STRATEGIES FOR THE REDUCTION OF ADIPOSE TISSUE AND RETENTION OF MUSCLE MASS IN OVERWEIGHT INDIVIDUALS

A Dissertation
Submitted to the Graduate Faculty
of the
North Dakota State University
of Agriculture and Applied Science

By

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In Partial Fulfillment of the Requirements
for the Degree of
DOCTOR OF PHILOSOPHY

Major Program:
Exercise Science and Nutrition

March 2020

Fargo, North Dakota

North Dakota State University

Graduate School

Title

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The Supervisory Committee certifies that this ***disquisition*** complies with North Dakota State University's regulations and meets the accepted standards for the degree of

DOCTOR OF PHILOSOPHY

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ABSTRACT

Purpose: The purpose of this study was to determine whether time-restricted feeding (TRF) was an effective dietary strategy for reducing fat mass and preserving fat-free mass while evaluating potential changes in cardiometabolic biomarkers, hormones, muscle performance, and energy and macronutrient intake after eight weeks of aerobic exercise and resistance training in overweight and obese adults. **Methods:** This study was a randomized, controlled trial. Sedentary, overweight and obese adults (mean ± SD; age: 44.48 ± 7.28 years; BMI: 29.61 ± 2.62 kg/m^2; females: 85.71%; males: 14.29%) were randomly assigned to a TRF or normal feeding (NF) dietary strategy group. The TRF group consumed all calories between 1200 and 2000 hours, whereas the NF group ate their typical diet. All groups completed eight weeks of aerobic exercise and supervised resistance training. Body composition, muscle performance, energy and macronutrient intake, physical activity, and physiological variables were assessed week zero and week nine. **Results:** A total of 21 participants completed the study (NF: n = 10; TRF: n = 11). A mild energy restriction was seen for the TRF (~300 kcal/day, 14.0%) and NF (~250 kcal/d, 11.0%) groups between baseline and week seven. Losses of total body mass were significantly greater for TRF (3.3%) relative to NF (0.2%), of which TRF had significantly greater losses of fat mass (9.0%) compared to NF (3.3%) despite similar reductions in energy intake. Lean mass increased across the intervention for both TRF (0.6%) and NF (1.9%), with no group differences. **Conclusion:** These data support the use of TRF and concurrent exercise training as a short-term dietary strategy for reducing fat mass and preserving lean mass in overweight and obese adults.

ACKNOWLEDGEMENTS

First, I would like to express my gratitude to my advisor Dr. Kyle Hackney for his continued mentorship throughout my graduate career at North Dakota State University. Dr. Hackney has always supported my research interests and provided me with many opportunities to grow and develop as an effective teacher and researcher. I would like to thank Dr. Sherri Stastny for her constant guidance and encouragement over these last several years. Dr. Stastny has gone out over her way to ensure that I am promoting and conducting myself professionally by critiquing my work and placing me in positions that facilitate my personal development. Of course, I need to thank the rest of my committee for their thought provoking comments and inspiration during my dissertation process.

To my fellow/former graduate students Mr. Nathaniel Johnson and Mr. Sean Mahoney, I want to thank them for their assistance with data collection. I truly value their support and, most importantly, their friendship.

I would also like to recognize the outstanding effort of the Wallman Wellness Center staff and personal trainers who collaborated on the project. The participants truly valued their experience with them.

Special appreciation to both Dr. Margaret Fitzgerald, College of Human Development and Education, and Dr. Yeong Rhee, Department of Health, Nutrition, and Exercise Sciences for their continued backing throughout my career.

Lastly, I would like to thank the National Institute of General Medical Sciences, 1U54GM115458, for funding the project. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

DEDICATION

This dissertation is dedicated to:

the great Jim Rohn for inspiring me;

my instructors for encouraging me;

my parents for supporting me;

my family for believing in me;

my friends for laughing with me;

myself for the continued positivity.

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LIST OF ABBREVIATIONS

1RM..... One-Repetition Maximum

BMD..... Bone Mineral Density

BMI ..... Body Mass Index

CER ..... Continuous Energy Restriction

DXA ..... Dual-Energy X-Ray Absorptiometry

GWAS ..... Genome-Wide Association Studies

HDL..... High-Density Lipoprotein Cholesterol

HOMA-IR..... Homeostatic Model Assessment of Insulin Resistance

HRR..... Heart Rate Reserve

hsCRP..... High-Sensitivity C-Reactive Protein

IER ..... Intermittent Energy Restriction

IF ..... Intermittent Fasting

IL-6..... Interleukin-6

IL-1B Interleukin-1B

IGF ..... Insulin-Like Growth Factor

KD..... Ketogenic Diet

LDL ..... Low-Density Lipoprotein Cholesterol

ND..... Normal Diet

NF..... Normal Feeding

RDA ..... Recommended Dietary Allowance

RF..... Ramadan Fasting

SES..... Socioeconomic Status

TNF-a ..... Tumor Necrosis Factor-a

TRF ..... Time-Restricted Feeding

US..... United States

1. INTRODUCTION

1.1. Overview of the Problem

Obesity prevalence continues to increase in the United States (U.S.) population, along with incidences of physical dysfunction and obesity-related conditions (i.e., cardiovascular disease, stroke, type 2 diabetes, and certain types of cancers; Hales, Carroll, Fryar, & Ogden, 2017; National Heart Lung and Blood Institute, 2013). These conditions represent a major health problem and are some of the leading causes of preventable death in the U.S (National Heart Lung and Blood Institute, 2013). While diet and exercise improve many health consequences of obesity and attenuate declines in muscle mass and strength, dietary strategies are not always followed nor manageable for long-term use (Anastasiou, Karfopoulou, & Yannakoulia, 2015; Beavers et al., 2015). Thus, alternative dietary strategies, such as time-restricted feeding (TRF), are undergoing significant research to validate their ability to preserve fat-free mass during weight loss and reduce disease risk (Barnosky, Hoddy, Unterman, & Varady, 2014; Moro et al., 2016; Tinsley et al., 2017).

1.2. Statement of Purpose

The purpose of this study was to:

1. Determine whether TRF was an effective dietary strategy for reducing fat mass while preserving fat-free mass in combination with aerobic and resistance training.
2. Evaluate potential changes in health-related biomarkers and indicators of muscle health (mass, strength) after eight weeks of TRF and concurrent exercise training.
3. Examine the influence of energy intake and macronutrient distribution on muscle health in TRF and normal feeding (NF) throughout the study intervention.

1.3. Research Questions

1. Does TRF help reduce fat mass and preserve fat-free mass in combination with concurrent training?
2. Does TRF cause changes in health-related biomarkers (cardiovascular profile and anabolic-catabolic hormones) and muscle health indicators (mass, strength, and quality) after eight weeks of concurrent training?
3. Will TRF affect the distribution of energy and macronutrient intake throughout the study intervention?

1.4. Dependent Variables

The dependent variables for this study included resting blood pressure and heart rate, body mass and height, hip and waist circumference, functional markers from dried blood spot testing (i.e., insulin, high-sensitivity C-reactive protein [hsCRP], hemoglobin A1c, triglycerides, cholesterol, high-density lipoprotein cholesterol [HDL], low-density lipoprotein cholesterol [LDL], and very low-density lipoprotein cholesterol [VLDL]) and saliva testing (i.e., estradiol, progesterone, testosterone, dehydroepiandrosterone sulfate [DHEAS], and cortisol), body composition and bone mineral density (BMD) from dual-energy x-ray absorptiometry (DXA), hand grip strength, heart rate recovery from a three-minute step test, knee extensor and flexor peak torque and total work from muscle performance, sedentary, light, moderate, vigorous, and very vigorous physical activity levels from accelerometry, and energy and macronutrient intake from three-day dietary intake logs.

1.5. Independent Variables

The independent variables for this study were dietary strategy (TRF or NF) and the concurrent aerobic and resistance exercise training.

1.6. Limitations

Limitations for this study included an inability to objectively confirm adherence to TRF, a reliance on a limited number of self-reported dietary intake records, uncontrolled nutrient intake among dietary strategies, an inclusion of primarily female participants, and intervention duration of only eight weeks.

1.7. Delimitations

Delimitations for this study included the use of an ActiGraph GT3X+ accelerometer which was unable to track activities such as cycling and weightlifting. A researcher suggested ad libitum approach to TRF was implemented to examine its influence on nutrient consumption. Finally, the recruitment of sedentary, overweight and obese adults between the ages of 35 and 60 years; therefore, the results may not be transferrable to other age groups or fitness levels.

