5 kcal/day vs. -185.9±13.0 kcal/day; p=0.0002) from pre-to-
post compared to females (Table 4.4; Figure 4.5).

Table 4.4. Gender-specific pre- and post-intervention means for body composition and anthropometric measures as well 
as estimated RMR (RMR_{estimate}). BW= body weight, FM_{BIA}= fat mass measured by bioelectrical impedance, FFM= fat free mass 
measured by bioelectrical impedance, BF% = body fat percentage, FFM% = fat free mass percentage, BMI= body mass index, WC= 
waist circumference. Δ = mean absolute change from pre- to post-intervention. Values reported as mean (SE). 
* Significantly different than Pre (p<0.05) 
^ Significantly different between genders (p<0.05)

<table>
<thead>
<tr>
<th></th>
<th>MALE (n= 16)</th>
<th></th>
<th></th>
<th></th>
<th>FEMALE (n= 16)</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre</td>
<td>Post</td>
<td>Δ</td>
<td></td>
<td>Pre</td>
<td>Post</td>
<td>Δ</td>
<td></td>
</tr>
<tr>
<td>BW (kg)</td>
<td>143.2 (4.2)</td>
<td>117.7 (3.9)*</td>
<td>-25.5 (2.3)^</td>
<td></td>
<td>119.1 (6.1)</td>
<td>100.3 (6.5)*</td>
<td>-18.8 (1.4)^</td>
<td></td>
</tr>
<tr>
<td>FM_{BIA} (kg)</td>
<td>62.2 (3.4)</td>
<td>42.7 (3.2)*</td>
<td>-19.5 (2.2)^</td>
<td></td>
<td>62.0 (4.3)</td>
<td>48.3 (4.8)*</td>
<td>-13.6 (1.4)^</td>
<td></td>
</tr>
<tr>
<td>FFM (kg)</td>
<td>81.0 (3.2)</td>
<td>74.9 (2.4)*</td>
<td>-6.0 (1.7)</td>
<td></td>
<td>57.1 (2.2)</td>
<td>52.0 (2.1)*</td>
<td>-5.1 (0.5)</td>
<td></td>
</tr>
<tr>
<td>BF% (%)</td>
<td>43.3 (1.8)</td>
<td>35.7 (1.9)*</td>
<td>-7.5 (1.3)</td>
<td></td>
<td>51.1 (1.4)</td>
<td>46.6 (2.0)*</td>
<td>-4.5 (1.0)</td>
<td></td>
</tr>
<tr>
<td>FFM% (%)</td>
<td>56.8 (1.8)</td>
<td>64.2 (1.9)*</td>
<td>7.4 (1.3)</td>
<td></td>
<td>48.7 (1.4)</td>
<td>53.5 (2.0)*</td>
<td>4.8 (1.0)</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m^2)</td>
<td>45.6 (1.3)</td>
<td>37.5 (1.2)*</td>
<td>-8.1 (0.7)</td>
<td></td>
<td>46.1 (2.3)</td>
<td>38.8 (2.4)*</td>
<td>-7.4 (0.6)</td>
<td></td>
</tr>
<tr>
<td>WC (cm)</td>
<td>144.2 (2.7)</td>
<td>126.0 (2.9)*</td>
<td>-18.1 (1.8)</td>
<td></td>
<td>131.0 (3.8)</td>
<td>112.2 (4.4)*</td>
<td>-18.8 (2.0)</td>
<td></td>
</tr>
<tr>
<td>RMR_{estimate} (kcal/day)</td>
<td>2520.1 (66.3)</td>
<td>2167.1 (60.2)*</td>
<td>-353.1 (31.5)^</td>
<td></td>
<td>1826.8 (61.7)</td>
<td>1640.8 (65.8)*</td>
<td>-185.9 (13.0)^</td>
<td></td>
</tr>
</tbody>
</table>

Both young and old age-groups exhibited a significant (p<0.05) time effect for all body 
composition and anthropometric variables in addition to RMR_{estimate} (Table 4.5). The young age-
group demonstrated a significant decrease in BW (-23.2±1.9 kg; p=0.0002), FM_{BIA} (-19.5±2.2 
kg; p=0.0002), FFM (-3.7±0.7 kg; p=0.008), BF% (-7.6±1.4%; p=0.0002), BMI (-7.9±0.6 kg/m^2; 
p=0.0002), WC (-20.2±2.2 cm; p=0.0002), and RMR_{estimate} (-280.3±31.3 kcal/day; p=0.0002) 
with a significant (p=0.0002) increase in FFM% (+7.6±1.4%) from pre- to post-treatment. The 
old age-group demonstrated a significant decrease in BW (-21.2±2.2 kg; p=0.0002), FM_{BIA} (-13.7±1.4 
kg; p=0.0002), FFM (-7.4±1.5 kg; p=0.0002), BF% (-4.4±0.9%; p=0.002), BMI (-7.6±0.7 kg/m^2; p=0.0002), WC (-16.8±1.3 cm; p=0.0002) and RMR_{estimate} (-258.6±33.2 kcal/day;
p=0.0002) with a significant (p=0.002) increase in FFM% (+4.6±0.9%) from pre- to post-treatment. A age by time interaction showed that the young group had a greater decrease in FM_{BIA} (-19.5±2.2 kg vs. -13.7±1.4 kg; p=0.02) and BF% (-7.6±1.4% vs. -4.4±0.9%; p=0.04) from pre- to post-treatment than the old (Table 4.5; Figure 4.5). The old age-group had a significantly (p=0.02) greater decline in FFM than the young (-7.4±1.5 kg vs. -3.7±0.7 kg).

Table 4.5. Age-group-specific pre- and post-intervention means for body composition and anthropometric measures as well as estimated RMR (RMR_{estimate}). BW= body weight, FM_{BIA}= fat mass measured by bioelectrical impedance FFM= fat free mass measured by bioelectrical impedance, BF%= body fat percentage, FFM%= fat free mass percentage, BMI= body mass index, WC= waist circumference. ∆= mean absolute change from pre- to post-intervention. Values reported as mean (SE). Young= age < 57; Old= age ≥ 57.

<table>
<thead>
<tr>
<th></th>
<th>YOUNG (n= 16)</th>
<th>OLD (n= 16)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre</td>
<td>Post</td>
<td>∆</td>
</tr>
<tr>
<td>BW (kg)</td>
<td>137.4 (5.2)</td>
<td>114.2 (5.5)*</td>
<td>-23.2 (1.9)</td>
</tr>
<tr>
<td>FM_{BIA} (kg)</td>
<td>67.8 (3.4)</td>
<td>48.3 (4.4)*</td>
<td>-19.5 (2.2)^</td>
</tr>
<tr>
<td>FFM (kg)</td>
<td>69.6 (3.5)</td>
<td>65.8 (3.6)*</td>
<td>-3.7 (0.7)^</td>
</tr>
<tr>
<td>BF% (%)</td>
<td>49.4 (1.6)</td>
<td>41.8 (2.5)*</td>
<td>-7.6 (1.4)^</td>
</tr>
<tr>
<td>FFM% (%)</td>
<td>50.6 (1.7)</td>
<td>58.2 (2.5)*</td>
<td>7.6 (1.4)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>46.6 (1.7)</td>
<td>38.7 (1.8)*</td>
<td>-7.9 (0.6)</td>
</tr>
<tr>
<td>WC (cm)</td>
<td>138.3 (3.1)</td>
<td>118.1 (3.7)*</td>
<td>-20.2 (2.2)</td>
</tr>
<tr>
<td>RMR_{estimate} (kcals/day)</td>
<td>2282.0 (101.3)</td>
<td>2001.7 (89.5)*</td>
<td>-280.3 (31.3)</td>
</tr>
</tbody>
</table>

There was a significant (p<0.05) gender by age interaction for pre-to-post change in FM_{BIA}, FFM, BF%, FFM%. Post hoc comparisons revealed a significantly (p=0.04) greater change in FM_{BIA} for young-males (-24.3±3.5 kg) compared to old-males (-14.7±1.7 kg) while no significant differences were demonstrated between female age cohorts (Figure 4.6). Changes in FFM for old-males (-9.9±2.7 kg) were significantly (p=0.007) greater than young-males (-2.2±0.7 kg) while no significant differences were detected between female age cohorts (Figure 4.6). Young-males also showed a significantly (p=0.03) greater change in FFM% than old-males (+10.6±1.9% vs. +4.2±1.0%) while a similar pre-to-post increase was demonstrated between female age groups. Pre to post change in BF% was significantly (p=0.03) greater in young-males (-10.7±1.9%) than old-males (-4.3±1.0%), young-females (-4.5±1.5%), and old-females (-4.5±1.5%). There were no significant differences for BF%-changes between female age groups.
Figure 4.5. Change from pre- to post-treatment in total bodyweight (BW), fat free mass (FFM), and fat mass measured by bioelectrical impedance analysis (FM\textsubscript{BIA}) for total sample, gender, and age-group. Values reported as mean ± SE. The numbers indicated within respective bars are mean values for change in FFM and FM\textsubscript{BIA}. The numbers outside the bars are mean values for change in BW.

* Significantly different between genders (p<0.05)

^ Significantly different between age-groups (p<0.05)

Figure 4.6. Gender by age interaction for pre-to-post change in total body weight (BW), fat free mass (FFM), and fat mass measured by bioelectrical impedance analysis (FM\textsubscript{BIA}). Values reported as mean ± SE. The numbers indicated within respective bars are approximate mean values for change in FFM and FM\textsubscript{BIA}. The numbers outside the bars are approximate mean values for total change in BW.

* Significant gender by age-group interaction (p<0.05)
4.1.4 Relative Weight-Loss Composition

The relative contributions of FM- and FFM-loss to total weight-loss for all study cohorts are displayed in Figures 4.7 and 4.8. There was an age effect for weight-loss composition as relative contributions from FM-loss was greater in young compared to old (81.4±3.7% vs. 64.8±4.1%; p=0.003) and relative contributions from FFM-loss was greater in old compared to young (35.0±4.1% vs. 18.7±3.7%; p=0.003). There were no significant differences in weight-loss composition between genders. A gender by age interaction showed differences for weight-loss composition between male age cohorts while female age groups exhibited no significant differences. Specifically, there was a significantly (p=0.002) greater relative contribution of FM-loss in young-males than old-males (90.5±3.5% vs. 61.8±6.3%). Further, FFM-loss accounted for 38.3±6.3% of total weight-loss in old-males which was significantly (p=0.002) greater than young-males (9.7±3.4%).

Figure 4.7. Relative contribution of fat free mass (FFM)- and fat mass (FM)-loss to total weight-loss in total sample and gender and age cohorts. Values reported as mean ± SE. Approximate values for mean relative contributions of FFM- and FM-loss are indicated in respective bars. *Significantly different between age-groups (p<0.05)
There was a significant (p<0.05) time effect for HbA1c, fasting glucose, total cholesterol, TAG, and VLDL (Table 4.6). From pre- to post-treatment, there was a significant decrease in HbA1c (-13.5±2.7%; p=0.0009), fasting glucose (-8.5±2.7%; p=0.01), total cholesterol (-8.9±2.7%; p=0.004), TAG (-21.2±4.6%; p=0.001), and VLDL (-20.1±6.7%; p=0.02) (Figures 4.9 and 4.10). There was a significant (p=0.04) gender effect for change in HbA1c as males demonstrated a greater decrease than females pre- to post-treatment (-18.0±4.3% vs. -7.3±1.5%) (Figure 4.11). There were no significant main effects for gender or age for pre to post changes in all other variables.

4.1.5 Blood Lipid and Metabolic Profile

Figure 4.8. Gender by age interaction for relative contribution of fat free mass (FFM)- and fat mass (FM)-loss to total weight-loss. Values reported as mean ± SE. Approximate values for mean relative contribution of FFM- and FM-loss are indicated in respective bars. *Significant gender by age-group interaction (p<0.05)
Table 4.6. Pre- and post-treatment hemoglobin A1c (HbA1c), fasting glucose, and lipid levels for total sample. TAG= triacylglycerol, HDL= high-density lipoprotein, LDL= low-density lipoprotein, VLDL= very-low density lipoprotein. Values reported as mean (SE). ∆= mean relative change from pre- to post-intervention.

* Significantly different than Pre (p<0.05)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Pre</th>
<th>Post</th>
<th>∆ (%)</th>
<th>Clinical Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c (%)</td>
<td>6.9 (0.3)</td>
<td>5.8 (0.1)*</td>
<td>-13.5 (2.7)</td>
<td>Normal= &lt;5.7</td>
</tr>
<tr>
<td>(n= 19) Diabetic</td>
<td></td>
<td></td>
<td></td>
<td>Pre-diabetes= 5.7-6.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Diabetes= &gt;6.4</td>
</tr>
<tr>
<td>Fasting Glucose (mg/dl)</td>
<td>113.2 (6.3)</td>
<td>102.1 (5.6)*</td>
<td>-8.5 (2.7)</td>
<td>Normal= 70-100</td>
</tr>
<tr>
<td>(n= 25) Diabetes</td>
<td></td>
<td></td>
<td></td>
<td>Pre-diabetes= 101-125</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Diabetes= &gt;125</td>
</tr>
<tr>
<td>Total Cholesterol (mg/dl)</td>
<td>160.0 (6.7)</td>
<td>144.8 (6.8)*</td>
<td>-8.9 (2.7)</td>
<td>Normal= &lt;200</td>
</tr>
<tr>
<td>(n= 23) Borderline</td>
<td></td>
<td></td>
<td></td>
<td>Borderline= 200-239</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>High= &gt;239</td>
</tr>
<tr>
<td>TAG (mg/dl)</td>
<td>152.1 (13.6)</td>
<td>112.3 (7.1)*</td>
<td>-21.2 (4.6)</td>
<td>Normal= &lt;150</td>
</tr>
<tr>
<td>(n= 23) Borderline</td>
<td></td>
<td></td>
<td></td>
<td>Borderline= 150-199</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>High= 200-499</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Very high= &gt;499</td>
</tr>
<tr>
<td>HDL (mg/dl)</td>
<td>48.8 (3.1)</td>
<td>48.2 (2.4)</td>
<td>2.7 (4.0)</td>
<td>Low= &lt;40 (men); &lt;50 (women)</td>
</tr>
<tr>
<td>(n= 23) Optimal</td>
<td></td>
<td></td>
<td></td>
<td>Optimal= &gt;59</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDL (mg/dl)</td>
<td>80.1 (6.1)</td>
<td>72.9 (5.5)</td>
<td>-5.0 (5.6)</td>
<td>Optimal= 100-129</td>
</tr>
<tr>
<td>(n= 23) Borderline</td>
<td></td>
<td></td>
<td></td>
<td>Borderline= 130-159</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>High= 160-189</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Very high= &gt;189</td>
</tr>
<tr>
<td>VLDL (mg/dl)</td>
<td>28.7 (3.2)</td>
<td>20.9 (1.7)*</td>
<td>-20.1 (6.7)</td>
<td>Normal= 2-30</td>
</tr>
<tr>
<td>(n= 15)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure 4.9. Pre- to post-treatment fasting glucose and lipid levels. TAG= triacylglycerol, HDL= high-density lipoprotein, LDL= low-density lipoprotein, VLDL= very-low density lipoprotein. Values reported as mean ± SE. *Significantly different than pre (p<0.05)
Figure 4.10. Pre- to post-treatment hemoglobin A1c (HbA1c). Values reported as mean ± SE.
*Significant main effect for time (p<0.05)

Figure 4.11. Relative change in hemoglobin A1c (HbA1c) from pre- to post-treatment for males and females. Value reported as mean ± SE.
*Significantly different between genders (p<0.05)
4.1.6 Correlations

There was a significant (p<0.0001) strong positive (r=0.88) correlation between FFM and RMR estimate pre-treatment and a significantly (p<0.0001) strong positive (r=0.90) correlation between FFM and RMR estimate post-treatment (Figure 4.12).