1.8. Assumptions

It was assumed that participants in the TRF group consumed all dietary energy intake and completed all concurrent exercise training between 1200 and 2000 hours and the participants honestly reported their physical activity levels before and during the study to the best of their ability.

1.9. Significance of Study

The study distinguishes itself by incorporating both an aerobic and resistance training intervention with TRF in sedentary, overweight and obese middle-aged adults, who are at a greater risk of cardiovascular disease and physical dysfunction. Our research shows that TRF, in combination with concurrent exercise training, effectively reduces fat mass while preserving fat-free mass. This is important because TRF does not require a restrictive energy intake, such as with continuous energy restriction (CER), which is associated with poor compliance and muscle

loss. Thus, TRF and concurrent exercise training may be an ideal dietary approach for reducing fat mass and preserving lean mass in overweight and obese adults

1.10. Definitions

Accelerometer is a device that measures acceleration from body movement which can be converted into objective measures of physical activity such as frequency, duration, and intensity (L. Choi, Liu, Matthews, & Buchowski, 2011).

Continuous energy restriction is a reduction in daily energy intake up to 40% and is a primary dietary strategy to help individuals decrease fat mass and lower the risk of cardiovascular disease (Longo & Mattson, 2014).

Dual-energy x-ray absorptiometry is a low dose x-ray used to diagnose osteoporosis, assess the risk of fracture, and monitor changes in BMD over time, and is considered a gold standard technique for assessing body composition (Baim et al., 2005).

Intermittent fasting is a revolving pattern of food intake, with intermittent periods of little or no energy intake (Mattson, Longo, & Harvie, 2017).

Physical activity is any body movement that expends energy (Caspersen, Powell, & Christenson, 1985)

Time-restricted feeding is a dietary strategy that allows ad libitum energy intake within a set window of time (e.g., eight hours), inducing a fasting window for the remaining hours of the day (Rothschild, Hoddy, Jambazian, & Varady, 2014).

2. LITERATURE REVIEW

2.1 Introduction

Obesity accounts for more than one-third (39.8%) of the U.S. population, and remains significantly high in all socioeconomic categories, regardless of racial and ethnic backgrounds (Hales et al., 2017; Ogden, Carroll, Kit, & Flegal, 2014). In the past 30 years (1980 to 2012), obesity has more than quadrupled (5% to 21%) in adolescents, and has led to an estimated annual medical cost of $147 billion dollars in 2008 (Finkelstein, Trogdon, Cohen, & Dietz, 2009; National Center for Health Statistics, 2012). Guidelines classify obesity as a body mass index (BMI) of 30 or higher, calculated by dividing body mass in kilograms by the square of height in meters (National Heart Lung and Blood Institute, 2013). Obesity occurs from an excess accumulation of adipose tissue, typically because of lifestyle factors such as poor dietary habits and lack of physical activity. The accumulation of this visceral, hepatic, and intramuscular adipose tissue is strongly associated with an increased risk of physical dysfunction and obesity-related conditions (e.g., cardiovascular disease, stroke, type 2 diabetes, and certain types of cancers; National Heart Lung and Blood Institute, 2013). These conditions represent a major health problem, and are some of the leading causes of preventable death in the U.S (National Heart Lung and Blood Institute, 2013).

Cardiovascular disease is the leading cause of death in the U.S., with 30% of adults older than 19 years of age having hypertension and 16.5% of all deaths being attributed to high blood pressure (Santulli, 2013). Physical dysfunction, in the form of sarcopenia and dynapenia, is the gradual and progressive age-related loss of muscle mass and strength, respectfully (Clark & Manini, 2010; Deschenes, 2004). Sarcopenia is recognized as a 3% to 8% loss of muscle mass per decade after the age of 30 years (Paddon-Jones & Rasmussen, 2009), affecting 30% of

individuals over 60 years and 50% of individuals over 80 years (Baumgartner et al., 1998). This age-related decline in muscle mass negatively affects strength, balance, and stability; leading to an increased risk of falls and impaired ability to perform activities of daily living such as walking, personal care, cooking, and chores (Tinetti et al., 2006; Tinetti, Speechley, Ginter, & Med, 1988). The most alarming consequence of decreased muscle strength is its ability to predict future mortality in middle-aged and older adults (Cooper, Kuh, & Hardy, 2010). While diet and exercise improve many health consequences of obesity and attenuate declines in muscle mass and strength, dietary strategies are not always followed nor manageable for long-term use (Beavers et al., 2015). Thus, highly compliant dietary strategies that facilitate fat loss while maintaining fat-free mass are needed.

Continuous energy restriction, a reduction in daily caloric intake up to 40%, is a primary dietary strategy to help individuals decrease fat mass and lower the risk of cardiovascular disease (Longo & Mattson, 2014). While CER is effective for weight loss and reducing cardiovascular disease risk, it is also associated with poor compliance and appears to accelerate the return of pre-deprivation body mass levels once the restraints over feeding are removed (Anastasiou et al., 2015; Borer, 2013). More importantly, CER is known for weight loss consisting of 10% to 60% fat-free mass, which suggests a large proportion of metabolically active skeletal muscle tissue is lost instead of adipose tissue (Chaston, Dixon, & O'brien, 2007). Time-restricted feeding, a variant of intermittent fasting (IF), is an increasingly popular dietary approach that may preserve fat-free mass during weight loss (Barnosky et al., 2014). Time-restricted feeding allows ad libitum energy intake within a set window of time (e.g., eight hours), inducing a fasting window for the remaining hours of the day (Rothschild et al., 2014). Literature from animal studies have demonstrated reductions in body mass, total cholesterol, and concentrations of triglycerides,

glucose, insulin, as well as improvements in insulin sensitivity (Rothschild et al., 2014). Recent studies in humans have found TRF, with resistance training, effective at reducing fat mass, maintaining muscle mass, and improving muscle performance in young men (Moro et al., 2016; Tinsley et al., 2017). While a promising dietary strategy, more research is needed to validate the ability of TRF to preserve fat-free mass during weight loss and reduce disease risk (Barnosky et al., 2014; Moro et al., 2016; Tinsley et al., 2017).

2.2. Overweight and Obesity Mechanisms

2.2.1. Introduction

Over the past century, the U.S. has become an environment that fosters opportunistic, non-homeostatic feeding. While medical innovations have reduced mortality from infectious diseases and prolonged lifespan, poor dietary habits and sedentary lifestyle has led to widespread chronic disease and obesity (Heymsfield & Wadden, 2017). Obesity is an excessive accumulation of adipose tissue, resulting in many metabolic disturbances and adverse health consequences, such as high blood pressure. These consequences are linked to cardiovascular disease, stroke, kidney disease, type 2 diabetes, and other metabolic conditions (Heymsfield & Wadden, 2017; Shen et al., 2003; Tchkonia et al., 2013). Proper regulation of food intake and energy expenditure is still the most effective way for reducing the accumulation of excess adiposity. With that said, today's environment is so influential that it can even affect the transcription and translation of genes, further contributing to obesity (Heymsfield & Wadden, 2017).

2.2.2. Mechanisms of Obesity

2.2.2.1. Environment. During the Late Paleolithic period (50,000 to 10,000 BC) body mass regulation was philosophized to be controlled by alternating cycles of feasting and fasting

(Borer, 2013). In a fasted state, hormones facilitate hunger and increase motivation for physical activity (Borer, 2013). This creates a negative energy balance and consequent weight loss, resulting in a reduced sympathetic activation of metabolism and preservation of energy stores (Borer, 2013). Growth hormone secretion increases, protecting oxidation of proteins for energy by diverting metabolism toward lipid oxidation (Borer, 2013). After feasting, hunger is suppressed through increased leptin and insulin concentrations, glycogen and fat depots are refilled, and the motivation for physical activity decreases (Borer, 2013). The main benefits of this pattern of eating are minimized utilization of stored fuels during fasting and more efficient storage of fuels after feasting (Borer, 2013). The feasting and fasting style of eating, however, does not exist today due to a shared environmental change towards positive energy balance and weight gain. Over the past several decades, the increase of easily accessible, energy-dense, and highly palatable foods, decrease of time spent in occupational physical activities and displacement of leisure-time physical activities with sedentary activities, and inadequate sleep, as well as other factors, have set the foundation for the parallel rise in chronic disease and obesity (Borer, 2013; Church et al., 2011; Heymsfield & Wadden, 2017; von Loeffelholz & Birkenfeld, 2018).