![Figure 4.12. Relationship between fat free mass (FFM) and estimated resting metabolic rate (RMR estimate) before treatment and their relationship after treatment. Circular markers represent pre-treatment measurements and the triangular markers indicate post-treatment measurements.](image)

![Figure 4.13. Relationship between change in fat free mass (FFM) and change in estimated resting metabolic rate (RMR estimate).](image)
There was a significant ($p=0.047$) moderate positive ($r=0.35$) relationship between change in FFM and change in RMR$_{\text{estimate}}$ (Figure 4.13). Pre-treatment RMR$_{\text{estimate}}$ was significantly ($p=0.043$) correlated with change in FM$_{\text{BIA}}$ with moderate and positive linearity (Figure 4.14).

4.1.7 Descriptive Analysis of Exercise History and Attitude Questionnaire

Of the total sample, 93.8% indicated that they do not engage in physical activity at least once per week. A module evaluating daily time spent for specific activities reported that patients spend 0.7 hours physically active, 2.7 hours watching television, 5.1 hours using the computer, 4.7 hours sitting at a desk, and 0.3 hours standing in one spot each day (Figure 4.15). As a general evaluation of walking function, 53% reported that they walk slowly with short strides, 35% have average or normal walking characteristics, 6% walk fairly brisk, and no patients reported that they have a brisk and striding walk (6% omission) (Figure 4.16). Figure 4.17 displays the relative interest level for a variety of physical activities among the total sample. The activity with the greatest rate of interest was strength training (94% interested) while 66% and 34% reported interest for walking and cycling, respectively.
Figure 4.15. Self-reported time spent daily for specific activities.

Figure 4.16. Self-reported evaluation of general walking function.
4.2 Specific Aim 2 (Prospective Study)

4.2.1 Descriptive and Control Variables

Baseline comparisons of descriptive measures between cohorts of Specific Aims 1 (N=32) and 2 (N=8) are displayed in Table 4.7. There were no significant differences for all measures between study cohorts. Descriptive variables, measured at experimental week 0, are reported for both CON (N=4) and RT (N=4) in Table 4.8. There were no significant group differences for all descriptive measures which included age as well as anthropometric, body composition, metabolic, and functional variables. Measures for activity and dietary control variables were compared between groups. Physical activity level, as measured by average daily steps and minutes spent on physical activity, was not significantly different between groups (CON: 6321.5±2189.2 steps/day, 84.8±15.2 min/day vs. RT: 6004.8±800.5 steps/day, 100.4±14.3 min/day). There were no reported issues related to pedometer use and physical contraindications. There were no significant group differences for daily caloric intake (CON: 1120±0 kcal/day vs. RT: 1120±0 kcal/day). No critical issues relating to dietary compliance were reported across the 12-week protocol.
### Table 4.7. Baseline comparisons of descriptive measures between cohorts of Specific Aim 1 and Specific Aim 2. BW= body weight, BMI= body mass index, WC= waist circumference, FM\textsubscript{BIA}= fat mass as measured by bioelectrical impedance analysis, FFM= fat free mass measured by bioelectrical impedance, BF\%= body fat percentage, FFM\%= fat free mass percentage. Values reported as mean (SE).

<table>
<thead>
<tr>
<th></th>
<th>AIM 1 (N=32)</th>
<th>AIM 2 (N=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>58.1 (1.5)</td>
<td>59.1 (3.5)</td>
</tr>
<tr>
<td>BW (kg)</td>
<td>131.2 (4.2)</td>
<td>127.3 (8.8)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>169.0 (1.9)</td>
<td>176.3 (3.9)</td>
</tr>
<tr>
<td>BMI (kg/m(^2))</td>
<td>45.8 (1.3)</td>
<td>41.1 (3.3)</td>
</tr>
<tr>
<td>WC (cm)</td>
<td>137.6 (2.6)</td>
<td>129.7 (5.5)</td>
</tr>
<tr>
<td>FM\textsubscript{BIA} (kg)</td>
<td>62.1 (2.7)</td>
<td>52.5 (7.1)</td>
</tr>
<tr>
<td>FFM (kg)</td>
<td>69.1 (2.9)</td>
<td>74.8 (5.1)</td>
</tr>
<tr>
<td>BF% (%)</td>
<td>47.2 (1.3)</td>
<td>40.4 (3.4)</td>
</tr>
<tr>
<td>FFM%</td>
<td>52.7 (1.3)</td>
<td>59.6 (3.4)</td>
</tr>
</tbody>
</table>

### Table 4.8. Baseline comparisons of descriptive measures between CON and RT. TBM= total body mass, BMI= body mass index, WC= waist circumference, FM= fat mass, BF\%= body fat percentage, LBM= lean body mass, LBM\%= lean body mass percentage, ASM= appendicular skeletal muscle mass index, RMR= resting metabolic rate, FO= fat oxidation, 1RM\textsubscript{UPPER}= upper body one repetition maximum, 1RM\textsubscript{LOWER}= lower body one repetition maximum. Values reported as mean (SE).

<table>
<thead>
<tr>
<th></th>
<th>CON (N=4)</th>
<th>RT (N=4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>53.3 (5.9)</td>
<td>65.0 (0.4)</td>
</tr>
<tr>
<td>TBM (kg)</td>
<td>134.0 (12.7)</td>
<td>118.7 (12.8)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>176.0 (6.8)</td>
<td>176.5 (5.1)</td>
</tr>
<tr>
<td>BMI (kg/m(^2))</td>
<td>43.8 (5.7)</td>
<td>38.5 (3.4)</td>
</tr>
<tr>
<td>WC (cm)</td>
<td>128.9 (6.8)</td>
<td>130.5 (9.8)</td>
</tr>
<tr>
<td>FM (kg)</td>
<td>61.4 (11.0)</td>
<td>50.5 (4.1)</td>
</tr>
<tr>
<td>LBM (kg)</td>
<td>69.3 (6.4)</td>
<td>65.0 (8.5)</td>
</tr>
<tr>
<td>BF% (%)</td>
<td>45.0 (4.8)</td>
<td>43.1 (2.0)</td>
</tr>
<tr>
<td>LBM% (%)</td>
<td>52.4 (4.5)</td>
<td>54.2 (1.8)</td>
</tr>
<tr>
<td>ASM (kg/cm(^2))</td>
<td>10.7 (0.7)</td>
<td>9.7 (1.2)</td>
</tr>
<tr>
<td>RMR (kcal/day)</td>
<td>2415.9 (275.3)</td>
<td>2329.8 (326.2)</td>
</tr>
<tr>
<td>FO (g/day)</td>
<td>229.3 (53.1)</td>
<td>213.5 (41.8)</td>
</tr>
<tr>
<td>1RM\textsubscript{UPPER} (kg)</td>
<td>54.4 (11.6)</td>
<td>63.5 (11.6)</td>
</tr>
<tr>
<td>1RM\textsubscript{LOWER} (kg)</td>
<td>106.6 (0.8)</td>
<td>110.0 (12.6)</td>
</tr>
</tbody>
</table>
4.2.2 Weekly Weight-Loss and Bi-Weekly RMR Trajectory

Both CON and RT exhibited a significant (p<0.05) time effect for BW; however no group differences were detected at any weekly time points (Figure 4.18). Pairwise comparisons of time points are specified in Figure 4.18 for each group. For CON, a significant (p<0.05) weight-loss from pre-intervention was detected at each subsequent time point starting week 3, resulting in a total BW-change of -20.4±2.9 kg (-16.4%; p=0.0001). RT experienced a significant (p<0.05) BW-change from pre-intervention at each ensuing time point starting week 4, with an overall weight-loss of 15.1±1.8 kg (-13.5%). CON (-14.2±3.1 kg; p=0.0002) and RT (-12.1±2.8 kg; p=0.0002) demonstrated a significant decrease in FM_{BIA} from pre to post with no significant between group differences at any time point. For FFM, CON demonstrated a significant (p=0.0006) pre to post change of -6.3±2.2 kg whereas RT showed no significant change over time. However, there were no significant group by time interactions.

![Figure 4.18. Weekly bodyweight-change from pre-intervention for CON and RT. Values are reported as mean ± SE. Numerical ranges indicate prior weekly time-points in which BW-change from pre-intervention was significantly different (p<0.05).](image)

RT and CON demonstrated a significant (p<0.05) time effect for BMI; however, no group differences were detected for any weekly time points (Figure 4.19). Pairwise comparisons
of weekly time-points are displayed in Figure 4.19 for each group. CON demonstrated a significant (p<0.05) decrease in BMI from pre-intervention at each time point throughout weeks 2-13. Overall, BMI decreased (p=0.0002) by 6.5±0.7 units or 14.7% from pre- to post-intervention for CON. RT exhibited a significant (p<0.05) BMI reduction from pre-intervention at each time point during weeks 5-13 ultimately resulting in a 12.6% total decline (-4.9±0.6 units; p=0.0002).

Both groups demonstrated a significant (p<0.05) decrease in WC. Specifically, CON demonstrated a 17.8±1.4 cm or 14% decrease (p=0.0002) from pre- to post-intervention, while WC was reduced by 24.5±5.4 cm or 18% for RT (p=0.0002) (Figure 4.20). Post hoc tests revealed a significantly (p<0.05) smaller WC from pre-intervention at each subsequent time point starting week 3 for CON and week 4 for RT. There were no significant group differences for WC at any weekly time point.
Figure 4.20. Weekly waist circumference-change from pre-intervention for CON and RT. Values are reported as mean ± SE. Numerical ranges indicate prior weekly time-points in which WC-change from pre-intervention was significantly different (p<0.05)

Figure 4.21. Bi-weekly resting metabolic rate (RMR$_{c}$)-change from pre-intervention for CON and RT. Values are reported as mean ± SE.

* Significantly different than Pre (p<0.05)
CON showed a significant (p<0.05) time effect for RMR\textsubscript{clinic} while RT demonstrated no significant changes over time (Figure 4.21). For CON, RMR\textsubscript{clinic} significantly (p<0.05) decreased from pre-intervention at all succeeding time points starting week 5. Overall, CON experienced a decrease (p=0.001) of 526.3±151.4 kcal/day which was nearly a -21% change from pre-intervention. RT, demonstrated no significant changes over time. No significant group differences were detected at any time points.

4.2.3 Body Composition (DXA) and Anthropometric Measures at Pre, Mid, and Post

4.2.3.1 Total body mass. A significant (p<0.05) decrease in TBM was detected over time for both CON and RT (Table 4.9 and Figure 4.22). CON exhibited a 12.9±1.2 kg or 9.8% decrease in TBM from pre- to mid-intervention (p=0.0002) and a 7.5±1.6 kg or 6.6% reduction from mid- to post-intervention (p=0.009). Overall TBM-change from pre- to post-intervention was -20.4±2.6 kg or -15.6% (p=0.0002). RT demonstrated a 10.2±1.4 kg or 8.6% decline for TBM from pre- to mid-intervention (p=0.0009) and no significant change from mid- to post-intervention (p=0.17). The total TBM-change for RT was -14.6±1.8 kg or -12.6% (p=0.0002). No significant group differences were found at any time points.

4.2.3.2 Total and regional fat mass and body fat percentage. A significant (p<0.05) decrease in FM was identified for both CON and RT (Table 4.9 and Figure 4.23). CON exhibited an 8.8±1.3 kg or 16.1% decrease in FM from pre- to mid-intervention (p=0.004) and a 6.4±1.2 kg or 15.1% reduction from mid- to post-intervention (p=0.04). Overall FM-change from pre- to post-intervention was -15.3±2.1 kg (-28.3%) (p=0.0002). RT demonstrated an 8.1±2.3 kg or 15.5% loss of FM from pre- to mid-intervention (p=0.008) and no significant change from mid to post (p=0.11). The total loss of FM for RT was 13.4±2.6 kg which was a -25.9% change from pre (p=0.0002). No significant group differences were found at any time points. There was a significant (p<0.05) decrease in android FM (FM\textsubscript{android}), gynoid FM (FM\textsubscript{gynoid}), and BF% from pre- to post-intervention for CON and RT; however, no significant group differences were found (Table 4.9).
4.2.3.3 Total lean body mass, appendicular skeletal muscle mass index, and LBM percentage. A significant (p<0.05) decline in LBM was detected for CON over time; however, RT exhibited no significant changes from pre-intervention (Table 4.9 and Figure 4.23). CON lost 4.1±0.8 kg of LBM from pre- to mid-intervention (-6.1%) (p=0.004) and no significant change from mid- to post-intervention. The total reduction in LBM from pre- to post-intervention was 5.0±1.0 kg (-7.4%) for CON (p=0.0008). RT showed no significant changes in LBM across the entire experimental period. CON lost 122.6% more (p=0.04) LBM than RT from pre- to post-intervention. CON and RT exhibited a 10.1% and 1.9% decrease in ASM from pre- to post-intervention, respectively; and these changes were significantly (p=0.04) different between groups (Table 4.9). Specifically, CON demonstrated an approximate 136.7% greater decline in ASM than RT. There was a significant increase in LBM% from pre- to post-intervention for CON (+10.0%; p=0.009) and RT (+11.2%; p=0.005), with no significant group differences (Table 4.9).
**Table 4.9.** Body composition and anthropometric measures at pre-, mid-, and post-intervention. TBM = total body mass, FM = fat mass, FM ANDROID = android fat mass, FM GYNOID = gynoid fat mass, BF% = body fat percentage, LBM = lean body mass, ASM = appendicular skeletal muscle mass index, LBM% = lean body mass percentage, BMI = body mass index. \( \Delta \) = 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)

<table>
<thead>
<tr>
<th></th>
<th>Pre</th>
<th>Mid</th>
<th>Post</th>
<th>( \Delta ) (%)</th>
<th>Pre</th>
<th>Mid</th>
<th>Post</th>
<th>( \Delta ) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CON (N=4)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TBM (kg)</td>
<td>134.0</td>
<td>121.1*</td>
<td>113.6**</td>
<td>-15.6 (2.2)</td>
<td>118.7</td>
<td>108.5*</td>
<td>104.0*</td>
<td>-12.5 (1.1)</td>
</tr>
<tr>
<td>FM (kg)</td>
<td>61.4</td>
<td>52.6*</td>
<td>46.2**</td>
<td>-28.3 (7.0)</td>
<td>50.5</td>
<td>42.4*</td>
<td>37.1**</td>
<td>-25.9 (3.0)</td>
</tr>
<tr>
<td>FM ANDROID (kg)</td>
<td>6.4 (0.7)</td>
<td>5.3 (0.9)</td>
<td>4.8* (1.0)</td>
<td>-28.1 (10.5)</td>
<td>5.6 (0.5)</td>
<td>4.5 (0.3)</td>
<td>3.4* (0.4)</td>
<td>-36.9 (9.4)</td>
</tr>
<tr>
<td>FM GYNOID (kg)</td>
<td>8.6 (2.0)</td>
<td>7.2 (1.8)</td>
<td>6.5* (2.0)</td>
<td>-28.1 (6.6)</td>
<td>8.1 (0.7)</td>
<td>6.4 (0.4)</td>
<td>5.1* (0.7)</td>
<td>-35.7 (9.9)</td>
</tr>
<tr>
<td>BF% (%)</td>
<td>45.0</td>
<td>42.3</td>
<td>38.8*</td>
<td>-15.7 (6.3)</td>
<td>43.1</td>
<td>39.8</td>
<td>36.7*</td>
<td>-15.3 (3.4)</td>
</tr>
<tr>
<td>LBM (kg)</td>
<td>69.3</td>
<td>65.2*</td>
<td>64.3*</td>
<td>-7.4* (1.4)</td>
<td>65.0</td>
<td>63.1</td>
<td>63.8</td>
<td>-2.7* (2.4)</td>
</tr>
<tr>
<td>ASM (kg/m²)</td>
<td>10.7 (0.7)</td>
<td>9.9 (0.8)</td>
<td>9.7 (0.9)</td>
<td>-10.1* (2.3)</td>
<td>9.7 (1.2)</td>
<td>8.9 (1.6)</td>
<td>9.6 (1.4)</td>
<td>-1.9* (3.3)</td>
</tr>
<tr>
<td>LBM% (%)</td>
<td>52.4</td>
<td>54.9</td>
<td>58.1*</td>
<td>10.0 (3.1)</td>
<td>54.2</td>
<td>57.4</td>
<td>60.4*</td>
<td>11.2 (2.4)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>43.8</td>
<td>39.4*</td>
<td>37.6**</td>
<td>-15.1 (2.5)</td>
<td>38.5</td>
<td>34.9*</td>
<td>33.3*</td>
<td>-13.4 (1.0)</td>
</tr>
<tr>
<td>WC (cm)</td>
<td>128.9</td>
<td>119.4</td>
<td>111.1*</td>
<td>-14.0 (1.6)</td>
<td>130.5</td>
<td>117.5*</td>
<td>106.1**</td>
<td>-18.4 (3.1)</td>
</tr>
</tbody>
</table>

Figure 4.23. Change in fat mass (FM) and lean body mass (LBM) from pre-intervention for CON and RT. Values are 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)
4.2.3.4 Weight-loss composition. The relative contributions of FM- and LBM-change to TBM-loss at mid- and post-intervention are displayed in Figures 4.24 for CON and RT. Weight-loss composition was not significantly different between groups at mid-intervention. At mid-intervention, CON lost 68.1±5.6% of their TBM as FM and 31.9±5.7% as LBM while RT lost 76.8±10.0% of their TBM as FM and 23.2±9.5% as LBM. At post-intervention, the total decrease in TBM in CON was 74.5±4.1% attributable to FM-loss, while LBM-loss was 25.5±4.0% responsible. As for RT, FM-loss accounted for 90.3±8.8% of the total loss of TBM while LBM-loss constituted 9.7±8.4%. The discrepancy between groups for weight-loss composition at post-intervention was significant (p=0.03).

Figure 4.24. Relative contribution of fat mass (FM)- and lean body mass (LBM)-loss to changes in total body mass (TBM) at mid- and post-intervention. Values reported as mean ± SE. Approximate values for mean relative contributions of FM- and LBM-loss are indicated in respective bars. * Significantly different between groups (p<0.05)
4.2.4 Resting Metabolism and Fat Oxidation Rate at Pre, Mid, and Post

4.2.4.1 Resting metabolic rate. Changes in RMR over time are displayed in Table 4.8 and Figure 4.25. CON experienced a significant (p=0.02) 350.7±89.4 kcal/day or 14.5% decrease in RMR from pre- to post-intervention. RT demonstrated no significant changes in RMR over time. Overall responses for RMR was significantly (p=0.003) different between groups. When adjusting for TBM, RMR remained unchanged for CON, while RT demonstrated significantly greater RMR at post-intervention compared to both pre- (+18.7%; p=0.003) and mid- (+11.3%; p=0.03) time points (p<0.05). The pre to post change in relative RMR to TBM was significantly (p=0.008) greater in RT than CON. When adjusting for LBM, RMR decreased significantly (p=0.03) by 7.9% from pre- to post-intervention for CON. RT demonstrated a significant (p=0.04) increase in RMR from pre to post (+7.0%) and mid to post (+6.8%) when adjusting for LBM.

[Figure 4.25. Change in resting metabolic rate (RMR) from pre-intervention for CON and RT. Values reported as mean ± SE. Values indicated by markers reflect mean RMR (kcal/day) at each respective time point.
* Significantly different than Pre (p<0.05)
# Significantly different between groups (p<0.05)]
Table 4.10. RMR and fat oxidation at pre-, mid-, and post-intervention. RMR= resting metabolic rate, TBM= total body mass, LBM= lean body mass. ∆= mean relative change from pre-post intervention. Values reported as mean (SE).

<table>
<thead>
<tr>
<th></th>
<th>CON (N=4)</th>
<th></th>
<th>RT (N=4)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre</td>
<td>Mid</td>
<td>Post</td>
<td>Δ (%)</td>
</tr>
<tr>
<td><strong>RMR</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(kcal/day)</td>
<td>2415.9 (275.3)</td>
<td>2126.4 (205.7)</td>
<td>2065.2* (245.7)</td>
<td>-14.5^ (3.0)</td>
</tr>
<tr>
<td>(kcal/day/kg TBM)</td>
<td>17.9 (1.1)</td>
<td>17.6 (0.8)</td>
<td>18.3 (1.5)</td>
<td>1.4^ (2.8)</td>
</tr>
<tr>
<td>(kcal/day/kg LBM)</td>
<td>34.7 (1.9)</td>
<td>32.4 (2.4)</td>
<td>32.0* (1.8)</td>
<td>-7.9^ (2.1)</td>
</tr>
<tr>
<td><strong>FAT OXIDATION</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(g/day)</td>
<td>229.3 (53.1)</td>
<td>179.4 (27.6)</td>
<td>164.9 (12.4)</td>
<td>-21.3 (10.8)</td>
</tr>
<tr>
<td>(g/day/kg TBM)</td>
<td>1.8 (0.4)</td>
<td>1.5 (0.2)</td>
<td>1.5 (0.1)</td>
<td>-7.0 (11.9)</td>
</tr>
<tr>
<td>(g/day/kg LBM)</td>
<td>3.2 (0.5)</td>
<td>2.7 (0.3)</td>
<td>2.6 (0.1)</td>
<td>-14.5 (12.6)</td>
</tr>
</tbody>
</table>

* Significantly different than Pre (p<0.05)
** Significantly different than Pre and Mid (p<0.05)
^ Significantly different between groups (p<0.05)

Figure 4.26. Change in fat oxidation rate (FO) from pre-intervention for CON and RT. Values reported as mean ± SE. Values indicated by markers reflect mean FO (g/day) at each respective time point.
4.2.4.2 Fat oxidation rate. There were no significant time-dependent changes demonstrated by CON or RT for FO (Table 4.10 and Figure 4.26). These outcomes were consistent even when adjusting for TBM or LBM. No significant group by time interaction was measured for FO even when adjusting for TBM or LBM.

4.2.5 Skeletal Muscle Contractile Kinetics at Pre, Mid, and Post

Table 4.11. Skeletal muscle contractile kinetics at pre-, mid-, and post-intervention. TBM= total body mass, LBM= lean body mass. ∆= mean relative change from pre-post intervention. Values reported as mean (SE).

<table>
<thead>
<tr>
<th></th>
<th>CON (N=4)</th>
<th>RT (N=4)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre</td>
<td>Mid</td>
</tr>
<tr>
<td><strong>ISOKINETIC:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>KNEE EXTENSION</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak Torque (Nm)</td>
<td>153.8</td>
<td>139.8</td>
</tr>
<tr>
<td>(19.4)</td>
<td>(18.7)</td>
<td>(14.8)</td>
</tr>
<tr>
<td>Peak Torque/TBM (Nm/kg)</td>
<td>1.2</td>
<td>1.2</td>
</tr>
<tr>
<td>(0.2)</td>
<td>(0.2)</td>
<td>(0.2)</td>
</tr>
<tr>
<td>Peak Torque/LBM (Nm/kg)</td>
<td>2.2</td>
<td>2.1</td>
</tr>
<tr>
<td>(0.2)</td>
<td>(0.2)</td>
<td>(0.2)</td>
</tr>
<tr>
<td>Avg. Power (W)</td>
<td>108.5</td>
<td>91.6</td>
</tr>
<tr>
<td>(20.5)</td>
<td>(17.9)</td>
<td>(14.0)</td>
</tr>
<tr>
<td><strong>ISOMETRIC:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>KNEE FLEXION</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak Torque (Nm)</td>
<td>164.9</td>
<td>153.4</td>
</tr>
<tr>
<td>(18.4)</td>
<td>(16.2)</td>
<td>(14.8)</td>
</tr>
<tr>
<td>Peak Torque/TBM (Nm/kg)</td>
<td>1.3</td>
<td>1.3</td>
</tr>
<tr>
<td>(0.2)</td>
<td>(0.2)</td>
<td>(0.2)</td>
</tr>
<tr>
<td>Peak Torque/LBM (Nm/kg)</td>
<td>2.4</td>
<td>2.4</td>
</tr>
<tr>
<td>(0.2)</td>
<td>(0.2)</td>
<td>(0.2)</td>
</tr>
<tr>
<td><strong>ISOMETRIC:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>KNEE FLEXION</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak Torque (Nm)</td>
<td>123.2</td>
<td>104.1</td>
</tr>
<tr>
<td>(14.6)</td>
<td>(12.4)</td>
<td>(12.9)</td>
</tr>
<tr>
<td>Peak Torque/TBM (Nm/kg)</td>
<td>1.0</td>
<td>0.9</td>
</tr>
<tr>
<td>(0.2)</td>
<td>(0.1)</td>
<td>(0.1)</td>
</tr>
<tr>
<td>Peak Torque/LBM (Nm/kg)</td>
<td>1.8</td>
<td>1.6</td>
</tr>
<tr>
<td>(0.3)</td>
<td>(0.2)</td>
<td>(0.2)</td>
</tr>
</tbody>
</table>
4.2.5.1 Isokinetic contraction. Data of contractile kinetic measures are displayed in Table 4.11, Figures 4.27 and 4.28. Peak extension torque significantly (p=0.004) decreased from pre- to post-intervention by 14.3% in CON. For RT, peak extension torque significantly increased from pre to mid (+22.1%; p=0.001) and from pre to post (+34.9%; p=0.0002). These pre to post changes for peak extension torque were significantly (p=0.0005) different between groups. When adjusting for TBM or LBM, peak extension torque remained unchanged for CON; however RT exhibited a 54.3% increase pre to post (p=0.0002) when adjusting for TBM and a 39.0% increase (p=0.0002) pre to post when adjusting for LBM. Pre to post changes for adjusted peak extension torque measures were significantly (p=0.005) greater for RT than CON. CON showed a significant (p=0.004) decline in average extension power from pre to post (-21.8%) while RT demonstrated a significant (p=0.02) improvement (+26.3%). There was a significant (p=0.004) group difference for these pre to post changes in average extension power.

CON demonstrated a significant (p=0.009) decrease in flexion peak torque from pre to post (-16.9%) while RT exhibited a significant (p=0.01) increase (+22.4%). These pre to post changes were significantly (p=0.002) different between groups. When adjusting for TBM or LBM, CON showed no significant changes for peak flexion torque while RT demonstrated a 39.2% pre to post increase (p=0.0002) when adjusting for TBM and a 25.7% pre to post increase (p=0.01) when adjusting for LBM. Pre to post changes for adjusted peak extension torque measures were significantly (p=0.002) greater for RT than CON. CON showed a significant (p=0.01) decline in average flexion power from pre to post (-23.4%) while RT demonstrated a significant (p=0.004) increase (+40.9%). There was a significant (p=0.003) group difference for these pre to post changes in average flexion power.

4.2.5.2 Isometric contraction. Peak extension torque significantly (p=0.003) declined from pre- to post-intervention by 13.2% for CON while RT demonstrated a significant (p=0.0002) increase from pre to post (+43.8%), and a significant (p=0.0007) increase from mid to post (+16.5%). Pre to post changes were significantly (p=0.002) greater in RT compared to CON. After adjusting for TBM or LBM, peak extension torque remained unchanged over time for CON. For RT, peak extension torque significantly increased from pre to post (+69.9%; p=0.0003) and mid to post (+21.9%; p=0.0002) when adjusted for TBM and pre to post
(+40.8%) when adjusted for LBM. Pre to post changes in peak torque was significantly (p=0.004) greater in RT than CON when normalized to TBM or LBM.

Peak flexion torque did not significantly change over time for CON; however RT exhibited a significant improvement from pre to post (+61.7%; p=0.003) and mid to post (+35.5%; p=0.046). Pre to post changes were significantly (p=0.005) greater in RT compared to CON. After adjusting for TBM or LBM, peak flexion torque remained unchanged over time for CON. For RT, peak flexion torque significantly increased from pre to post (+84.7%; p=0.0005) and mid to post (+28.6%; p=0.02) when adjusted for TBM and pre to post (+66.5%; p=0.002) and mid to post (+31.5%; p=0.046) after adjusting for LBM. Pre to post changes in peak torque was significantly (p=0.0005) greater in RT than CON when adjusted for TBM or LBM.

Figure 4.27. Pre- to post-change in contractile kinetics for CON and RT. Values reported as mean ± SE. Pwr. = power.
* Significant pre- to post-change (p<0.05)
^ Significantly different between groups (p<0.05)
4.2.6 Upper and Lower Body Isotonic Strength at Pre, Mid, and Post

**4.2.6.1 Upper body 1RM.** There were no significant changes in $1RM_{UPPER}$ over time for CON; however, RT demonstrated a significant increase ($+47.4\%, p=0.001$) from pre- to post-intervention (Figure 4.29). RT demonstrated a significantly 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 significant changes over time, while RT exhibited a significant increase from pre to mid ($p=0.03$) and pre to post ($p=0.0004$) (Figure 4.30). Relative $1RM_{UPPER}$ to TBM was significantly ($p=0.02$) greater in RT than CON at post-intervention. When adjusted for LBM, $1RM_{UPPER}$ was significantly ($p=0.046$) reduced from pre to post for CON; RT showed significant improvements from pre to mid ($p=0.02$), pre to post ($p=0.0003$), and mid to post ($p=0.02$) (Figure 4.30). Relative $1RM_{UPPER}$ to LBM was significantly greater in RT than CON at mid- ($p=0.04$) and post-intervention ($p=0.006$).
Figure 4.29. Change in upper body one-repetition maximum (1RM) from pre-intervention for CON and RT. Values reported as mean ± SE.
* Significantly different than Pre (p<0.05)
# Significantly different between groups (p<0.05)

Figure 4.30. Pre-, mid-, and post-intervention upper body one-repetition maximum (1RM) after adjusting for total body mass (TBM) and lean body mass (LBM). 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)
4.2.6.2 Lower body 1RM. There was a significant decrease in $1RM_{\text{LOWER}}$ from pre to post (-28.3%; $p=0.009$) for CON; RT demonstrated a significant increase from mid to post (+27.0%; $p=0.002$) and a 49.9% increase ($p=0.0002$) from pre to post (Figure 4.31). RT demonstrated a significantly greater $1RM_{\text{LOWER}}$ gain at mid ($p=0.01$) and post ($p=0.0008$) compared to CON. After adjusting for TBM, CON showed a significant ($p=0.01$) decrease in $1RM_{\text{LOWER}}$ from pre to post, while RT exhibited a significant increase from pre to post ($p=0.0002$) and mid to post ($p=0.001$) (Figure 4.32). Relative $1RM_{\text{LOWER}}$ to TBM was significantly ($p=0.003$) greater in RT than CON at post-intervention. When adjusted for LBM, $1RM_{\text{LOWER}}$ significantly ($p=0.01$) decreased from pre to post for CON while RT experienced a significant increase from pre to post ($p=0.0002$) and mid to post ($p=0.0007$) (Figure 4.32). Relative $1RM_{\text{LOWER}}$ to LBM was significantly ($p=0.003$) greater in RT than CON at post-intervention.