There are many elements within today's environment that impact healthy behavior and weight status. These elements are well documented and include factors such as socioeconomic status (SES), physical and social environment, gender, age, and cultural identity (Williams, Mesidor, Winters, Dubbert, & Wyatt, 2015). In a recent meta-analysis by Newton, Braithwaite, and Akinyemiju (2017), lower life course SES and obesity were strongly correlated in women. Interestingly, mean waist circumference was higher among women and lower among men with lower life course SES when compared to those with higher life course SES (Newton et al., 2017).

With that said, individuals with lower life course SES had a higher mean BMI than those with higher life course SES (Newton et al., 2017).

Physical environmental factors, such as sidewalks, parks, etc., have received a lot of study over the last several years, and have been found to significantly affect body size and mass in children, adolescents, and adults (Duncan et al., 2014; Nesbit, Kolobe, Sisson, & Ghement, 2014; Papas et al., 2007; Rodriguez, Aytur, Forsyth, Oakes, & Clifton, 2008). Social and cultural practices, such as family and friends, work, and celebrations, often contribute to unhealthy eating practices and habits through the consumption of energy-dense foods (Hough & Sosa, 2015). In fact, influence on weight gain appears strongest for same sex friends, while obesity risk was 40% higher if an individual had an obese sibling and 35% higher with an obese spouse (Christakis & Fowler, 2007). In relation, parental modeling of healthy food choices has been shown to be a significant predictor of lower BMI among children (Larson, Wall, Story, & Neumark-Sztainer, 2013).

2.2.2.2. Energy balance. The regulation of food intake and energy expenditure is controlled by two sets of neurons, located in the hypothalamic arcuate nucleus, that become inhibited or excited by circulating hormones (i.e., leptin, insulin) previously mentioned (Borer, 2013; Heymsfield & Wadden, 2017). Microbiome and cells within the stomach, pancreas, adipose tissue, and other organs create a coordinated network of central mechanisms and peripheral signals that control short-term and long-term energy balance (van der Klaauw & Farooqi, 2015). Sensory-signal input, cognitive processes and the hedonic effects of food consumption, memory, and attention, are brain regions outside the hypothalamus that also play an important role in energy-balance regulation today (Borer, 2013; van der Klaauw & Farooqi, 2015).

A negative energy balance, through a decrease in food intake or increase in physical activity, leads to relative reductions in resting energy expenditure, food preoccupation, and many other metabolic and psychological processes that depend on the extent and duration of the energy reduction (Leibel et al., 2015; MacLean, Higgins, Giles, Sherk, & Jackman, 2015). The underlying mechanisms of these effects, though maintainable in a weight-reduced state, remain unclear in humans (Leibel et al., 2015; MacLean et al., 2015). Additional research on obesity has shown that previously obese persons may not be physiologically and metabolically identical to those who were never obese (Leibel et al., 2015; MacLean et al., 2015). This is supported by high relapse rates of obesity, and further emphasizes the seriousness of obesity as a chronic disease that requires long-term attention (Heymsfield & Wadden, 2017).

Focusing solely on creating an energy deficit and consuming diets that are high in sugars and refined starches has been shown to promote obesity (Lucan & DiNicolantonio, 2015). In fact, unfavorable lipid levels, insulin resistance, fatty liver, type 2 diabetes, cardiovascular disease, metabolic syndrome, visceral adiposity, and hyperuricemia have all been associated with added sugar and sugar-sweetened beverages (Assy et al., 2008; Bhupathiraju et al., 2012; Bomback et al., 2010; Bremer, Auinger, & Byrd, 2009; Chan et al., 2014; de Koning et al., 2012; Duffey, Gordon-Larsen, Steffen, Jacobs Jr, & Popkin, 2010; Fung et al., 2009; Lin et al., 2013; Montonen, Järvinen, Knekt, Heliövaara, & Reunanen, 2007; Odegaard, Choh, Czerwinski, Towne, & Demerath, 2012). Even after controlling for BMI or total energy intake there was no decrease in any of these associations (Bhupathiraju et al., 2012; Bomback et al., 2010; Chan et al., 2014; de Koning et al., 2012; Dhingra et al., 2007; Duffey et al., 2010; Fung et al., 2009). Added sugar alone, which represents 15% of the daily calories in the U.S., leads to an 18% increase in the risk of cardiovascular disease mortality (Yang et al., 2014). This data, however,

only demonstrates associations, and more plausible mechanisms to demonstrate the direct effects of sugar on cardiovascular disease and type 2 diabetes risk factors are needed (Stanhope, 2016).

2.2.2.3. Genetic factors. Although environmental change and the regulation of food intake and energy expenditure may be primarily attributed for the increase in obesity prevalence, genetic factors do play a significant role. It is believed that environmental factors can influence genetic background, and that epigenetic mechanisms, in which environmental factors cause changes in gene expression, could be used to explain observed increases in obesity (Albuquerque, Stice, Rodríguez-López, Manco, & Nóbrega, 2015; Heymsfield & Wadden, 2017). Heritability can describe a proportion of phenotypic variation among individuals (Albuquerque et al., 2015). Considering parental obesity has been shown to have a small to medium effect on childhood obesity and is an important risk factor for childhood and adolescent obesity this is not surprising (Danielzik, Langnäse, Mast, Spethmann, & Müller, 2002). Additionally, pre-natal and post-natal environmental exposures may account for other between-individual differences in BMI and phenotypic obesity traits (Bray et al., 2016; Heymsfield & Wadden, 2017).

Research on twins, families, and adoptions, although varying in estimates, have shown a high rate of heritability of BMI, ranging from 40% to 70% (Bray et al., 2016; Heymsfield & Wadden, 2017). Among monozygotic (identical) and dizygotic (non-identical) twins, heritability of fat mass was reported to range from 70% to 90% and 35% to 45% respectfully (Stunkard, Foch, & Hrubec, 1986). In adopted children, body fat strongly correlated with the BMI of their biological parents than of their adoptive parents (Stunkard, Sørensen, et al., 1986). Prevalence between racial groups is also noted as a genetic component for obesity. Knowler, Pettitt, Saad,

and Bennett (1990) found that Caucasian and Asian populations had a lower (<35%) obesity prevalence compared to Pima Indians (>50%) living in New Mexico.

These genetic and phenotypic factors, as well as many others, have helped establish three distinct forms of obesity: monogenic syndromic obesity, monogenic non-syndromic obesity and polygenic or common obesity (Albuquerque et al., 2015).

2.2.2.3.1. Monogenic non-syndromic obesity. In only ten genes, there are more than 200 mutations that have been found to cause human obesity (Mutch & Clément, 2006; Rankinen et al., 2006). For monogenic non-syndromic form, early-onset extreme obesity can be explained, up to 10%, by eight common gene mutations (González-Jiménez, Aguilar, Padilla, & García, 2012). These gene mutations include leptin, leptin receptor, pro-opiomelanocortin, proconvertase 1, melancortin-4 receptor, brain-derived neurotrophic factor, neurotrophic tyrosine kinase rector type 2, and single-minded homolog 1 (Farooqi & O'Rahilly, 2005; González-Jiménez et al., 2012; Ranadive & Vaisse, 2008). They all code for key proteins in the leptin-melanocortin signaling pathway in the hypothalamus, affecting the regulation of food intake and energy expenditure (González-Jiménez et al., 2012).

2.2.2.3.2. Monogenic syndromic obesity. Obesity that occurs in a distinct set of associated clinical phenotypes, such as mental retardation or organ-specific developmental abnormalities, is referred to as syndromic (Ichihara & Yamada, 2008). Over 30 Mendelian disorders result in obesity (Mutch & Clément, 2006). Research is beginning to explain the pathogenesis of the chronic positive energy balance by studying the genetic basis of several of these syndromes (Albuquerque et al., 2015)., Prader-Willi, WAGR (Wilm's tumor, aniridia, genitourinary anomalies and mental retardation), Bardet-Bield, and Altrom and Cohen

syndromes are a few of the common forms of syndromic obesity for which the genetic basis is, at least, partially understood (Albuquerque et al., 2015).

2.2.2.3.3. Polygenic (common) obesity. As previously mentioned, today's environment strongly favors weight gain rather than weight loss due to an abundance of easily accessible food and lack of physical activity. This has led to an increase of common obesity in both children and adults, and overall increase worldwide (Albuquerque et al., 2015). The genetic profile of polygenic obesity results from the effects of several altered genes, and research hypothesizes that the specific set of variants relevant for this type of obesity vary greatly between obese persons (Hinney, Vogel, & Hebebrand, 2010; Rankinen et al., 2006). This makes polygenic obesity very difficult to study because each genetic variation requires the presence of additional variants and an obesogenic environment to determine the specific obese phenotype (Razquin, Marti, & Martinez, 2011).

Genome-wide association studies (GWAS) are the most common methodology used in polygenic research (Albuquerque et al., 2015). The process uses powerful statistics to identify loci associated with a phenotype through the scanning of numerous polymorphisms across the entire genome (Albuquerque et al., 2015). Though GWAS have identified over 300 loci, they account for less than 5% of the individual variation in BMI and adiposity traits (Pigeyre, Yazdi, Kaur, & Meyre, 2016).

2.2.3. Pathophysiological Characteristics

2.2.3.1. Anatomical, metabolic, and physiological effects. Adiposity typically increases slowly over time due to long-term, positive energy balance (Heymsfield & Wadden, 2017). Lipids are deposited in the adipose tissue, along with volume increases in skeletal muscle, the liver, and other organs and tissues (Heymsfield, Gonzalez, Shen, Redman, & Thomas, 2014).

Increases in pharyngeal soft tissues can block airways during sleep, leading to sleep apnea (Ashrafian et al., 2015). The risk of osteoarthritis in persons with obesity is also increased, due to the mechanical stress placed on joints from excess adiposity (Goldring & Otero, 2011). Many of the metabolic disturbances and adverse health outcomes associated with obesity are linked to visceral fat depots, including omental and mesenteric adipose tissue (Shen et al., 2003; Tchkonia et al., 2013).

During a positive energy balance, the storage of macrophages and other immune cells in adipose tissue increases and causes an impairment of adipocyte function (Aouadi et al., 2013; Grant & Dixit, 2015; Olefsky & Glass, 2010). These immune cells secrete proinflammatory cytokines, such as tumor necrosis factor-a (TNF-a), interleukin-1B (IL-1B), and interleukin-6 (IL-6), that increase to account for 40% of the cells in adipose tissue (Heymsfield & Wadden, 2017; Kang et al., 2016; Weisberg et al., 2003). These inflammatory cytokines and lipid intermediates, along with elevated free fatty acid levels, contribute to impaired insulin signaling and insulin resistance (Tchkonia et al., 2013). For example, in obese humans, when the exaggerated expression of TNF-a is blocked an improvement in insulin sensitivity can be seen (Hotamisligil, Arner, Caro, Atkinson, & Spiegelman, 1995; Stanley et al., 2011). This is just one of the several mechanisms underlying the dyslipidemia of obesity, type 2 diabetes, obesity-related liver diseases, and osteoarthritis (Heymsfield & Wadden, 2017).

In some patients with obesity, there is chronic overactivity of the sympathetic nervous system that may contribute to several pathophysiological processes, such as high blood pressure (Hall et al., 2010). High blood pressure is the main pathophysiological mechanism of heart disease, stroke, and chronic kidney diseases, and is associated with insulin resistance, obesity-associated dyslipidemia, and type 2 diabetes (Heymsfield & Wadden, 2017)

2.3. Strategies for Weight Loss and Muscle Mass Retention

2.3.1. Introduction

Weight loss is traditionally accomplished by creating a negative energy balance, either through reducing food intake, increasing physical activity levels, or both. Moderate reductions (5% to 10%) in baseline weight have shown to improve many obesity-related risk factors and can translate to disease prevention (American College of Cardiology & American Heart Association Task Force on Practice Guidelines, 2014; Apovian et al., 2015; Garvey et al., 2016; Heymsfield & Wadden, 2017). Although effective, not all risk factors and chronic disease states respond equally to weight loss (American College of Cardiology & American Heart Association Task Force on Practice Guidelines, 2014; Garvey et al., 2016). Continuous energy restriction remains the primary dietary strategy to reduce the metabolic and hormonal risk factors associated with increased adiposity (Most, Tosti, Redman, & Fontana, 2017). With that said, CER is associated with poor compliance and can reduce large amounts of fat-free mass during weight loss. Additionally, once restraints over feeding are removed, an accelerated return of pre-deprivation body mass levels often occurs (Anastasiou et al., 2015; Borer, 2013).

Intermittent fasting, a dietary approach that alternates periods of feeding and fasting, may be a promising alternative to CER. It has become a popular weight loss strategy because it does not require a restriction on energy intake every day, or at all, like CER (Antoni, Johnston, Collins, & Robertson, 2017; Harvie & Howell, 2017). While some studies have shown the losses of fat-free mass between IF and CER are equivalent, IF, with higher protein consumption, has shown to preserve larger portions of fat-free mass (Harvie et al., 2013; Mattson et al., 2017; Soenen, Martens, Hochstenbach-Waelen, Lemmens, & Westerterp-Plantenga, 2013). In young

men, TRF with resistance training preserved fat-free mass, maintained muscle mass, and improved muscle performance (Moro et al., 2016; Tinsley et al., 2017).

While resistance training alone has shown little evidence to reduce weight, it can help attenuate the age-related losses of muscle mass and strength (Figueroa et al., 2013; Haskell et al., 2007; Swift, Johannsen, Lavie, Earnest, & Church, 2014; Villareal et al., 2011; Winett & Carpinelli, 2001). Aerobic training, on the other hand, is very useful for eliciting weight loss, as well as promoting numerous cardiometabolic benefits in overweight and obese individuals (Swift et al., 2014). Research on concurrent training for weight loss, lean mass preservation, and cardiometabolic health improvement has not been vastly explored, but shows promising results (Church et al., 2010; Swift et al., 2014).

2.3.2. Dietary Interventions

2.3.2.1. Continuous energy restriction. One popular dietary strategy to facilitate weight-loss is CER, a daily restriction on food consumption. Continuous energy restriction is the most studied nutritional intervention in animals for the purpose of extending lifespan (Most et al., 2017). In rat and mice models, a 20% to 50% reduction in energy intake, without malnutrition, has been shown to prolong lifespan up to 50%, and prevent or attenuate many chronic diseases, such as obesity, type 2 diabetes, cancer, nephropathy, cardiomyopathy, neurodegeneration and multiple autoimmune diseases (Fontana, Partridge, & Longo, 2010; Heilbronn & Ravussin, 2003; Weindruch & Sohal, 1997). While the benefits of CER in animals are well defined, the benefits of CER on metabolic and molecular adaption in humans are still growing (Most et al., 2017). A few of the most significant of these benefits are found in the Comprehensive Assessment of Long-term Effects of Reducing Intake of Energy (CALERIE) trials initiated by the U.S. National Institute of Aging. These studies were divided into two trials,

CALERIE-1 and CALERIE-2, and are the first clinically controlled trials of CER in healthy, non-obese humans.

CALERIE-1 consisted of three separate pilot studies that evaluated the feasibility and effects of CER on metabolic health after six or 12 months in overweight volunteers (24 to 60 years). Negative energy balance was created through either 1) reduced energy intake, 2) increased exercise energy expenditure, or 3) both combined (Most et al., 2017). The first pilot study compared a 25% CER to a combined 12.5% CER and 12.5% increase in exercise energy expenditure, a positive weight loss control, and a weight-maintenance control group after six months (Heilbronn et al., 2006; Redman et al., 2007). Results showed no changes in the metabolic cost of spontaneous activity and a reduction in the energy expenditures of free-living activity, suggesting an individual behavioral adjustment to decrease physical activity during CER (Redman et al., 2009). Fasting insulin concentrations declined, and advanced glucose analysis suggested CER elicits benefits on carbohydrate metabolism that reduce the risk of developing type 2 diabetes (Most et al., 2017). Additionally, insulin sensitivity improved by 40% and the acute insulin-response to glucose-infusion increased by 29% (Larson-Meyer et al., 2006). Participants in the study, although younger and overweight (aged, 39 years; BMI, 27.8 kg/m^2), were estimated to have a 29% reduction (38% with exercise) in the 10-year risk for cardiovascular disease, based on values for total cholesterol, HDL, systolic blood pressure, age, and gender (Lefevre et al., 2009).