Figure 4.31. Change in lower body one-repetition maximum (1RM) from pre-intervention for CON and RT. 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 ($p<0.05$)
4.2.7 Biochemical Responses at Pre, Mid, and Post

4.2.7.1 Biomarkers for fat metabolism. For CON, there was a significant decrease in serum FFA level (−40.3%; p=0.03) from pre to post and a significant decrease (−49.2%; p=0.0005) from mid to post (Figure 4.33). For RT, FFA levels significantly (p=0.001) increased from pre to mid by 257.5%, subsequently returning to the pre-intervention level; thus there was no significant change from pre to post. Pre to mid (p=0.0009) and pre to post (p=0.01) change in FFA level was significantly greater in RT than CON.

Free glycerol level was significantly (p=0.03) elevated by 31.7% from pre to mid for CON, subsequently returning to baseline levels at post (Figure 4.34). RT demonstrated a significant increase from pre to mid (+113.7%; p=0.0009), which then returned to baseline at post. Pre to mid (p=0.004) and pre to post (p=0.003) change in free glycerol level was significantly greater in RT than CON.
Serum β-HB level significantly decreased (p=0.03) by 31.6% from pre to post for CON while RT showed no significant changes over time (Figure 3.35). Pre to post changes in β-HB were significantly (p=0.005) greater in RT than CON.

Figure 4.33. Change in serum free fatty acid (FFA) level from pre-intervention for CON and RT. Values reported as mean ± SE.

^ Significantly different than Pre and Post (p<0.05)
** Significantly different than Pre and Mid (p<0.05)
# Significantly different between groups (p<0.05)

Figure 4.34. Change in serum free glycerol level from pre-intervention for CON and RT. Values reported as mean ± SE.

^ Significantly different than Pre and Post (p<0.05)
# Significantly different between groups (p<0.05)
4.2.7.2 Hormonal and growth factor responses. There were no significant changes in cortisol for both CON and RT over time (Figure 4.36). Serum IGF-1 level decreased significantly by 30.1% from pre to mid (p=0.02) and by 45.2% from pre to post (p=0.0007) for CON (Figure 4.37). As for RT, IGF-1 significantly (p=0.002) decreased from pre to post by 33.7%. There were no significant group differences for the changes in IGF-1. Serum IGFBP-3 remained unchanged for CON, while RT demonstrated a significant pre to mid (+25.5%; p=0.006) and pre to post (+18.9%; p=0.04) elevation (Figure 4.38). There were no significant group differences for the changes in IGFBP-3. IGF-1 to IGFBP-3 ratio was significantly decreased from pre to post by 48.2% for CON (p=0.01) and by 42.9% for RT (p=0.03) (Figure 4.39). There were no significant group differences for these changes in IGF-1: IGFBP-3.
Figure 4.36. Change in serum cortisol from pre-intervention for CON and RT. Values reported as mean ± SE.

Figure 4.37. Change in serum insulin-like growth factor-1 (IGF-1) level from pre-intervention for CON and RT. Values reported as mean ± SE.

* Significantly different than Pre (p<0.05)
Figure 4.38. Change in serum insulin-like growth factor-1 binding protein-3 (IGFBP-3) level from pre-intervention for CON and RT. Values reported as mean ± SE.
* Significantly different than Pre (p<0.05)

Figure 4.39. Change in insulin-like growth factor-1 (IGF-1) : insulin-like growth factor-1 binding protein-3 (IGFBP-3) from pre-intervention for CON and RT. Values reported as mean ± SE.
* Significantly different than Pre (p<0.05)
4.2.8 Correlation

There was a strong positive ($r=0.73; p=0.04$) correlation between the relative pre to post changes for LBM and RMR (Figure 4.40).

Figure 4.40. Relationship between the pre to post changes for lean body mass (LBM) and resting metabolic rate (RMR).
CHAPTER FIVE

DISCUSSION

5.1 Specific Aim 1: Systematic Evaluation of a Proprietary VLCD Treatment for Obesity

The main objective of this single-center clinical trial was to evaluate the efficacy by which periodized resistance training would enhance body composition, energy metabolism, and function in obese patients undergoing a 12-week modified Very-Low Calorie Diet (VLCD) under the medical care of the TMH Bariatric Center. In pursuit of this objective, we first examined the adaptive responses for a range of morphometric, anthropometric, and clinical variables to a 12-week unmodified proprietary VLCD (i.e. Optifast®), as described in section 3.1.2. This aim (i.e. Specific Aim 1) was intended not only to systematically evaluate treatment efficacy under standard medical administration, but to also highlight and confirm the current unmet clinical need for treatment optimization as it pertains to long-term weight-management. Indeed, a single-center evaluation of the Optifast® system may be constraint in terms of total sample size; however this limitation may be balanced by the homogeneity of overall patient treatment, in particular of those composing our sample size.

As a major component of Specific Aim 1, we evaluated the trajectory as well as the composition of weight-loss across the 12-week VLCD treatment with special emphasis on gender- and age-specific effects. Because VLCD treatments are intended to generate clinically significant weight-loss, various biomarkers for metabolic and cardiovascular health were also examined in conjunction to anthropometric and body composition data. Ultimately, our findings are expected to add valuable support to facilitate restructuring of present VLCD treatment programs towards outcomes concomitant with the preservation of lean tissue, metabolic rate, and muscular function. In so doing, the medical use of VLCDs for the treatment of obesity would be a more efficient approach, both economically and clinically speaking, by improving the opportunity for chronic weight management.

5.1.1 Treatment Outcomes for Overall Patient Cohort

We hypothesized that patients who completed the 12-week VLCD program would demonstrate a 15-27% decrease in BW from pre- to post-treatment. In agreement, patients lost 17% of their initial BW reflecting a total absolute weight-loss of 22.5 kg, which is less than
results of Wadden et al. \(^{141}\) (-27.1 kg) but more comparable to those of Walsh and Flynn \(^6\) (-21.4 kg). Overall, the acute weight-loss efficacy of the VLCD treatment supersedes reported outcomes for conventional 1,200 kcal/day-LCDs (i.e. 5-10 kg or about -9.7% loss)\(^4,140\). Unique from others \(^4,6,136,140\), we acquired more frequent BW measurements offering a week-by-week analysis of cohort-specific weight-loss trajectory across the treatment period. For the entire sample, weekly BW data indicated a weight-loss pattern reflective of the usual clinical prognoses, i.e. initial rapid decline and subsequent deceleration. In specific quantifiable terms, our longitudinal data indicate that weight-loss occurs most rapidly during the first three weeks of treatment (weeks 1-4) at a mean rate of 2.9 kg/week. Starting week 5, weight-loss decelerates by half to a mean rate of 1.5 kg/week, which appears to remain constant for the rest of the treatment period. This trend is illustrated in Figure 4.1 as each BW measurement between weeks 1-4 was significantly less than all respective weeks prior. At the beginning of week 5, however, weekly BW measures were significantly less than all preceding weeks with the exception of the immediate week prior. From a practical outlook, it would be of high clinical value to delay the point at which weight-loss decelerates or at least blunt the magnitude in which the rate decreases. However, a lower rate of weight-loss could also be deemed favorable and perhaps more advantageous if a greater percentage of said weight-loss was accounted for by fat reduction with the loss of lean tissue less contributory. This conjecture is based on evidence supporting the positive role of lean tissue on metabolic rate and muscle function, which are important determinants for prolonged weight-loss success \(^{18}\).

The composition of the observed weight-loss was examined by data derived from repeated bioelectrical impedance analysis (BIA) measurements. As expected, there was a significant decrease in FM from pre- to post-treatment which was reflected by a mean loss of almost 17 kg. Patients also experienced an approximate 6-kg loss of FFM across the treatment period. Rather consistent with our hypothesis and previous VLCD experiments \(^7,10,27,294,295\), FM- and FFM-loss accounted for 73% and 27% of total weight-loss, respectively (Figure 4.7). Accompanying these results, resting metabolism was negatively affected as RMR was repressed by an estimated 270 kcal/day (Table 4.3). Although this change in resting metabolism was based on crude regression-based assessment \(^{296}\), previous findings support the detrimental effects of VLCDs on RMR even through more sophisticated measurements, e.g. indirect calorimetry \(^{10,27,145,153-156,169,170}\). These adaptive responses for resting metabolism also appear to
be associated with the altered mass of metabolically active tissues, particularly the lean organ compartment. Resting metabolic rate was strongly and positively correlated (r= 0.88) with FFM at pre-treatment (Figure 4.12). This relationship, both in strength and direction, remained even after a 22.5-kg weight-loss, corresponding to reports from Leibel et al.\textsuperscript{145} who showed similar dynamics following a 10\% and 20\% decrease in BW. Our findings also demonstrated a significant positive correlation (r= 0.35) between absolute RMR-change and FFM-change, implying that the degree of lean tissue loss could influence the magnitude in which resting metabolism is suppressed during the VLCD treatment. In summary, the VLCD treatment induced a pronounced weight-loss that was significantly attributable to not only body fat reduction but also a significant decrease in lean tissue. Thus, overall outcomes may be perceived as suboptimal given the negative effects of lean tissue loss on resting metabolism and the consequential impetus for weight-regain. On a related note, the issue of weight-regain becomes a more critical issue when considering the health benefits of weight-loss in severely obese individuals.

One of the central objectives for a VLCD intervention in obese patients is to produce an overall weight-loss that is clinically significant. Correspondingly, our study cohort exhibited a weight-loss that was accompanied by dramatic improvements in metabolic and lipid profiles (Table 4.6). Before treatment, there was a marked presence of type II DM which was corroborated by a mean hemoglobin A1c (HbA1c) score of 6.9. Following VLCD treatment, HbA1c decreased significantly by almost 14\% to a score of 5.8, which in clinical terms, stratifies patients to the lower threshold for pre-diabetes (i.e. pre-diabetes= 5.7-6.4; diabetes\(\geq 6.4\)). Supporting data from the Health Professionals Follow-Up Study\textsuperscript{105} reported a 20-kg weight-loss to be concomitant with a 15-fold reduction in diabetes risk or even total eradication of the risk. Thus, it appears that the present VLCD treatment and the resultant weight-loss (-22.5 kg) effectively mitigated the risk for type II DM and improved overall glucose control in obese patients. As for our lipid panel results, pre-treatment measures were unexpectedly within acceptable ranges which is inconsistent with previously reported data indicating high-risk lipid profiles at baseline\textsuperscript{5}. This discrepancy might be due to the limited sample size with available lipid data (n= 23) at the TMH Bariatric Center. Nevertheless, total serum cholesterol decreased significantly from 160.0 to 144.8 mg/dl while TAG levels fell approximately 21\% across the treatment period. Together, our findings reflect a clinically meaningful weight-loss, which is
indeed critical for this population in which heightened risk for metabolic and cardiovascular diseases is quite pervasive\textsuperscript{97,99,102}.

In the context of mortality, we turn to responses for BMI given its consideration as a strong predictor of overall survival\textsuperscript{58}. Collectively, BMI decreased by nearly 17% from 45.9 to 38.1 kg/m\textsuperscript{2} at a rate of 0.6 units per/week, thereby shifting weight-class stratification from Class III (very severe) to Class II (severe). Although patients remained categorized as obese by BMI standards, this was an anticipated outcome since VLCD prescriptions, at least in clinical scenarios, are intended for very severe obese individuals with high mortality risk. Thus, despite being successful in significantly reducing BW and improving various health parameters, patients on average still remain classified as obese following treatment. Nonetheless, the observed reduction in BMI would be a considerable advantage in the context of mortality risk as research suggested that reducing BMI from a range of 40-45 kg/m\textsuperscript{2} to 30-35 kg/m\textsuperscript{2} may improve survival by approximately 6 years\textsuperscript{91}.

5.1.2 Gender-Specific Responses

A divergent course of weight-loss was evident between gender cohorts (Figure 4.2) as males experienced a more dramatic week-to-week and overall reduction in BW compared to females. However, significant gender differences for absolute weight-loss were not detected until weeks 12 (males: -24.5±1.7 kg vs. females: -17.7±1.3 kg) and 13 (males: -26.0±2.1 kg vs. females: -18.9±1.3 kg) while all preceding weeks, albeit subjectively different, only trended towards significance. In relative terms, overall weight-loss was approximately 32% greater in males than females. These discrepancies for total weight-loss across genders is solely justified by differentiated fat-loss between males (-19.5±2.2 kg) and females (-13.6±1.4 kg) since changes in FFM were comparable (males: -6.0±1.7 kg; females: -5.1±0.5 kg) (Figure 4.5). Nonetheless, both genders exhibited a significant reduction in both FM and FFM from pre- to post-treatment. Interestingly, when examining tissue-specific changes as a relative contribution to total weight-loss, i.e. weight-loss composition, no gender differences were evident (Figure 4.7). For males, the loss of FM and FFM constituted 76.1±5.1% and 24.0±5.1% of total weight-loss, respectively, which was statistically similar to female responses (70.1±3.5% and 29.7±3.5%, respectively). Together, although males lost more overall absolute weight and body fat than females, weight-
loss compositions were equivalent, therefore suggesting that both genders respond comparably to the VLCD program, at least in relative terms.

To speculate on potential determinants for differentiated fat-loss between genders, we examined descriptive measurements obtained before treatment (Table 4.1). Based on general consensus, greater overall mass in males is suggested to be the major impetus for their superior weight-loss; however, our correlational analyses add further conjecture. At pre-treatment, males had greater BW, height, BMI, WC, FFM, BF%, FFM%, and RMR estimate than females. Of these variables, only RMR was significantly and positively ($r=0.38$) associated with total fat-loss (Figure 4.14). Because a causal relationship cannot be established through correlational analysis, it can only be inferred that males exhibit a greater loss in FM, and thereby BW, not due to initial body mass differences per se but rather a higher initial resting metabolism when compared to their female counterparts.

As for gender-specific responses for clinical health parameters, metabolic and lipid profiles appear comparable between male and female cohorts. However, a gender by time interaction was detected for HbA1c scores. Males demonstrated a greater decrease in HbA1c compared to females from pre- to post-treatment (-18.0±4.3% vs. -7.3±1.5%). From a clinical perspective, however, the changes in HbA1c exhibited by both genders were indicative of enhanced glucose control and improved diabetes risk stratification. For instance, males improved HbA1c from 7.4 to 5.9, thereby shifting from diabetic to pre-diabetic classification. Females were pre-diabetics at baseline with an HbA1c of 6.1, decreasing to 5.6 following treatment. This places the female cohort slightly below the 5.7 threshold for normal classification.