The second pilot study randomized overweight subjects (50 to 60 years) for one year to a 20% CER group, 20% increase in energy exercise expenditure group, or control group (Racette et al., 2006). Researchers found that CER-induced weight loss improved insulin sensitivity, increased adiponectin, and reduced the serum concentrations of leptin, insulin, LDL, and C-

reactive protein (Villareal et al., 2006; Weiss et al., 2007). Although various cardiometabolic indicators were improved in the study, decreases in bone mass, muscle size and strength, and maximal aerobic capacity were also observed (Villareal et al., 2006; Weiss et al., 2007). The final pilot study randomized overweight individuals (24 to 42 years) to a low versus high glycemic load during a 30% CER for six months (Das et al., 2007). Individuals under CER experienced a reduction in body mass, and improvement in fasting insulin concentrations, insulin sensitivity, first-phase acute insulin secretion, and lipid profile (Das et al., 2007; Pittas et al., 2006).

CALERIE-2 was designed to test whether a two-year 25% CER would result in similar metabolic and hormonal adaptations as seen in rodents (Ravussin et al., 2015). The compliance associated with this study, however, was not great. The average compliance during the first six months of CER was 19.5% but dropped to 9.1% over the last 18 months of the study. All significant reductions in body mass and composition were achieved by the twelfth month. Body mass was reduced by 11.5%, with a 4.3% and 23% reduction in fat-free mass and fat mass respectfully (Ravussin et al., 2015; Villareal et al., 2016). The major results of this study determined that mild CER can improve cardiometabolic risk factors, even in healthy, lean or slightly overweight young and middle-aged men and women (Most et al., 2017). Total cholesterol, LDL, C-reactive protein, TNF-a, blood pressure, and insulin resistance all decreased significantly while HDL increased in CER, even in subjects who had a normal risk factor at baseline (Ravussin et al., 2015).

Overall, CER, with optimal intake of nutrients, appears to reduce metabolic and hormonal risk factors associated with type 2 diabetes, cardiovascular disease, stroke, cancer, and

vascular dementia and remains the primary dietary strategy in the prevention and treatment of obesity (Most et al., 2017).

2.3.2.2. Intermittent fasting. Intermittent fasting is a revolving pattern of normal food intake, with intermittent periods of little or no energy intake (Mattson et al., 2017). The appeal of this dietary strategy is that individuals do not need to restrict energy intake every day, or at all, to attain weight loss and metabolic benefits (Antoni, Johnston, Collins, et al., 2017; Harvie & Howell, 2017). Animal studies have discovered the cellular and molecular mechanisms by which animals respond to IF, and how these pathways can increase their overall fitness and resistance to injury and a wide array of diseases (Longo & Mattson, 2014). Recent literature in humans have supported these claims, showing that IF improves many health indicators in those with chronic disease, as well as in healthy individuals (Mattson et al., 2017). There are many variants of IF, including: complete fasting every other day; intermittent energy restriction (IER); and TRF (Anson et al., 2003; Antoni, Johnston, Steele, et al., 2017; Chaix, Zarrinpar, Miu, & Panda, 2014; Harvie & Howell, 2017). Intermittent energy restriction typically involves a 60% to 70% energy restriction, below estimated intake, on two consecutive days per week or in an alternating (every other day) pattern (Antoni, Johnston, Collins, et al., 2017; Harvie & Howell, 2017). Time-restricted feeding allows individuals to consume ad libitum energy intake within a set window of time (e.g., eight hours), inducing a fasting window for the remaining hours each day (Rothschild et al., 2014).

Although results differ between styles of IF, all variants result in several key metabolic changes that define a fasting period. These include maintained, low to normal range levels of blood glucose, reduction of glycogen stores, increased fatty acid metabolism and creation of ketone bodies, reduced circulating levels of leptin, and elevated adiponectin levels (Johnson et

al., 2007; Wan et al., 2010). It is important to note that energy intake has often been reduced when following IF protocols. Thus, the extent of the physiological response to IF may be mediated by an overall CER (Mattson et al., 2017). In rodent studies, the most common CER strategy (limited daily feeding) is technically a form of IF or TRF (Mattson et al., 2017). Animals in CER groups are usually provided their daily food in one portion, causing a fasting window of extended time (Pugh, Klopp, & Weindruch, 1999).

Most human studies were designed to determine whether IF is efficient for reducing body mass and reversing the metabolic effects of obesity. This is important considering CER is associated with poor compliance and appears to accelerate the return of pre-deprivation body mass levels once the restraints over feeding are removed (Anastasiou et al., 2015; Borer, 2013). Intermittent fasting has shown high levels of compliance, between 65% to 75% on IF days, and doesn't appear to lead to a compensatory over-consumption on the non-dieting days (Harvie et al., 2011, 2013). Supporters of IF claim that the dietary strategy may help preserve fat-free mass. Extensive research still needs to be completed to fully support this claim.

Some studies show the losses of fat-free mass between IF and CER are equivalent and dependent on overall protein intake, rather than the specific method of energy restriction (Mattson et al., 2017; Soenen et al., 2013). With that said, IF with a higher protein consumption (1.2 grams per kilogram of body weight) has been shown to preserve a larger portion of fat-free mass (Harvie et al., 2013). Additionally, recent studies in young men found that eight weeks of TRF and resistance training results in a loss of fat mass, retention of lean mass, and improvement in muscle endurance and strength (Moro et al., 2016; Tinsley et al., 2017). These studies show that IF does not adversely affect, and can even enhance, physical performance. In humans, IF has also shown to protect against metabolic syndrome and associated disorders, including diabetes

and cardiovascular disease. Recent small trials of IF in patients with cancer and multiple sclerosis have been promising, and provide strong justification for larger IF clinical trials in patients with a range of chronic age- and obesity-related disorders (I. Y. Choi et al., 2016; Safdie et al., 2009).

2.3.2.2.1. Intermittent energy restriction. Intermittent energy restriction continues to undergo extensive research as an ideal alternative to CER because it only requires energy restriction for defined number of days per week, and because many of the metabolic effects achieved with weight loss are attenuated when the individual is no longer in a state of negative energy balance (Harvie & Howell, 2017; Wing et al., 1994). Harvie et al. (2011) conducted a large comparative study between IER and CER on weight loss, insulin sensitivity and other metabolic disease risk markers in 107 overweight or obese women. Subjects were assigned to a 25% IER (2266 kJ per day for two days per week) or CER (6276 kJ per day for seven days per week) for six months. Results of the study found that IER and CER were equally effective at reducing body mass, as well as leptin, free androgen index, high sensitivity C-reactive protein, total cholesterol, LDL, triglycerides, and blood pressure, and increasing sex hormone binding globulin, and insulin-like growth factor (IGF) binding proteins 1 and 2. One of the more interesting effects of IER was a greater reduction of insulin and insulin resistance. Although only postmenopausal women were recruited for this study, the results supported IER as an effective alternative weight loss strategy to CER and novel approach for reducing disease risk.

2.3.2.2.2. Time-restricted feeding. Time-restricted feeding is increasingly popular due to its unrestrictive energy intake design, and potential for preserving fat-free mass during weight loss. Chaix et al. (2014) conducted one of the most extensive TRF studies in mice; exposing them to many diverse nutritional challenges. Results showed that mice had a decreased metabolic

disease incidence from a variety of obesogenic diets, and the benefits observed were in direct proportion to the length of the TRF. Importantly, researchers found that the protective effects of TRF were maintained even when temporary ad libitum food access was allowed. The study supported TRF as an effective strategy for the prevention and treatment of obesity and metabolic disorders, including type 2 diabetes, hepatic steatosis, and hypercholesterolemia (Chaix et al., 2014).

Most human studies on TRF lack control groups and do not seem to randomize subjects by condition, making it difficult to draw accurate conclusions. With that said, an extensive review of human studies by Rothschild et al. (2014) confirmed that data on TRF supports the benefits concluded in animal studies. For example, TRF in humans tends to demonstrate decreases in body mass, lower concentrations of triglycerides, glucose, and LDL, and increases in HDL. Additional improvements in various metabolic risk factors, such as plasma lipids, fasting glucose and insulin levels, insulin sensitivity, and certain inflammatory cytokines have also been seen. Recent literature has demonstrated that eight-hour TRF improves insulin sensitivity and decreases triglycerides, fasting insulin, homocysteine, and fat mass in obese subjects after 12 weeks (Gabel et al., 2018). When compared to a historically matched control, TRF induced mild energy restriction and weight loss, as well as reductions in systolic blood pressure (Gabel et al., 2018). More studies are still needed, especially on various age groups, to confirm and support findings (Rothschild et al., 2014).

2.3.2.2.2.1. Ramadan fasting. Ramadan is a holy month for Islam in which Muslims do not eat or drink during the daylight hours (Chennaoui et al., 2009). Many TRF studies have been conducted on athletes during Ramadan fasting (RF). While RF is a form of TRF, it is not a perfect or exact replica of the dietary strategy discussed in this paper. Ramadan fasting occurs

from dusk until dawn, and, while many studies report a 10 to 12 hour feeding window, the feeding window may be closer to three to four hours due to necessary sleep. Additionally, RF occurs throughout the entire day, whereas TRF typically occurs from the evening until afternoon. Bouhlel et al. (2008) explored RF changes in body composition, blood glucose regulation, growth hormone, IGF-1, IGF-3, and insulin concentrations in nine male athletes during submaximal exercise. Significant decreases in body mass and body fat compared to baseline measurements were observed. Plasma concentrations of glucose, insulin, etc. did not change significantly between the athletes before and after Ramadan, implying that RF does not disturb glucose regulation or activity of the growth hormone and IGF-1 system. While the study did not show any negative aspects of RF, other studies have found RF to cause major sleep disturbances, energy deficiency, and fatigue, as well as proinflammatory hormonal changes (Chennaoui et al., 2009).

2.3.2.2.2.2. TRF four-hour feeding training study. Tinsley et al. (2017) conducted an eight-week randomized controlled trial with and without TRF to assess nutrient intake, body composition, and muscle strength changes in recreationally active males. The nutritional goal of the program was to consume all calories within a four-hour period, four days per week. Eighteen healthy men were randomized into a resistance training program with a normal diet (RT-ND) or a resistance training program with TRF (RT-TRF). Training involved both upper and lower body exercise for four sets of eight to 12 repetitions (until failure) and was completed three times a week for eight weeks. Dietary analysis, body composition, and muscle performance assessments were completed at baseline, week four, and week eight. Lower body and upper body maximal strength was assessed by obtaining one-repetition maximum (1RM) on the hip sled and bench

press exercise. Total body composition and cross-sectional area were measured by DXA and ultrasound, respectively.

The RT-TRF demonstrated a large reduction in energy intake (~650 kcal per day) on TRF days, but the reduction did not have any significant contribution to total body composition. Both groups increased bicep brachii and rectus femoris cross-sectional aera, as well as maximal strength for the hip sled and bench press exercise. While no differences in total body composition were observed, individual participants were said to be dissimilar in their body composition alterations. Some subjects in the RT-TRF lost up to 22% of initial fat, and half had a higher absolute lean soft tissue mass at the end of the study. Several limitations of the study included unsupervised resistance training, self-reported food intake, a small sample size, and the lack of a dietary control. The study concluded that TRF, although causing a reduced energy intake, did not have any adverse effects on lean mass or muscle improvements.

2.3.2.2.2.3. TRF eight-hour feeding training study. One of the better designed studies on TRF was conducted by Moro et al. (2016). The study recruited 34 healthy, resistance-trained males and randomized them into either a TRF or ND group. Subjects in the TRF group were required to consume all their calories in three separate meals within an eight-hour period each day (1:00 pm, 4:00 pm, 8:00 pm). Normal diet subjects also consumed all their caloric needs within three meals, but had a longer feeding window (8:00 am, 1:00 pm, 8:00 pm). The kilocalories consumed, and macronutrient distribution were matched for each group. Testing was performed before and after eight weeks of their diet assignment and standardized resistance training program. Dual-energy x-ray absorptiometry was used for fat mass and fat-free mass measurement, while muscle area of thigh and arm was assessed by an anthropometric system. Maximal strength was measured using a 1RM bench press and leg press test. Total and free

testosterone, IGF-1, blood glucose, insulin, adiponectin, leptin, triiodothyronine, thyroid stimulating hormone, IL-6, IL-1B, TNF-a, total cholesterol, HDL, LDL, and triglycerides were analyzed.

After eight weeks of training, the TRF group significantly decreased fat mass compared to the ND group (16.4% vs 2.8%). Interestingly, significantly reduced levels of total testosterone and IGF-1 occurred in the TRF group. While these anabolic hormones were reduced, they did not cause any reduction in fat-free mass or muscle strength. In fact, fat-free mass, as well as arm and thigh cross-sectional area, were maintained in both groups. Leg press 1RM increased significantly and, while not significant, bench press 1RM increased in both groups. This improvement is important, not just because of the reduced anabolic hormone levels, but because subjects were classified as highly resistance trained. Another interesting effect of TRF were reduced blood glucose and insulin levels, which contributed to a significant improvement in Homeostatic Model Assessment of Insulin Resistance (HOMA-IR). Adiponectin increased, while leptin decreased with TRF. Once normalized for fat mass, however, these two hormonal responses were not significant, and were considered normal effects due to the loss of fat mass in the TRF group. Lastly, triiodothyronine and triglycerides decreased significantly and TNF-a and IL-1B were lower in TRF compared to ND.

Some important notes from this study were the reductions of testosterone and IGF-1. While IF may mimic CER through various pathways, previous research on RF and newer research on CER in humans has not shown reductions in IGF-1 (Bouhlel et al., 2008). Additionally, the observed increases in adiponectin and decreases in insulin in the TRF group were said to be linked to an enhanced regulation of insulin sensitivity and improved anti-

inflammatory effect. Overall, the study supports TRF as a dietary strategy to improve health-related biomarkers, decrease fat mass, and maintain fat-free mass.

2.3.2.2.3. Ketogenic diets. The ketogenic diet (KD) is a high-fat, low-carbohydrate dietary strategy (80% fat, 5% carbohydrate, 15% protein) designed to elicit a metabolic state of ketosis, where ketone bodies are created and used as an alternative energy source by the body (Paoli, Bianco, & Grimaldi, 2015). This metabolic process occurs as a result of fasting or from a drastic reduction in carbohydrate consumption (below 20 grams per day) and is derived from the overproduction of acetyl-CoA (Paoli, 2014; Paoli et al., 2015). The KD is strongly supported as an effective weight loss strategy (Bueno, de Melo, de Oliveira, & da Rocha Ataide, 2013; Paoli et al., 2015). The mechanisms behind its effectiveness, however, are still debated. One hypothesis is that the KD leads to a greater wasting of energy compared with other types of diets (Paoli et al., 2015).

Unlike with CER and severe energy restriction, an energy-sufficient KD, with adequate protein intake (1.3 to 1.5 grams per kilogram of body weight), does not lead to the metabolic imbalances that can occur during nutrient-deficient weight loss (Paoli et al., 2015). In fact, three weeks of a severe energy-restricted (450 to 700 calories per day) modified KD (55% to 60% protein, 5% carbohydrate, 35% to 40% fat), providing adequate protein (1.2 to 1.5 grams per kilogram of body weight), successfully reduced body mass without causing significant differences in total body lean mass (Merra et al., 2016). Thus, a KD with adequate protein may help avoid muscle loss and lead to beneficial alternations in metabolic pathways and processes as seen during fasting (Paoli et al., 2015). It appears that the pathways that help to control hunger and improve fat oxidative metabolism during a KD also contribute to a lack of muscle mass

increase (Paoli, 2014; Paoli et al., 2015). Specifically, this means the use of ketone bodies and free-fatty acids slows protein catabolism, conserving lean mass (Paoli et al., 2015).

While weight loss with the KD is well documented, few studies have investigated its long-term adaptation effects on exercise performance (Wilson et al., 2017). Wilson et al. (2017) examined the effects of a modified KD on 25 resistance training males. Subjects were randomly assigned to a traditional western-style diet (20% protein, 55% carbohydrate, 25% fat) or a KD (20% protein, 5% carbohydrate, 75% fat). Lean body mass, strength, and power improved similarly in both groups. Interestingly, total testosterone increased significantly with the KD (118 ng/dl) compared to the western-style diet (36 ng/dl). The study demonstrates how the KD can be used in combination with resistance training to cause favorable changes in body composition, performance, and hormonal profiles in resistance training men.