5.1.3 Age-Specific Responses and Gender by Age Interactions

As presented in Figure 4.3, no age-specific differences were detected for weight-loss trajectory as both cohorts demonstrated similar BW changes each week. Consequently, total absolute weight-loss following the 12-week treatment was comparable between age-groups (Young: -23.2±1.9 kg and Old: -21.2±2.2 kg). From a body composition perspective, however, our analyses indicated that the said weight-loss outcomes were indeed distinct between the two age cohorts. Relative to the young age-group, overall fat-loss that was about 35% less (Old: -13.7±1.4 kg vs. Young: -19.5±2.2 kg) and FFM-loss was 67% greater (Old: -7.4±1.5 kg vs.
Young: -3.7±0.7 kg) in the older patients, thereby offsetting any age-related discrepancies for total weight-loss (Figure 4.5). When normalizing these outcomes to overall BW reduction (Figure 4.7), younger patients lost 81.4±3.7% of their weight as FM and only 18.7±3.7% as FFM. As for the old-group, total weight-loss, which again was similar to their younger counterpart, was only 64.8±4.1% attributable to fat-loss and 35.0±4.1% due to the decline in FFM. These age-specific weight-loss compositions were found significantly different (p=0.003), suggesting that advancing age compromises the quality of overall weight-loss when induced by the VLCD treatment. In summary, older adults have an increased propensity for losing FFM and a lower capacity for fat reduction during VLCD consumption. On that basis, the matter of sarcopenia becomes an important question to probe during these rapid weight-loss situations.

As a critical manifestation of aging and obesity, previous literature supports a condition in which obese older adults demonstrate a reduced FFM to BW ratio, poor muscle quality, and impaired physical function\(^{297-301}\). This condition has been termed sarcopenic-obesity, which is essentially the coexistence of age-related muscle wasting and excessive adiposity\(^{299}\). As a consequence, the proper clinical approach to obesity treatment for older adults becomes an immense challenge due to the adverse effects of weight-loss on FFM as evidenced by our current findings. In other words, weight-loss therapeutics, such as VLCDs, may exacerbate the sarcopenic progression for older adults. Our findings are corroborated by Weinheimer and colleagues\(^{144}\) who conducted a systematic review of 52 studies that examined age-specific changes in BW and FFM in response to a period of energy restriction. When evaluating weight-loss composition, one-half of their study cohorts lost ≥ 25% of their BW as FFM. From our current analysis, a significant gender by age interaction revealed that the age-related differences in weight-loss composition were primarily driven by the male cohort (Figure 4.6 and 4.8). First of all, age appears to have no bearing on weight-loss and weight-loss composition in females; however, outcomes differed for male patients. Our results indicated that older males lost 61.8±6.3% of their BW due to FM and 38.3±6.3% from FFM. This is reflected by an absolute loss of 14.7±1.7 kg of FM and 9.9±2.7 kg of FFM Younger males, however, exhibited an overtly and significantly (p=0.002) divergent composition as 90.5±3.5% of their weight-loss was accounted for by FM (-24.3 kg), while the decrease in FFM (-2.2 kg) was only 9.7±3.4% contributable. To note, total weight-loss did not differ between male age-cohorts. Overall, this gender by age interaction suggests that among all gender-age cohorts, older males might be most
susceptible to severe lean tissue loss during VLCD treatment. These responses are quite intriguing when considering the number of previous reports indicating the morphological and functional manifestations of sarcopenia to be more severe in men than women\textsuperscript{302-305}.

Collectively, sarcopenic-obesity renders a complex issue for medical practitioners who need to prescribe an appropriate weight-loss treatment that moderates the health risks related to obesity while also preserving muscle to minimize the severity of sarcopenia. On the basis of our findings, these considerations appear more critical for older male patients who lose a greater percentage of weight from FFM and less from FM compared to other gender-age cohorts. Our comprehensive evaluation of age-specific responses confirms the need to restructure the current VLCD-based programs to better optimize weight-loss characteristics for older adults due to the aforesaid issues. These findings stress the importance for healthcare professionals to thoroughly evaluate the risks and benefits of VLCD prescriptions especially for older adults and tailor treatment programs accordingly. This leads us to question how VLCD systems, like Optifast\textsuperscript{®}, can be enhanced through practical interventions.

5.1.4 Implications for Clinical Practice and Research

The most noteworthy contribution of Specific Aim 1 is that proprietary weight-loss systems can be evaluated and translated in a scientifically apt manner. We expect our report to enable both the patient and practitioner a better opportunity to assess the risk and efficacy of proprietary VLCD programs with information beyond what is commercially advertised. We also anticipate our current investigation to act as a model for the nutrition industry to systematically evaluate dietary weight-loss products through scientifically sound research and fully disclose their findings to consumers and providers. As in the pharmaceutical industry, product evaluations and reporting should be mandated within the nutrition industry to prevent falsified or misleading advertising, which unfortunately has become quite pervasive.

On a separate note, our findings demonstrate the considerable need for treatment optimization as it pertains to the post-VLCD management of BW and adiposity. Given the supported health benefits of VLCD-induced weight-loss for the severely obese, it becomes an imperative goal to generate post-treatment conditions that would minimize the chance for a patient to relapse into unhealthy weight-gain. Based on our current assessment of the 12-week Optifast\textsuperscript{®} program, patients experience a reduction in lean tissue, which in certain cohorts, i.e.
old males, is presented more severely than others. Because the preservation of lean tissue, metabolic rate, and physical function plays a critical role in the long-term maintenance of adiposity, practical interventions with large potential to address these factors should be integrated into the programming of VLCD-based treatments.

As others have noted, exercise continues to be a key component of dietary weight-loss endeavors. Exercise affects a wide range of physiological, behavioral, and psychosocial variables, which in most cases are considered more positive than negative for the weight-loss patient. Also, exercise training, mostly aerobic, has been previously scrutinized as a means of enhancing weight-loss composition and/or metabolic rate during dietary restriction in obese participants but has shown equivocal outcomes. Although our analysis of exercise history and attitude was intended only for descriptive purposes, our data reflect the sedentary lifestyle of our overall study cohort (Figure 4.15). Based on patient responses, approximately 53% of the day is spent on activities signifying sedentary behavior, such as watching television, using the computer, sitting at a desk, and standing in one place. Alarmingly, patients reported physical activity to constitute only 2% of their day. These results corroborate data indicating substandard walking function, which in turn may imply poor functionality among these patients (Figure 4.16). Therefore, it appears that physical activity or formal exercise training is relatively non-existent among the patients who are prescribed to undergo VLCD treatment. Further, typical VLCD systems and treatment programs fail to integrate sophisticated and structured applications of exercise assumingly due to the limited availability and translation of data to properly guide medical practitioners. Overall, our findings from Specific Aim 1 support the need for the clinical integration of structured exercise training with the purpose of 1) optimizing weight-loss composition as well as metabolic and functional outcomes; and 2) promoting lifestyle modifications conducive to healthy weight status and long-term management. This ultimately leads us to Specific Aim 2 of our study, which tested the efficacy by which periodized resistance training enhances weight-loss composition, energy metabolism, and muscular function in patients of the same clinical site undergoing a 12-week, protein-supplemented Optifast® treatment. From an added perspective, the use of periodized resistance training for our study may be of benefit to the participants regardless of outcome given that 94% of the study cohort reported interest for strength training (Figure 4.17).
5.2 Specific Aim 2: Periodized Resistance Training Intervention

5.2.1 Outcomes for Body Composition, Energy Metabolism, and Function

Altogether, periodized resistance training demonstrated a favorable impact on weight-loss composition corresponding to positive adaptations for energy metabolism and muscular function. Yet given the limited sample size, it may appear that our findings would lack sufficient representation for this specific clinical population. This limitation, however, might be balanced by data indicating no differences in baseline descriptive measures between the patient cohorts of Specific Aims 1 and 2. Thus, it can be argued that participants of Specific Aim 2, though limited in size, were reflective of the standard VLCD-treated patient at our clinical site. With regard to Specific Aim 2a, we hypothesized that obese patients undergoing periodized resistance training during a protein-supplemented Optifast® treatment would demonstrate enhanced maintenance of lean tissue, fat-loss, metabolic rate, and muscular function when compared to a control condition.

In accordance with our hypothesis, our training protocol was effective in preserving lean tissue and preventing the 5-kg loss associated with the standard treatment control (protein-supplemented Optifast® + steps/day program) (Figure 4.23). When examining the morphometric trajectories of lean tissue, it appears that the initial six weeks (pre to mid) of hypocaloric treatment rendered the greatest decline in LBM for CON (-4 kg or -6%; p<0.05) and RT (-2 kg or -3%; p>0.05). Although no group difference was detected for these early decrements to lean mass, the within-group responses from pre to mid were significant for CON, however not for RT. Moreover, CON exhibited a continual decline in lean mass following week 6 eventually resulting in a significant overall loss of 5.0±0.9 kg (-7.4%). Interestingly for RT, a rebound-like effect for lean mass was evident after the initial 2-kg loss shown at week 6. From that point forward, RT gained almost 1 kg of lean mass resulting in a total pre to post change of -1.2±1.1 kg (p>0.05). This overall change was significantly less than that exhibited by CON. From a practical perspective, it can be suggested from our data that a periodized resistance training intervention during a protein-supplemented VLCD must span at least 6-12 weeks in order for measurable maintenance or perhaps even growth to occur in lean tissue. On the basis of our repeated DXA measures, the catabolic strain putatively imposed by the hypocaloric treatment was merely blunted by our exercise intervention during the initial 6 weeks. However, it appears that the adaptive anabolic response to resistance training was permissible under energy restrictive...
conditions following mid-intervention, during which time RT demonstrated a vertical trend towards lean tissue growth while CON showed continual declines.

There are two interlinked rationales that can be derived from these outcomes for lean tissue. First, the two most well-supported and well-known adaptive responses to progressive resistance training are enhanced neural activation and myofiber hypertrophy, both of which are contributory to muscular strength development\(^{306-310}\). 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)\(^{306}\). In the latter phases of a progressive resistance training regimen (i.e. \(\geq 6\) weeks), myofiber hypertrophy predominates the overall adaptive changes and is typically reflected by a total increase in LBM\(^{306,309}\). The question, however, was whether these delayed hypertrophic adaptations are permitted during severe hypocaloric conditions, such as those presented during our dietary treatment. 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\(^{7}\). Results from RT indicate that periodized resistance training is able to produce a positive trend towards lean tissue growth from weeks 6 to 12 (i.e. second mesocycle) under severe hypocaloric intake, especially when compared to the standard clinical treatment, e.g. conditions of CON. Thus, it appears that the initial stages of intervention failed to elicit any marked influence on muscle growth due to the delayed hypertrophic effect of resistance training. It is conceivable through previous evidence indicated earlier\(^{306}\) and our muscular torque and strength records (Table 4.11), that neural adaptations predominated the first mesocycle of resistance training (i.e. weeks 1-6).

A second rationale for the observed morphometric patterns for lean tissue is derived from data indicating a reduced rate of decline following the first 6 weeks of control treatment (i.e. -6.1% from pre to mid and -1.4% 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. This is moderately supported by biochemical data for circulating cortisol, a major catabolic hormone shown to be a deterrent to muscular growth or maintenance especially during energy deprived conditions\(^{182,187,191,215}\). When data were pooled, cortisol levels significantly increased in the initial half of the treatment, subsequently returning to baseline levels by week 12. Although group-specific responses failed to show significance over time
(perhaps due to a limited sample size), pooled data illustrated a time-dependent pattern consistent with the responses for LBM. We speculate that the diminishing catabolic imposition of the hypocaloric treatment from mid- to post-treatment eventually made conditions permissible for an anabolic and thereby hypertrophic response to manifest in training participants.

Further, it appears from biochemical data that any anabolic response to support the preservation of lean tissue in RT were independent of systemic growth factor levels. Our data demonstrated a temporal response in the circulating IGF-1 system consistent with reports from Henning et al.\textsuperscript{214} 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 level are imperfect indicators of growth potential in muscle, others\textsuperscript{253,257,258} have shown an increase in circulating IGF-1 levels to be concomitant with muscular hypertrophy in response to resistance training. From our current findings, periodized resistance training appears to have no bearing on declining growth factor levels with prolonged hypocaloric treatment, suggesting that the preservation of lean tissue in RT was independent of the IGF-1 system, at least at the systemic level. To speculate on these outcomes, circulating IGF-1, although not as potent, share similar functions as insulin for its regulatory role in maintaining blood glucose homeostasis (i.e. hypoglycemic action)\textsuperscript{311,312}. As evidenced in Specific Aim 1, the Optifast\textsuperscript{®} treatment rendered an approximate 9% reduction in blood glucose levels, which would be likely succeeded by a hypoinsulinemic effect. Given the similar metabolic role of circulating IGF-1, it could be argued that systemic levels were reduced during the hypocaloric treatment in response to decreasing blood glucose levels. Our resistance training protocol may have lacked potency in stimulating a robust increase in circulating bioactive IGF-1 since the consequences would be unfavorable for the maintenance of blood glucose within the given circumstances. Further supporting our data, is Ormsbee et al who showed an increase in insulin sensitivity and

Although our current design was not intended to examine the effects of supplementary protein on weight-loss outcomes, previous findings suggests that the custom protein composition of the Optifast\textsuperscript{®} system is quite inadequate especially when combined with a resistance training intervention. For instance, without protein supplementation, our participants at a mean BW of 127 kg would consume a VLCD providing only 0.66 g of protein/kg of BW/day. Thus, participants would have undergone a VLCD treatment with a protein content below the RDA of

103
Further, meta-analyses suggested that higher-protein consumption of approximately 1.20 g/kg/day promotes greater lean tissue maintenance than diets lower in protein (<0.7 g/kg/day) under weight-loss circumstances, particularly when combined with resistance training.\textsuperscript{144,237} In fact, Pasiakos et al.\textsuperscript{238} showed that consuming 2-3 times above the RDA protein intake lowers the relative contribution of lean tissue 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\textsuperscript{®} protein content, remains insufficient for the preservation of LBM, especially for the average 127-130 kg patient. Based on mean BW data from both Specific Aims 1 and 2 in addition to the aforesaid protein recommendation (1.20 g/kg/day), approximately 150 g of protein per day would be required for the maintenance or perhaps growth of lean tissue 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 150 g/day. Although ~320 kcals were added to the diet, weight-loss appears, at least subjectively, to be unaltered based on BW data from Specific Aim 1 and 2. Specifically, patients of Aim 1, who again underwent an unmodified VLCD and thereby 80 g of protein/day, exhibited a weight-loss of about 22 kg while CON with an additional 80 g of protein and 320 kcals per day lost 20 kg. Although our design limits a cross-evaluation of body composition data between participants undergoing either a protein-supplemented Optifast\textsuperscript{®} or an unmodified treatment, further investigation is warranted given the overt inadequacies of current VLCD programs in terms of protein content and perhaps overall nutrient composition.

With respect to weight-loss quality, the overall reduction in TBM, as measured through DXA, was approximately 20.4±2.6 kg (-16%) for CON and 14.6±1.8 kg (-13%) for RT (minutely different from scale-BW) (Figure 4.22). Statistically speaking, periodized resistance training had no bearing on absolute weight-loss; although from a practical standpoint, a difference of 5 kg would be deemed substantial by most. In fact, some may even consider treatment effectiveness to be compromised by the current training protocol if weight-loss efficacy was delimited to the total reduction in BW. However, when considering the tissue composition of TBM changes, it can be conjectured that RT achieved a more ideal pattern of weight-loss based on differentiated group responses for lean tissue (indicated above) and paralleled group responses for fat-loss (CON: -15.2±2.2 kg vs. RT:-13.4±2.6 kg). Consequently, there was an overt and significant discrepancy for relative weight-loss composition between
groups. For CON, the loss of FM and LBM contributed 75% and 25% towards total weight-loss, respectively, which corroborates findings from Specific Aim 1 as well as reports from others. As for RT, total weight-loss, which again was statistically similar to CON, was 90% attributable to fat-loss and just 10% due to changes in LBM. These group-specific weight-loss compositions were found significantly different, implying that periodized resistance training enhances the quality of weight-loss during a protein-supplemented VLCD treatment. This is supported by the work of Bryner et al who reported similar weight-loss composition following a 12-week resistance training intervention in VLCD-treated participants. Indeed, 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 at least in the context of body composition. For energy metabolism and muscular function, however, our data demonstrated advantages of our training model in contrast to Bryner et al. and other non-periodized attempts.

One of the major tenets underlying the need to preserve lean tissue during diet-induced weight-loss is to maintain RMR at a level favorable for the continual management of body fat. CON experienced a significant 15% or 350.7±89.4 kcal/day suppression of RMR across the entire treatment period with the most dramatic decline occurring in the initial 6 weeks (Figure 4.25). RT, on the other hand, initially exhibited a slight, non-significant decrease, which was then fully recovered by post-intervention. In fact, although not significant over time, RMR was enhanced by 4% from pre- to post-intervention, which was a response 128% greater than CON (p<0.05). In contrast to CON, RMR after adjusting for TBM was significantly improved over time in RT, thereby supporting the use of periodized resistance training as a means to preserve or even perhaps enhance metabolic rate during a large-scale reduction in body mass. We speculate these outcomes for RMR to be largely driven by the observed changes in lean tissue. To support our argument, the responses for RMR and LBM appear to share the same trajectory over time in both groups (Figure 4.23 and 4.25). This relationship is reinforced by data indicating a strong positive correlation (r=0.73) between the relative pre to post changes for RMR and LBM (Figure 4.39). The preservation of lean tissue, thereby, is implicated as a major determinant for the maintenance of energy expenditure during severe hypocaloric treatment.
It also appears that the changes in RMR were slightly disproportionate to the changes in lean mass. This is reflected by the longitudinal course of RMR when normalized to LBM (RMR/LBM) (Table 4.10). RT exhibited a 7% total elevation in RMR/LBM while CON showed an 8% decrease with both responses being significantly different within- and between-groups. If the changes in RMR and LBM were completely proportionate, the ratio between these two variables should remain stable. Therefore, the enhanced metabolic activity exhibited by RT must be partly explained by factors beyond what is solely attributable to changes in lean mass. Schuenke et al.\(^3^{13}\) demonstrated a transient elevation in energy expenditure following a single bout of high-intensity resistance exercise. This acute metabolic response is termed excess post-exercise oxygen consumption or EPOC and is manifested by enhanced energy expenditure for periods up to 38 hours following a resistance exercise bout. Others have even reported a 100 kcal/day increase in energy expenditure for up to 72 hours post-exercise\(^3^{4}\). Therefore, recurring EPOC effects during a resistance training program could expand total energy expenditure to a degree beyond what is due to LBM alone. This would likely contribute towards an upward change in RMR, or at least support its preservation provided that resistance training is simultaneously undertaken with severe caloric restriction. These findings demonstrate the value of resistance training as a utility for weight-management especially during and following a stringent dietary intervention.

Another facet of energy metabolism that was assessed via indirect calorimetry was resting whole-body fat oxidation rate (FO) (Figure 4.26). Our findings were not significant within or between groups although the longitudinal trends for FO showed similarities to that of RMR in each group. The lack of statistical significance was likely due to the large within-group variation as denoted by standard error scores. Interestingly though, circulating β-HB, a biomarker of β-oxidation rate, demonstrated a temporal response quite consistent with that of FO in both groups (Figure 4.35). In CON, both FO and β-HB decreased from pre to post; however only the latter response demonstrated a significant time effect. For RT, FO and β-HB remained unchanged across the 12-week period, yet both variables similarly trended towards a slight initial decrease followed by a rebound-effect towards baseline values. Ultimately, the overall change in β-HB was significantly different between groups; however these outcomes failed to compose divergent responses at the tissue level as CON and RT lost similar amounts of body fat. In fact, this also remained true for changes in circulating FFA and free glycerol levels, which are
indicators of lipolytic activity\textsuperscript{287,288}, at least systemically (Figures 4.33 and 4.34). As a cumulative interpretation of these variables, RT demonstrated greater fat mobilization compared to CON at mid- and post-intervention; however like outcomes for FO, these responses failed to manifest in differences at the tissue level. Although evidence is equivocal, it could be suggested that a periodized resistance training intervention during a modified VLCD may help sustain a heightened rate of fat catabolism and oxidation, which is certainly favorable for the post-treatment management of adiposity. These implications are supported by the works of Kirk et al.\textsuperscript{35} who showed a significant decrease in RQ following 6 months of resistance training reflecting a greater reliance on fat as a bioenergetic fuel source. Further, Ormsbee et al.\textsuperscript{273} showed improved whole-body FO and energy expenditure for up to 40 minutes following a bout of whole-body resistance exercise in obese participants.

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\textsuperscript{7,9,176}, 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 therapeutics especially given the poor existing level of function in severely obese patients as shown through Specific Aim 1 and prior reports\textsuperscript{81-83}. In the current study, there were dramatic group-dependent responses for a spectrum of muscular performance measures, which included contractile kinetics and whole-body isotonic strength. In the present study, we utilized knee extensor and flexor kinetics as a proxy for whole-body neuromuscular function. Corresponding to the standard treatment control, participants exhibited a decline in contractile performance, reflected by significantly reduced muscular torque and power outputs (Table 4.11). These detriments appear to occur proportionally to their observed decline in lean tissue as peak torque values remained stable when adjusted for LBM (Figure 4.28). Thus, in addition to maintaining metabolic rate, the maintenance of lean tissue 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 conducive to unhealthy weight-gain/regain.

In that regard, a periodized 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 44% from pre to post which was a considerable discrepancy to the 13.2% decrease exhibited by CON. These responses for contractile kinetics appear to occur irrespective of lean tissue changes in RT as isometric peak torque improved significantly from pre to post even when normalized to LBM (Figure 4.28). These normalized responses were also pertinent to lower and upper isotonic strength (Figures 4.30 and 4.32). 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 2 kg of LBM during the first 6 weeks of treatment, isometric peak torque was enhanced by approximately 23%. From mid- to post-intervention, during which time LBM remained relatively stable, RT demonstrated continual strength development as evidenced by both kinetic 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 weight-loss circumstances and cross-evaluated with outcomes from a standard treatment control condition.

5.2.2 Application to Clinical Practice and Future Research Implications

Our findings, from a comprehensive perspective, offer compelling support for the integration of periodized resistance training in clinical weight-management programs utilizing VLCD programs with added protein support. On the basis of our findings, the current training intervention should not be applied as a means to facilitate acute fat-loss but rather to optimize treatment outcomes towards conditions that are most conducive to chronic weight-management. Thus, as the overall premise for this study, the preservation or improvement of LBM, metabolic rate, and muscular function are key defining components of weight-loss efficacy, extending beyond former perceptions that only emphasized the total loss of BW. We and others provide empirical evidence in support of resistance training in addressing these components during VLCD or hypocaloric conditions. The current design was unique, however, in that our experimental intervention was systematic, integrative, and tested under real clinical scenarios in participants reflective of the archetype patient. As a result, 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.

As evidenced in Specific Aim 1, treatment responses diverge as a function of gender and/or age, especially in regards to weight-loss composition. For instance, our data indicated that old male patients compared to other gender-age cohorts exhibit the poorest composition of weight-loss as a result of blunted fat reduction and accelerated lean tissue loss. Thus, it is likely that participants under conditions of Specific Aim 2 would respond in a gender- or age-dependent manner. It would, thereby, be an ideal approach to adjust for gender and age when statistically analyzing data from Specific Aim 2. Unfortunately, a limited sample size precluded such analyses, and therefore, data were pooled within groups. This limitation perhaps is balanced by our clinically integrative approach; however, it is an imperative objective for future research to improve sample size possibly by utilizing a multi-center approach for clinical trials. In so doing, a more global representation of treatment efficacy would be achievable. Furthermore, the definitive goal of our research is to minimize the level of futility for weight-loss endeavors incorporating propriety VLCD systems. Therefore, upon reaching an appropriate sample size, follow-up investigations are necessary to validate the long-term implications of our findings as it relates to the incidence of weight-regain following VLCD treatment.
APPENDIX A

THE FLORIDA STATE UNIVERSITY INSTITUTIONAL REVIEW BOARD APPROVAL OF STUDY PROTOCOL

Office of the Vice President For Research
Human Subjects Committee
Tallahassee, Florida 32306-2742
(850) 644-8673 · FAX (850) 644-4392

APPROVAL MEMORANDUM

Date: 11/30/2012
To: Edward Johnson
Address: [Redacted]
Dept.: NUTRITION FOOD AND EXERCISE SCIENCES
From: Thomas L. Jacobson, Chair

Re: Use of Human Subjects in Research
The effects of resistance training and protein supplementation on body composition, metabolic rate, and muscular function during dietary weight-loss treatment

The application that you submitted to this office in regard to the use of human subjects in the research proposal referenced above has been reviewed by the Human Subjects Committee at its meeting on 11/21/2012. Your project was approved by the Committee.

The Human Subjects Committee has not evaluated your proposal for scientific merit, except to weigh the risk to the human participants and the aspects of the proposal related to potential risk and benefit. This approval does not replace any departmental or other approvals which may be required.

If you submitted a proposed consent form with your application, the approved stamped consent form is attached to this approval notice. Only the stamped version of the consent form may be used in recruiting research subjects.

If the project has not been completed by 11/30/2013, you must request a renewal of approval for continuation of the project. As a courtesy, a renewal notice was sent to you prior to your expiration date; however, it is your responsibility as the Principal Investigator to timely request renewal of your approval from the Committee.

You are advised that any change in protocol for this project must be reviewed and approved by the Committee prior to implementation of the proposed change in the protocol. A protocol change/amendment form is required to be submitted for approval by the Committee. In addition, federal regulations require that the Principal Investigator promptly report, in writing, any unanticipated problems or adverse events involving risks to research subjects or others.

By copy of this memorandum, the chairman of your department and/or your major professor is reminded that he/she is responsible for being informed concerning research projects involving human subjects in the department, and should review protocols as often as needed to ensure that the project is being conducted in compliance with our institution and with DHHS regulations.

This institution has an Assurance on file with the Office for Human Research Protection. The Assurance Number is IRB00000446.

Cc: Jeong-Su Kim [Redacted]
HSC No. 2012.9236
APPENDIX B

TALLAHASSEE MEMORIAL HEALTHCARE INSTITUTIONAL REVIEW BOARD APPROVAL OF STUDY PROTOCOL

November 14, 2012

Jeong-Su Kim

Dear Dr. Kim:

Following your presentation to the Institutional Review Board (IRB) at Tallahassee Memorial Healthcare (TMH) on November 13, 2012 IRB #2012-47 Titled: "The Independent and Combined Effects of Progressive Resistance Training and Whey Protein Supplementation on Measures of Body Composition, Resting Metabolic Rate, Muscular Function and Lean-Tissue Metabolism in Clinically Obese Subjects undergoing Medical Dietary Treatment was unanimously approved with the provision that modifications may be submitted to the IRB Chair for consideration using the expedited review guidelines. The approval expires on November 12, 2013.

IRB # 2012-47

The Independent and Combined Effects of Progressive Resistance Training and Whey Protein Supplementation on Measures of Body Composition, Resting Metabolic Rate, Muscular Function and Lean-Tissue Metabolism in Clinically Obese Subjects undergoing Medical Dietary Treatment

Principal Investigator: Jeong-Su Kim
Intramural Investigator: Angelina Cain
Research Coordinator(s): Eddie Jo
Informed Consent: Informed Consent Form version 9/19/06
Support Materials: Data collection forms

Reporting Requirements:
- Report to the IRB any planned change in the study or informed consent and do not implement any change without receiving prior approval, except to eliminate immediate hazard;
- Report to the IRB any unanticipated problems involving risks to subjects;
- Report to the IRB any new information on the project that adversely influences the risk/benefit ratio;
- Report to the IRB any serious or unexpected adverse events;
- Report to the IRB any major protocol violations within ten days. Minor protocol deviations may be reported at the time of the Study Progress Report (Application for Renewal). Maintain a log throughout the year and establish a plan of correction to
APPENDIX C

INFORMED CONSENT FORM
Informed Consent Form

Title of Project: The Independent and Combined Effects of Progressive Resistance Training and Whey Protein Supplementation on Measures of Body Composition, Resting Metabolic Rate, Muscular Function, and Lean-Tissue Metabolism in Clinically Obese Subjects Undergoing Medical Dietary Treatment

Principal Investigator: Dr. Jeong-Su Kim

Other Investigators: Dr. Angelina Cain, Dr. Michael Ormsbee, Dr. Carla Prado, Katie Snyder, Dawn Smith, Ann Frost, and Edward Jo (co-PI)

Participant’s Printed Name: ________________________________

This is a research study. Research studies include only people who want to take part. This form gives you information about this research, which will be discussed with you. It may contain words or procedures that you do not understand. Please ask questions about anything that is unclear to you. Discuss it with your family and friends and take your time to make your decision.

1. Purpose of the Research
You are being offered the opportunity to take part in this research because you are currently a patient at Tallahassee Memorial Hospital prescribed by the physician to undergo a medical weight-loss program which includes a meal replacement diet.

The purpose of this research is to test the effects of resistance training, protein supplementation, or a combination of both on body composition, metabolic rate, and muscular strength during the 12-week medical weight-loss program that you are prescribed to undergo by the physician.

Approximately 48 people will take part in this research at Tallahassee Memorial Hospital Bariatric Center and The Florida State University.

2. Procedures to Be Followed
Approximately one to two weeks prior to the start date of the medical dietary weight-loss treatment at Tallahassee Memorial Hospital (TMH) Bariatric Center, you will meet with the researcher at the center during which time you will provide the researcher with a completed Physician’s Approval Form. Then you will review and sign the informed consent. The researcher will then explain the procedures that you will go through for the first laboratory visit which will be scheduled within the week before the start date of your medical dietary weight-loss treatment. For the first laboratory visit, you will be instructed to arrive at the study site after 8 hours of overnight fasting (no food or drinks except water). You will first be measured for body weight and height. Next, you will be tested for your resting metabolic rate (RMR) or the rate at which you use energy while you rest. The test is safe and requires you to lie down still on your back on a cushion in a dimly lit room for 45 minutes while breathing into a ventilated hood connected to a machine called a metabolic analyzer. The next procedure will be to examine your body composition through a safe technique called dual x-ray absorptiometry (DXA), which will be administered by a qualified technician. This assessment will require you to lay flat on your back on a cushioned machine for about 5 minutes. Afterwards, we will draw 10 ml or about 2 teaspoons of blood

Initials ________

from your arm. After the blood draw, you will be advised to eat a meal-replacement formula, which you will bring with you to the laboratory. Afterwards, you will be tested for leg strength on a machine called an isokinetic dynamometer, which is a commonly used device for therapy and muscle testing. After a light warm-up activity, a trained researcher will position you properly on the seat of the machine and strap you in securely. You will perform 2 practice repetitions of an exercise that requires you to extend your lower leg and then bring it back towards you. These motions will be performed one after the other with full effort. Then, you will perform the exercise for 4 more repetitions of each motion. You will then perform 3 trials of the same motions against an immovable device attached to the dynamometer with full effort. You will be provided sufficient rest time between each strength test. This will be the end of the first laboratory visit. You will then be randomly assigned into one of four groups.