The overall goal of the KD is to mimic limited food availability and trigger the body's natural adaptive responses (Paoli et al., 2015). The dietary strategy may be one of the most widely studied and characterized nutritional system that exists for weight loss, and is supported by many biochemical, physiological, and observational studies (Paoli et al., 2015). By modifying the KD with adequate protein and nutrient consumption, the KD can lead to fat loss with little to no loss of muscle mass or any long-term health issues (Paoli et al., 2010).

2.3.3. Physical Activity Interventions

The American College of Sports Medicine recommends between 150 and 250 minutes per week of physical activity to prevent weight gain, and 50 to 60 minutes per day to total 300 minutes of moderate, or 150 minutes of vigorous, per week of physical activity to promote weight loss and improve health (American College of Sports Medicine, 2017; Donnelly et al., 2009). Regular physical activity, including resistance exercise, and high protein intake (1.25 to

1.5 times the recommended dietary allowance (RDA) for sedentary and greater than 1.5 times the RDA for those who exercise) are recommended for persons with obesity who undergo weight-loss therapy to improve insulin sensitivity and limit muscle mass loss (Cava, Yeat, & Mittendorfer, 2017; Holloszy, 2005; Wang et al., 2013).

2.3.3.1. Resistance training. Little evidence is available to suggest resistance exercise as a reliable method for promoting weight loss (Swift et al., 2014). However, resistance training does contribute to the reduction of body fat mass (Donnelly et al., 2009). Resistance exercise also has many other health benefits, including maintaining and potentially increasing muscle strength while aging, preserving BMD, and attenuating the loss of muscle mass during hypocaloric dieting (Figueroa et al., 2013; Haskell et al., 2007; Villareal et al., 2011; Winett & Carpinelli, 2001).

2.3.3.2. Aerobic training. Research has shown high-volume aerobic training, 225 to 420 minutes per week, can promote significant weight loss without the need of CER (Swift et al., 2014). Even without weight loss, aerobic training has numerous health benefits, including improved cardiorespiratory fitness, glucose control, endothelial function, lipoprotein particle size, HDL, and quality of life, for overweight and obese adults at risk for disease (Church et al., 2010; Church, Earnest, Skinner, & Blair, 2007; Kodama et al., 2007; Kraus et al., 2002; Myers et al., 2013; Swift, Earnest, Blair, & Church, 2011). Vigorous intensity aerobic training has been shown to have enhanced health benefits when compared to moderate intensity aerobic training (Swift et al., 2014). Weight loss, however, when matched for energy expenditure or exercise dose, does not differ between moderate and vigorous intensity aerobic training (Swift et al., 2014). In terms of muscle mass preservation, the research on aerobic exercise training is less clear. Research has shown both preservation and loss of muscle mass (Cava et al., 2017).

2.3.3.3. Concurrent training. The combination of aerobic and resistance training as a method for facilitating reductions in body mass compared to aerobic or resistance training alone has been minimally explored. Evidence suggests similar results in body mass and fat mass loss, with enhanced effects for other health indicators, such as glucose control (Church et al., 2010; Swift et al., 2014; Willis et al., 2012). If the goal of training is to reduce fat mass, aerobic training may be more efficient because it requires less exercise duration than concurrent training (Willis et al., 2012). With that said, concurrent and resistance training appear to attenuate the loss of lean mass and BMD better than aerobic training (Villareal et al., 2017). As such, exercise should include resistance training if an increase or preservation of muscle mass and strength is desired (Willis et al., 2012). Overall, concurrent training appears to be the optimal method for improving overall functional ability and physical performance when compared to aerobic or resistance training alone (Hunter, McCarthy, & Bamman, 2004; Villareal et al., 2017; Willis et al., 2012). This makes concurrent training very important for attenuating age-related declines in muscle mass and strength and maintaining activities of daily living.

Table 1

Summary of Weight Loss Studies (Dietary Interventions: < 6 Months)

Publication	Subjects	Duration	Groups	Measures & Prescription	Highlighted Outcome
Chennaoui et al., 2009	8 Middle-distance athletes 25 years	38 days	RF	MAV, cortisol and testosterone, IL-6, and metabolic and hormonal parameters, mood state, and nutritional and sleep profiles.	Mean body mass and body fast did not change statistically. Testosterone and cortisol did not change significantly. Fatigue scores ↑ at the end of RF, with IL-6 ↑ and melatonin ↓. All parameters recovered at 7 days post RF.
Merra et al., 2016	25 (M, F) BMI (29.21-33.69) Healthy 18 to 65 years	3 weeks	Very low carbohydrate KD: 450-700 kcal per day Very low CER: 450-700 kcal per day	Caloric breakdown by meal: KD 35-40% fat, 5% carbohydrate, 55-60% protein CER 35-40% fat, 15-20% carbohydrate, 45-50% protein. Measurements: Body composition.	BMI ↓: KD 6.91 kg, CER 7.91 kg; Weight ↓: KD 6.99 kg, CER 7.98 kg; Fat mass ↓: KD 2.45 kg, CER 2.47 kg; FFM ↑: KD 1.92 kg; FFM ↓: CER 3.30 kg.
Bouhlel et al., 2008	9 Rugby players 19 years	4 weeks	RF	Body composition, blood glucose regulation, plasma GH, IGF-1, IGFBP-3, and insulin concentrations. Performed progressive cycle exercise tests.	RF induced significant ↓ in body mass and body fat; Plasma concentrations of glucose, insulin, GH, IGF-1 and IGFBP-3 did not change at rest or following exercise. RF induced positive body composition changes without disturbing glucose regulation or activity of the GH/IGF-1 system.
Johnson et al., 2007	10 (M, F) Obese	8 weeks	AL every other day, while consuming <20% of their normal caloric intake on intervening days → IER	Blood was collected for analyses of markers of general health, oxidative stress and inflammation. Asthma control. Pre and post bronchodilator spirometry.	9 subjects adhered to diet. Weight ↓: 8%; Asthma related symptoms, control and QOL improved significantly. Peak Expiratory Flow ↑ significantly. Serum B-hydroxybutyrate ↑ and leptin ↓ on CER days → indicating shift toward fatty acid utilization. Clinical findings show ↓ serum cholesterol and triglycerides, oxidative stress markers, and ↑ antioxidant uric acid. TNF-a and brain-derived neurotrophic factor significantly ↓.
More et al., 2016	34 (M) Resistance trained 29 years	8 weeks	TRF w/ RT: Meals consumed in 8h window ND w/ RT: Meals consumed in 12h window	Caloric breakdown by meal: TRF 40%, 25%, 35% ND 25%, 40%, 35%. Whey protein (20g) consumed after each training session. Training consisted of a 3-day, split routines: 3 sets of 6-8 repetitions at 85-90% 1RM w/ rest of 180 seconds.	Fat mass significantly decreased in TRF by 16.4% compared to ND (2.8%). FFM and CSA of the arm and thigh was maintained. TRF group experienced decreased total testosterone and IGF-1, as well as blood glucose and insulin. TNF-a and IL-1B were lower in TRF.

Table 1. *Summary of Weight Loss Studies (Dietary Interventions: < 6 Months) (continued)*

Publication	Subjects	Duration	Groups	Measures & Prescription	Highlighted Outcome
Tinsley et al., 2016	18 (M) Resistance trained 22 years	8 weeks	TRF w/ RT: Meals consumed in 4h window for 4 d/week RT group no TRF	Training consisted of a 3-d, split routines: 3 sets of 8-12 repetitions. Measurements included body composition by DXA, muscle CSA by ultrasound, upper and lower body strength and endurance.	TRF ended up reducing energy intake 650 kcal per day of TRF, but it did not affect total body composition. RT without TRF ↑ lean mass 2.4 kg. Upper and lower body strength and lower body muscle endurance increased in both groups, with greater ↑ in the TRF group. TRF didn't affect lean mass retention or muscle improvements.
Wilson et al., 2017	25 (M) Resistance trained College aged	11 weeks	KD WD	Caloric breakdown by meal: KD 75% fat, 5% carbohydrate, 20% protein WD 25% fat, 55% carbohydrate, 20% protein. Measurements: Body composition, strength, power, and blood lipid profiles.	FFM ↑: KD 2.4%, WD 4.4%; Fat mass ↓: KD 2.2 kg, WD 1.5 kg; Testosterone: ↑ KD 118 ng/dl, ↓ WD 36 ng/dl.
Gabel et al., 2018	23 (M, F) Obese 25 to 65 years	12 weeks	TRF: AL feeding in 8h window Historical control	Measures included, weight loss, blood pressure, fat mass, FFM, visceral fat mass, LDL and HDL cholesterol, triglycerides, fasting glucose and insulin, insulin resistance, and homocysteine.	Fat Mass ↓: TRF 2 kg; SBP ↓: TRF 7 mmHg; Triglycerides ↓: TRF 12 mg/dl; Fasting insulin ↓: TRF 2.6 uIU/ml; Homocysteine ↓: TRF 0.9 umol/l; Insulin resistance ↓: TRF 0.6 via HOMA-IR.
Harvie et al., 2013	115 (F) Overweight 20 to 69 years	4 months	IER 2500-2717 kJ/d, <40 g carbohydrate/d for 2 d/week CER 6000 kJ/d for 7 d/week IER w/ AL protein & fat	Measures included weight loss and metabolic disease risk markers.	Insulin resistance ↓: IER 0.34, IERPF 0.38; Fat mass ↓: IER 3.7%, IER AL 3.7%, CER 2.0%. IER was superior to CER for improved insulin sensitivity and body fat reduction.