When randomly assigned to a group you will undergo one of the two following exercise training programs for 12 weeks:
- 1) Steps per day exercise program: You will be instructed to achieve a goal number of steps per day. Male participants will take 11,000–12,000 steps per day and females will take 8,000–12,000 steps per day. You will record the number of steps indicated on your pedometer and the type and duration of physical activity you performed during that day on an exercise log at the end of your day. You will be provided with a pedometer free of charge, which you will attach to your clothing at the waist area throughout your entire day;
- 2) Resistance training program: You will perform 3 non-consecutive days of resistance training each week at a training facility. You will be supervised and assisted by a qualified fitness trainer that will exercise you through a total body workout, which will take about 45–60 minutes each training session.

When randomly assigned to a group you will undergo one of the two following nutritional supplementation programs in addition to your exercise program for 12 weeks:
- 1) Protein supplement: You will ingest a serving of a 40 gram pure whey protein supplement twice a day with the meal-replacement formula.
- 2) Placebo supplement: You will consume a serving of placebo supplement twice a day with the meal-replacement formula.

The nutritional supplements indicated above will be a tasteless powder and a single serving will be mixed into 2 separate servings of your meal-replacement powder formula from the medical dietary weight-loss treatment. This mixture will be pre-packaged into individual bags labeled “A” or “B”, which contains one of the two supplements. The information regarding which supplement is included in packages “A” or “B” will only be known to an individual outside of the research team, sealed in an envelope, and will not be revealed until the researcher has completed the study. The reason for this is so that both you and the researcher will not know which supplement you will be given (double-blind). This is to make sure there is no bias in the way you are treated as a participant.

Therefore, you will be randomly assigned to one of these four groups: 1) Steps per day program plus supplement A; 2) Steps per day program plus supplement B; 3) Resistance training program plus supplement A; or 4) Resistance training program plus supplement B.

After you are assigned to a group, you will visit the Bariatric Center (clinical visit) the following week on a designated time and day after a 4 hour period of fasting (no food or drink except water) and no
physical activity. During this clinical visit, you will undergo medical screening and treatment consultation by a physician, a short body composition assessment, a brief measurement of RMR through a handheld device, and attend a group education class led by a registered dietician. All assessments will be administered by a well-trained researcher and are safe and relatively short in duration. You will be provided a week’s worth of meal-replacement formulas and nutritional supplements. You will be required to visit the center, for the purposes mentioned above, every week on the same designated time and day. You will not see the physician every week, but on the 6th and last visit to the center. However, the physician will be present at the center to address any concerns or questions you may have. At the end of your visit to the center, you will be given detailed instructions for your specific exercise program (i.e., steps per day or resistance training program). You will then visit the training facility twice in that same week for an exercise familiarization session and a strength testing session 2 days later. During the strength testing session researchers will test the heaviest amount of weight you can lift properly on 4 specific exercises. After you are tested for these 4 exercises you will be excused from the facility if you are assigned to the steps per day program; however, if you are in the resistance training program you will perform strength tests for 6 additional exercises and then be excused.

If you are in the steps per day program, researchers will monitor your activity each week during your visit to the center. Researchers will collect your exercise logs and provide you with a new one for the following week. If you are in the resistance training program, the researcher will schedule your exercise sessions for the following week during each visit to the center.

You will participate in your assigned exercise and nutritional supplement program until week 12 of your medical dietary treatment. At week 6 of your medical dietary treatment you will visit the laboratory as you did the first time. You will undergo the same tests as you did before. When you have completed 12 weeks of the medical dietary treatment you will also have completed the exercise and nutritional supplementation program. You will then attend your last visit to laboratory for testing. After the final laboratory visit, you will have officially completed the study as a participant. All blood samples collected from you will be stored securely and will not be identified by your personal information.

3. Discomforts and Risks:
There is a minimal level of risk involved if you participate in the study. Risks will be minimized by using well-trained and experienced researchers, exercise-specialists, and laboratory technicians who will ensure that your safety is priority. During resistance training, there is a risk for bodily injury while performing any exercise. This risk will be minimized as a well-trained exercise specialist will be monitoring and assisting you at all times to ensure your safety. There is minor risk involved with the laboratory test procedures. The risks from the blood draw are small and include discomfort with possible bruising or swelling on your arm. The risk of infection is very small. The risk will be minimized by the use of skilled technicians using sterile techniques and equipment. For laboratory muscle strength testing, there is an expected risk of soreness of the thigh muscle. This risk will be minimized by a proper warm-up activity prior to the test. A well-trained and qualified technician will administer all the laboratory tests to minimize the risk involved. There is minimal risk in the use of the nutritional supplements as they occur naturally in whole-foods. Subjects will be under the care and supervision of a registered dietician and bariatric physician during the entire period of use to ensure there are no physical or medical complications with supplementation of whey protein or carbohydrate placebo.

4. Possible Benefits:

Initials ________

a. Possible benefits to the participant:

The possible benefit you may experience from participating in this research includes learning about positive lifestyle modifications through exercise and nutrition for improving health and fitness, gaining knowledge about your body composition, bone health, resting metabolic rate, muscular strength level, and physical fitness, and potential to improve overall health, fitness, strength, body composition and quality of life. You will also be provided with costly assessment procedures, free of charge. There is no guarantee that you will benefit from being in this research.

b. Possible benefits to others:

This study will provide valuable insight as to the benefits of resistance exercise training and protein supplementation in patients undergoing medical treatment for weight-loss. The information gained from this study will potentially help clinicians improve treatment plans for those needing to lose weight for better health and physical function.

5. Other Options that Could be Used Instead of this Research:

You do not have to take part in this research study.

6. Time Duration of the Procedures and Study:

If you agree to take part in this study, your involvement will last approximately 14 weeks. You will be asked to visit the center each week for the 12 weeks you are undergoing the experimental exercise and nutritional programs. Each visit to the center will take approximately 60 minutes. You will be asked to visit the laboratory 3 times, once before, middle, and after the 12 week experimental exercise and nutritional program. Each visit to the laboratory will take approximately 2 hours. If you are assigned to undergo resistance training, you will visit the training facility 3 days per week for 12 weeks, with each session lasting approximately 1 hour.

7. Statement of Confidentiality:

a. Privacy and confidentiality measures

Your research records that are reviewed, stored, and analyzed at The Florida State University and the TMH Bariatric Center will be kept in a secured area in a locked office with access only to the principal investigator. You will be assigned a subject code number and all records and data sheets acquired from this study will only be associated with the subject code and none of your personal information. Your blood samples collected for research purposes will be labeled with your subject code number and will be stored in a secure laboratory with access restricted to the research team.

In the event of any publication or presentation resulting from the research, no personally identifiable information will be shared.

Some of these records could contain information that personally identifies you. Reasonable efforts will be made to keep the personal information in your research record private and confidential but absolute confidentiality cannot be guaranteed.

7b. The use of private health information:

Health information about you will be collected if you choose to be part of this research study. Health information is protected by law as explained in the U.S. Department of Health and Human Services Privacy Notice. If you have not received this notice, please request a copy from...
the researcher. At The Florida State University and TMH Bariatric Center your information will only be used or shared as explained and authorized in this consent form or when required by law. It is possible that some of the other people/groups who receive your health information may not be required by Federal privacy laws to protect your information and may share it without your permission.

To participate in this research you must allow the research team to use your health information. If you do not want us to use your protected health information, you may not participate in this research.

Your permission for the use, retention, and sharing of your identifiable health information will expire upon completion of the research study. At that time, the research information not already in your medical record will be destroyed or information identifying you will be removed from such research results at The Florida State University and TMH Bariatric Center. Any research information in your medical record will be kept indefinitely.

If you choose to participate, you are free to withdraw your permission for the use and sharing of your health information at any time. You must do this in writing. Write to Dr. Jeong-Su Kim and let him know that you are withdrawing from the research study. His mailing address is: 

If you withdraw your permission:
- We will no longer use or share medical information about you for this research study, except when the law allows us to do so.
- We are unable to take back anything we have already done or any information we have already shared with your permission.
- We may continue using and sharing the information obtained prior to your withdrawal if it is necessary for the soundness of the overall research.
- We will keep our records of the care that we provided to you as long as the law requires.

The research team may use the following sources of health information.
- Patient/subject name
- Telephone number
- Blood samples
- Health information will only be used during the time span of the research study

Representatives of the following people/groups within Tallahassee Memorial Hospital Bariatric Center and The Florida State University may use your health information and share it with other specific groups in connection with this research study.
- The principal investigator, Dr. Jeong-Su Kim
- The TMH and The Florida State University Institutional Review Board
- The TMH and The Florida State University Human Subjects Protection Office
- The co-principle investigator, Edward Jo
- The intramural principal investigator, Dr. Angelina Cain

Initials __________

FSU Human Subjects Committee Approved on 11/28/2012. Void after 11/20/2013. HSC # 2012-9236
The above people/groups may share your health information with the following people/groups outside TMH Bariatric Center and The Florida State University for their use in connection with this research study. These groups, while monitoring the research study, may also review and/or copy your original TMH Bariatric Center and The Florida State University records.

- The Office of Human Research Protections in the U.S. Department of Health and Human Services

We will do our best to make sure that the personal information in your medical record will be kept private. However, because of the need to release information to the above parties, absolute confidentiality cannot be guaranteed. Once your personal health information is released, it may be redisclosed and no longer protected by federal privacy regulations. Your personal information may also be given out if required by law and in rare circumstances may be subpoenaed by a court.

8. Costs for Participation:
   a. Costs:

   There will be no direct cost to you for participation in this study.

   b. Treatment and compensation for injury:

   Every effort to prevent injury as a result of your participation will be taken. It is possible, however, that you could develop complications or injuries as a result of participating in this research study. In the event of injury resulting from this research, medical treatment is available but will be provided at the usual charge. It is the policy of this institution to provide neither financial compensation nor free medical treatment for research-related injury.

   Costs for the treatment of research-related injuries will be charged to your insurance carrier or to you. Some insurance companies may not cover costs associated with research studies. If for any reason these costs are not covered by your insurance, they will be your responsibility. You will also be responsible for any deductible, co-insurance and/or co-pay.

   You will not lose any legal rights by signing this form.

9. Compensation for Participation:
   You will not receive any compensation for being in this research study.

10. Research Funding:
    The institution and investigators are not receiving any funds to support this research study.

11. Voluntary Participation:
    Taking part in this research study is voluntary. If you choose to take part in this research, your major responsibilities will include to maintain compliance to the experiment conditions for which you are assigned to undergo. You do not have to participate in this research. If you choose to take part, you have the right to stop at any time. If you decide not to participate or if you decide to stop taking part in the research at a later date, there will be no penalty or loss of benefits to which you are entitled.
Your research doctor may take you out of the research study without your permission. Some possible reasons for this are: continuing the research would be harmful, your condition has become worse, or you did not follow the instructions of the researcher and principle investigator. If your participation in the research ends early, you may be asked to visit the research doctor for a final visit.

12. Contact Information for Questions or Concerns:
You have the right to ask any questions you may have about this research. If you have questions, complaints or concerns or believe you may have developed an injury related to this research, contact Dr. Jeong-Su Kim at [redacted].

If you have questions regarding your rights as a research participant or you have concerns or general questions about the research or about your privacy and the use of your personal health information, contact the research protection advocate Chair of the Human Subjects Committee, Institutional Review Board, Office of the Vice President for Research, [redacted] and Cynthia Blair, Administrative Liaison/IRB, Tallahassee Memorial HealthCare, [redacted]. You may also call this number if you cannot reach the research team or wish to talk to someone else.

For more information about participation in a research study and about the Institutional Review Board (IRB), a group of people who review the research to protect your rights, please visit the TMH IRB’s Web site. Included on this web site, under the heading “Participant Info”, you can access federal regulations and information about the protection of human research participants. If you do not have access to the internet, copies of these federal regulations are available by calling TMH at 850-431-5676.

Signature and Consent/Permission to be in the Research
Before making the decision regarding enrollment in this research you should have:
• Discussed this study with an investigator,
• Reviewed the information in this form, and
• Had the opportunity to ask any questions you may have.

Your signature below means that you have received this information, have asked the questions you currently have about the research and those questions have been answered. You will receive a copy of the signed and dated form to keep for future reference.

**Participant**: By signing this consent form, you indicate that you are voluntarily choosing to take part in this research.

<table>
<thead>
<tr>
<th>Signature of Participant</th>
<th>Date</th>
<th>Time</th>
<th>Printed Name</th>
</tr>
</thead>
</table>

**Participant’s Legally Authorized Representative**: By signing below, you indicate that you give permission for the participant to take part in this research.

<table>
<thead>
<tr>
<th>Signature of Participant’s Legally</th>
<th>Date</th>
<th>Time</th>
<th>Printed Name</th>
</tr>
</thead>
</table>

Initials ________

Authorized Representative

(Signature of Participant’s Legally Authorized Representative is required for people unable to give consent for themselves.)

Description of the Legally Authorized Representative’s Authority to Act for Participant

**Person Explaining the Research:** Your signature below means that you have explained the research to the participant/participant representative and have answered any questions he/she has about the research.

Signature of person who explained this research  Date  Time  Printed Name
(Only approved investigators/research coordinators and those trained in obtaining research informed consent and familiar with this research may explain the research and obtain informed consent.)

In addition to the main part of the research study, there is an optional part of the research. You can participate in the main part of the research without agreeing to take part in this optional part.

**Optional Tissue Storage for Future Use**
As part of this study, we are obtaining blood from you. If you agree, the researchers would like to store leftover samples of your blood so that your blood can be studied in the future after this study is over. These future studies may provide additional information that will be helpful in understanding muscle and bone loss or gain, but it is unlikely that these studies will have a direct benefit to you. The results of these tests will not have an effect on your care. Neither your doctor nor you will receive results of these future research tests, nor will the results be put in your health record. If you have any questions, you should contact Dr. Jeong-Su Kim at [Phone number]

Your leftover samples will be labeled with a code number. These samples will be stored in Dr. Jeong-Su Kim’s locked laboratory at The Florida State University. If you consent to the collection of samples of your blood for future research, the period for the use of the samples is unknown. If you agree to allow your blood to be kept for future research, you will be free to change your mind at any time. You should contact Dr. Jeong-Su Kim at [Phone number] and let him know you wish to withdraw your permission for your blood to be used for future research. Any unused blood will be destroyed and not used for future research studies.

**Participant:** By signing below, you indicate that you have read the information written above and have indicated your choices for the optional part of the research study.

Signature of Participant  Date  Time  Printed Name

Initials

*SU Human Subjects Committee Approved on 11/28/2012. Void after 11/20/2013. HSC # 2012.9236*
Participant's Legally Authorized Representative: By signing below, you indicate that you have read the information written above and have indicated your choices for the optional part of the research study.

Signature of Participant's Legally Authorized Representative

Date

Time

Printed Name

(Signature of Participant's Legally Authorized Representative is required for people unable to give consent for themselves.)

Description of the Legally Authorized Representative's Authority to Act for Participant

Person Explaining the Research: Your signature below means that you have explained the optional part of the research to the participant/participant representative and have answered any questions he/she has about the research.

Signature of person who explained this research

Date

Time

Printed Name

Initials

Page 9 of 9

APPENDIX D
STRENGTH TEST DATA SHEET

<table>
<thead>
<tr>
<th>EXERCISE</th>
<th>SETTINGS</th>
<th>10RM</th>
<th>Extrapolated 1-RM</th>
<th>EXERCISE</th>
<th>SETTINGS</th>
<th>10RM</th>
<th>Extrapolated 1-RM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leg Extension</td>
<td>WU1:</td>
<td></td>
<td></td>
<td></td>
<td>WU1:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>WU2:</td>
<td></td>
<td></td>
<td></td>
<td>WU2:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1:</td>
<td></td>
<td></td>
<td></td>
<td>1:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2:</td>
<td></td>
<td></td>
<td></td>
<td>2:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3:</td>
<td></td>
<td></td>
<td></td>
<td>3:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>4:</td>
<td></td>
<td></td>
<td></td>
<td>4:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>5:</td>
<td></td>
<td></td>
<td></td>
<td>5:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seated Back Row</td>
<td>WU1:</td>
<td></td>
<td></td>
<td></td>
<td>WU1:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>WU2:</td>
<td></td>
<td></td>
<td></td>
<td>WU2:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1:</td>
<td></td>
<td></td>
<td></td>
<td>1:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2:</td>
<td></td>
<td></td>
<td></td>
<td>2:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3:</td>
<td></td>
<td></td>
<td></td>
<td>3:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>4:</td>
<td></td>
<td></td>
<td></td>
<td>4:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>5:</td>
<td></td>
<td></td>
<td></td>
<td>5:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seated Leg Curls</td>
<td>WU1:</td>
<td></td>
<td></td>
<td></td>
<td>WU1:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>WU2:</td>
<td></td>
<td></td>
<td></td>
<td>WU2:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1:</td>
<td></td>
<td></td>
<td></td>
<td>1:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2:</td>
<td></td>
<td></td>
<td></td>
<td>2:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3:</td>
<td></td>
<td></td>
<td></td>
<td>3:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>4:</td>
<td></td>
<td></td>
<td></td>
<td>4:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>5:</td>
<td></td>
<td></td>
<td></td>
<td>5:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shoulder Press</td>
<td>WU1:</td>
<td></td>
<td></td>
<td></td>
<td>WU1:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>WU2:</td>
<td></td>
<td></td>
<td></td>
<td>WU2:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1:</td>
<td></td>
<td></td>
<td></td>
<td>1:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2:</td>
<td></td>
<td></td>
<td></td>
<td>2:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3:</td>
<td></td>
<td></td>
<td></td>
<td>3:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>4:</td>
<td></td>
<td></td>
<td></td>
<td>4:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>5:</td>
<td></td>
<td></td>
<td></td>
<td>5:</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## ISOTONIC MUSCULAR STRENGTH VALUES (ALL GROUPS)

<table>
<thead>
<tr>
<th>EXERCISE</th>
<th>1RM</th>
<th>65%</th>
<th>70%</th>
<th>75%</th>
<th>80%</th>
<th>85%</th>
<th>90%</th>
<th>95%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest Press</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leg Press</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### VALUES FOR RT PRESCRIPTION (RT-GROUPS ONLY)

<table>
<thead>
<tr>
<th>EXERCISE</th>
<th>65%</th>
<th>70%</th>
<th>75%</th>
<th>80%</th>
<th>85%</th>
<th>90%</th>
<th>95%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leg Extension</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seated Back Row</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seated Leg Curls</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shoulder Press</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Back Squats</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lat Pulldown</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triceps Extension</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biceps Curls</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Extrapolated 1RM = 10RM Load x \(1 + (0.033 \times 10)\) or refer to Baechle-referenced chart

### COMMENTS

- 
- 
- 
- 
- 

### SUBJECT

- **#**: 
- **Initials**: 
- **Group** (circle one): A / B / RT+A / RT+B

### Tester

- **Initials**: 
- **Strength Testing Session**: Familiarization / Pre / Mid / Post

### Date

- **Date**: 
- **Time of Completion**: 

---

FSU/TMH Weight-Loss Study (2 of 2)

Eddie Jo

123
# APPENDIX E

## LABORATORY TEST DATA SHEET

<table>
<thead>
<tr>
<th>Measures</th>
<th>Trial 1</th>
<th>Trial 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Body Weight (kg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Height (cm)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body Mass Index (kg/m²)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Waist Circumference (cm)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Measures</th>
<th>Whole-Body</th>
<th>ROI-Extremities</th>
<th>ROI-Trunk</th>
<th>ROI-Android</th>
<th>ROI-Gynoid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Mass (kg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fat Mass (kg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fat Percentage (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lean Mass (kg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone Mineral Content (g)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone Mineral Density (g/cm²)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

## RESTING METABOLIC RATE (ParvoMedic)

<table>
<thead>
<tr>
<th>Metabolic Analyzer Calibrated</th>
<th>Time Start:</th>
<th>Time End:</th>
<th>Time Used:</th>
</tr>
</thead>
<tbody>
<tr>
<td>RMR (kcal/day)</td>
<td>RMR (kcal/min)</td>
<td>RMR (kcal/day/kg TBM)</td>
<td>RMR (kcal/day/kg LBM)</td>
</tr>
</tbody>
</table>

## BLOOD DRAW CHECKLIST

BLOOD DRAW COMPLETED = SERUM SEPARATED AND ALIQUOTED = SAMPLES LABELED & STORED IN FREEZER =

(INSTRUCT PARTICIPANT TO CONSUME MEAL REPLACEMENT FORMULA)
# ISOKINETIC AND ISOMETRIC DYNAMOMETRY (Biodex)

## PRE-TEST CHECKLIST:

1. Subject consumed meal [ ]
2. 5 minute warm-up activity completed [ ]
3. Dynamometer position set [ ]

## DYNAMOMETER POSITION SETTINGS

<table>
<thead>
<tr>
<th>Lateral Arm Position</th>
<th>Forward Seat Position</th>
<th>Back Support Position</th>
<th>Attachment Length</th>
<th>Limb Side</th>
</tr>
</thead>
</table>

## ISOKINETIC STRENGTH TESTING: 60°·s⁻¹

<table>
<thead>
<tr>
<th>JOINT MOVEMENT</th>
<th>PEAK TORQUE (Nm)</th>
<th>RELATIVE PEAK TORQUE (Nm/TBM kg)</th>
<th>RELATIVE PEAK TORQUE (Nm/LBM kg)</th>
<th>AVG POWER (W)</th>
<th>RELATIVE AVG POWER (W/TBM kg)</th>
<th>RELATIVE AVG POWER (W/LBM kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Knee Extension</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Knee Flexion</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

## ISOMETRIC STRENGTH TESTING: 0°·s⁻¹, 60°

<table>
<thead>
<tr>
<th>JOINT MOVEMENT</th>
<th>PEAK TORQUE (Nm)</th>
<th>RELATIVE PEAK TORQUE (Nm/TBM kg)</th>
<th>RELATIVE PEAK TORQUE (Nm/LBM kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Knee Extension</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Knee Flexion</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

## COMMENTS:

__________________________________________

__________________________________________

__________________________________________

__________________________________________

__________________________________________

TIME OF COMPLETION: ___________                      TESTER (initials): ________

FSU/TMH Weight-Loss Study

Eddie Jo
APPENDIX F

CLINICAL VISIT DATA SHEET

Clinical Visit Assessments @ TMH Bariatric Center: Data Sheet

<table>
<thead>
<tr>
<th>SUBJECT #</th>
<th>SUBJECT (initials)</th>
<th>GROUP (circle one): A / B / RT+A / RT+B</th>
<th>TESTER (initials)</th>
<th>CLINICAL VISIT (circle one): 1 / 2 / 3 / 4 / 5 / 6 / 7 / 8 / 9 / 10 / 11 / 12 / 13</th>
<th>DATE:</th>
<th>TIME OF ARRIVAL:</th>
<th>4-hour fast? Y / N</th>
<th>48-hour no activity? Y / N</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>BODY COMPOSITION (BIA Tanita Analyzer)</th>
<th>MEASURES</th>
<th>lbs</th>
<th>kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Body Weight</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lean Body Mass</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fat Mass</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fat Percentage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body Mass Index (kg/m²)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Impedance (ohms)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>RESTING METABOLIC RATE (Med Gem)</th>
<th>MEASURES</th>
<th>TRIAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Med Gem Calibrated □</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subject rested for 10 minutes □</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time Start:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time End:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resting Metabolic Rate (kcal/day)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resting VO₂ (ml/min)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

OPTIFAST DIETARY LOG COLLECTED AND COPIED □
EXERCISE LOG COLLECTED □
NEW WEEKLY EXERCISE LOG DISBURSED □
EMPTY BAGS COLLECTED □
NEW WEEKLY SUPPLEMENTS DISBURSED □
WEEKLY APPOINTMENTS SCHEDULED IF NECESSARY □

COMMENTS:

TIME COMPLETED: ________

FSU/TMH Weight-Loss Study

Eddie Jo
## APPENDIX G

### DAILY ACTIVITY LOG

<table>
<thead>
<tr>
<th></th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
<th>Day 5</th>
<th>Day 6</th>
<th>Day 7</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Week 1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total Steps</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Types of Activity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total Time of Activity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Comments</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
APPENDIX H

RESISTANCE EXERCISE LOG

<table>
<thead>
<tr>
<th>EXERCISE</th>
<th>DESCRIPTION / SETTINGS</th>
<th>SET</th>
<th>LOAD RxE</th>
<th>LOAD LIFTED</th>
<th>REPS</th>
<th>RPE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Squats</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Chest Press</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Leg Press</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Lat Pulldown</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Leg Extension</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Shoulder Press</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Leg Curls</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Back Row</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Triceps Ext</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Biceps Curls</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
APPENDIX I
EXERCISE HISTORY AND ATTITUDE QUESTIONNAIRE

Exercise History and Attitude Questionnaire

Name: ___________________________ DOB: ___________ Date: ________________

General Instructions: Please fill out this form as completely as possible. If you have any questions, ask the trainer at your first meeting.

1. Please rate your exercise level on a scale of 1 to 5 (1 = easy, 5 = very strenuous) at each age.
   Age: 15-20 ______ 21-30 ______ 31-40 ______ 41-50 ______ 51-60 ______ 61+ ______

2. Were you a high school and/or college athlete?
   □ Yes □ No  If yes, please explain: ____________________________________________

3. Rate yourself on a scale of 1 to 5 (1 = least and 5 = most).

<table>
<thead>
<tr>
<th>Athletic Ability</th>
<th>Competition</th>
<th>Cardiovascular Capacity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 2 3 4 5</td>
<td>1 2 3 4 5</td>
<td>1 2 3 4 5</td>
</tr>
<tr>
<td>Muscular Capacity</td>
<td>Flexibility Capacity</td>
<td></td>
</tr>
<tr>
<td>1 2 3 4 5</td>
<td>1 2 3 4 5</td>
<td></td>
</tr>
</tbody>
</table>

4. When you start an exercise program
   □ I stick with it until I accomplish my goal.
   □ I stick with it most of the time.
   □ I'm good for a month and then miss a month and then back on again repeatedly.
   □ I usually don't stick with it very long and then quit.

5. How much time are you willing to devote to an exercise program?
   ______ minutes per day ______ days per week

6. Do you currently do cardiovascular exercise?
   Type(s): ___________________________ ________ minutes per day ________ days per week

7. Rate your perception of exertion during your cardiovascular exercise.
   □ Light □ Fairly Light □ Somewhat Hard □ Hard

8. How long have you been exercising regularly?
   ______ months ______ years

9. What other exercise, sport or active recreational activities have you participated in?
   In the past 6 months? ____________________________
   In the past 5 years? ____________________________

10. Can you exercise during your work day? □ Yes □ No
11. What types of exercise interest you?

☐ Walking  ☐ Cycling  ☐ Stair Climbing  ☐ Jogging  ☐ Group Exercise  ☐ Yoga/Pilates  
☐ Elliptical  ☐ Swimming  ☐ Strength Training  ☐ Racquet Sports  ☐ Rock Climbing  
Other

12. What do you want exercise to do for you?

________________________________________________________________________

________________________________________________________________________

13. Rate each goal separately: Not Important Somewhat Important Extremely Important

1  2  3

a. Improve cardiovascular fitness

b. Lose weight

c. Lose body fat

d. Reshape my body

e. Improve performance for sports or other activity

f. Improve my ability to cope with stress

g. Improve flexibility

h. Increase strength

i. Improve balance

j. Increase energy level

k. Feel better

l. Prevent/treat a medical condition

14. How many pounds would you like to lose? ________ pounds

15. What is your usual pace of walking?

a. _______ casual or strolling (less than 2 mph)

b. _______ average or normal (2-3 mph)

c. _______ fairly brisk (3-4 mph)

d. _______ brisk or striding (> 4 mph)

16. How many flights of stairs do you climb each day? ________ flights/day

17. How many hours do you spend watching TV per day? ________ hours/day

18. How many hours do you spend using your computer? ________ hours/day

19. How much of your work day is spent at a desk? ________ hours/day

20. How much of your work day is spent walking around? ________ hours/day

21. How much of your day is spent standing in one spot? ________ hours/day

22. At least once/week do you participate in regular activity like brisk walking, jogging, biking, swimming, etc. long enough to work up a sweat?

☐ No  ☐ Yes  How many times/week? ________ Activity ______________________

Signature: __________________________ DOB: __________ Date: __________

Reviewed by Exercise Specialist: __________________________ Date: __________  
Sept. 2011
REFERENCES

1. Flegal KM, Carroll MD, Kit BK, Ogden CL. Prevalence of obesity and trends in the

2. Joint WHO/FAO Expert Consultation on Diet Nutrition and the Prevention of Chronic
Diseases (2002 : Geneva Switzerland)., World Health Organization. Dept. of Nutrition for Health
and Development. Diet, nutrition and the prevention of chronic diseases : report of a joint
Organization; 2003.

http://www.cdc.gov/nchs/data/databriefs/db82.htm#Ref6.)

4. Tsai AG, Wadden TA. Systematic review: an evaluation of major commercial weight loss

5. Wadden TA, Frey DL. A multicenter evaluation of a proprietary weight loss program for

6. Walsh MF, Flynn TJ. A 54-month evaluation of a popular very low calorie diet program.


combined with an 800 calorie liquid diet on lean body mass and resting metabolic rate. J Am

11. McIver CM, Wycherley TP, Clifton PM. MTOR signaling and ubiquitin-proteosome
gene expression in the preservation of fat free mass following high protein, calorie restricted

12. Chaston TB, Dixon JB, O'Brien PE. Changes in fat-free mass during significant weight

13. Ravussin E, Lillioja S, Knowler WC, et al. Reduced rate of energy expenditure as a risk


129. Standard for formula foods for use in very lowenergy diets for weight reduction. at www.codexalimentarius.net/STANDARD/volume4/vol4 E.htm.)


225. Layman DK. The role of leucine in weight loss diets and glucose homeostasis. J Nutr 2003;133:261S-7S.


BIOGRAPHICAL SKETCH

Edward Jo was born in Bellflower, California to Yung Hak and Eun Im Jo. He attended Sonora High School in La Habra, CA where he played a number of sports including, football and track and field. In 2001, he began his pursuit of a B.S in Kinesiology at California State University, Long Beach with an emphasis in Fitness. Edward graduated from CSULB in 2006 with honors. During this time Edward became a certified personal trainer through the National Strength and Conditioning Association. Immediately following his undergraduate education, Edward was accepted into the Kinesiology graduate program at California State University, Fullerton. During his graduate education there, Edward became a Certified Strength and Conditioning Specialist also through the National Strength and Conditioning Association. Edward earned his M.S in Kinesiology in 2009 and subsequently moved to Tallahassee, FL to pursue a doctoral education in Exercise Physiology at Florida State University in the Department of Nutrition, Food, and Exercise Sciences. Edward is conducting research in the area of skeletal muscle physiology, obesity, and weight-loss. During his graduate education, Edward has published a number of peer-reviewed articles and presented his research at national conferences. Edward will continue his scholarly work and professional career as an assistant professor in Kinesiology and Exercise Physiology.