Note. Male (M), Female (F), Continuous Energy Restriction (CER), CER + Exercise (CERX), Exercise (EX), Dual-energy X-ray Absorptiometry (DXA), Body Mass Index (BMI), Dehydroepiandrosterone Sulfate (DHEAS), Deoxyribonucleic Acid (DNA), Low Calorie Diet (LCD), Magnetic Resonance Imaging (MRI), Cardiovascular Disease (CVD), Visceral Adipose Tissue (VAT), Fat Cell Size (FCS), Ectopic Fat in Liver (IHL) and Muscle (IMCL), Homeostasis Model Assessment of Insulin Resistance (HOMA-IR), Insulin Sensitivity Index (ISI), High-density Lipoprotein (HDL), Low-density Lipoprotein (LDL), Diastolic Blood Pressure (DBP), C-reactive Protein (CRP), Tumor Necrosis Factor-a (TNF-a), Bone Mineral Density (BMD), High Glycemic (HG), Low Glycemic (LG), Ad Libitum (AL), Triiodothyronine (T3), Intermittent Energy Restriction (IER), Normal Protein Diet (NPD), High Protein Diet (HPD), Resting Energy Expenditure (REE), Fat-free Mass (FFM), Insulin-like Growth Factor (IGF), Insulin-like Growth Factor Binding Protein (IGFBP), Time-Restricted Feeding (TRF), Normal Diet (ND), Ketogenic Diet (KD), Western Diet (WD), Resistance Training (RT), One-repetition Maximum (1RM), Interleukin (IL), Maximal Aerobic Velocity (MAV), Cross-sectional Area (CSA), Ramadan Fasting (RF), Growth Hormone (GH), Increase (↑), Decrease (↓), Day (d), kilojoules (kJ), kilocalorie (kcal), gram (g), kilogram (kg), hour (h), with (w/), centimeter (cm), milligram (mg).

Table 2

Summary of Weight Loss Studies (Dietary Interventions: 6 Months)

Publication	Subjects	Duration	Groups	Measures & Prescription	Highlighted Outcome
Redman et al., 2007	35 (16M, 19F) Overweight 25 to <50 years	6 months	CER 25% CERX 12.5% + 12.5% Control	Changes in body composition by DXA; Changes in abdominal fat by multislice computed tomography; Diet: fat 30%, protein 15%, carbohydrate 55%; Exercise: Treadmill, stationary cycle, or Stairmaster 5d/week until 12.5% caloric expenditure achieved.	Weight ↓ 10%: CER 8.3kg, CERX 8.1kg; Fat mass ↓ 24%: CER 5.8kg, CREX 6.4; Visceral fat ↓ 27%: CER 0.98kg, CERX 0.80kg; FFM ↓ 2 to 3kg with no difference between CER and CERX.
Heilbronn et al., 2006	48 (M, F) Overweight 26 to 48 years	6 months	CER 25% CERX 12.5% + 12.5% LCD until 15% weight reduction Control	Body composition, DHEAS, glucose, insulin, protein carbonyls, DNA damage, 24h energy expenditure and core body temperature.	Weight ↓: CER 10%, CERX 10%, LCD 13.9%; Fat mass ↓: CER 24%, CERX 25%, LCD 32%; FFM ↓: CER 5%, 3 CERX %, LCD 6%; Fasting insulin ↓ in CR and CERX; 24h energy ↓ in CER, CERX, and LCD.
Redman et al., 2009	48 (M, F) Overweight 26 to 48 years	6 months	CER 25% CERX 12.5% + 12.5% LCD until 15% weight reduction Control	Total daily energy expenditure, activity related energy activity.	Total daily energy expenditure ↓: CER (454 kcal/day), LCD (633 kcal/day); CER results in a metabolic adaptation and a behavioral adaptation with decreased physical activity levels.
Larson-Meyer et al., 2006	48 (M, F) Overweight 26 to 48 years	6 months	CER 25% CERX 12.5% + 12.5% LCD until 15% weight reduction Control	VAT, FCS, IHL, IMCL, and ISI.	FCS was the strongest determinant of ISI; VAT ↓: CER 28%, CERX 27%, LCD 36%; FCS significantly ↓: CER 19%, CERX 26%, LCD 26%; IHL significantly↓: CER 37%, CERX 29%, LCD 40%; ISI significantly ↑: CERX 37%, LCD 70%, and trended to ↑ in CER 40%.
Lefevre et al, 2009	36 (M, F) Overweight 25 to <50 years	6 months	CER 25% CERX 12.5% + 12.5% Control	Cardiovascular disease risk factors: triacylglycerol, Factor VIIc, HDL, LDL, DBP, and CRP.	Triacylglycerol ↓: CER 31 mg/dL, CERX 22 mg/dL; Factor VIIc ↓: CER 10.7%, CERX 7.9%; LDL ↓: CERX 16 mg/dL; DBP ↓: 4 mmHg; HDL ↑ in all groups; CRP ↓: CERX, control; 10-year CVD risk significantly ↓ in CER (29%) and CERX (38%).

Table 2. *Summary of Weight Loss Studies (Dietary Interventions: 6 Months) (continued)*

Publication	Subjects	Duration	Groups	Measures & Prescription	Highlighted Outcome
Antoni et al., 2017	67 (M, F) Obese	6 months	IER 2638 kJ 2 d/week CER 2510 kJ 7 d/week	Anthropometry and established fasting cardiometabolic disease risk markers.	Weight ↓: IER 5%, CER 3%; Fat mass ↓: IER 11%, CER 2%; Waist circumference ↓: IER 4%, CER 2%. Both groups improved at least one cardiometabolic disease risk factor. Body weight and adiposity changes were greater in IER. IER was superior in ↓ fasting insulin and triacylglycerol, as well superior changes in HDL and systolic blood pressure.
Soenen et al., 2013	72 (24M, 48F) Overweight & Obese 44 years	6 months	CER w/ protein: NPD 0.8 g/kg of body weight HPD 1.2 g/kg of body weight	Body weight, body composition, and metabolic responses.	Weight ↓: NPD 7.2 kg, HPD 7 kg; Fat mass ↓: NPD 6.4 kg, HPD 6.8 kg; FFM ↓: NPD 0.8 kg, HPD 0.1 kg; FFM, REE compared with predicted REE, and DBP changed favorably with HPD. HPD demonstrated preservation of REE and FFM and lowering DBP.
Wing et al., 1994	93 (M, F) Obese 30 to 70 years	6 months	CER 400 kcal/d (CER4) CER 1000 kcal/d (CER1)	Compared fasting glucose, fasting insulin, and insulin sensitivity.	Both groups had similar ↓ in weight loss. CER4 has lower fasting glucose (7.61 mM vs. 10.13 mM),) and greater insulin sensitivity (1.79 vs. 1.13) than CER1. The degree of CER and magnitude of weight loss have independent effects on glycemic control and insulin sensitivity.

Note. Male (M), Female (F), Continuous Energy Restriction (CER), CER + Exercise (CERX), Exercise (EX), Dual-energy X-ray Absorptiometry (DXA), Body Mass Index (BMI), Dehydroepiandrosterone Sulfate (DHEAS), Deoxyribonucleic Acid (DNA), Low Calorie Diet (LCD), Magnetic Resonance Imaging (MRI), Cardiovascular Disease (CVD), Visceral Adipose Tissue (VAT), Fat Cell Size (FCS), Ectopic Fat in Liver (IHL) and Muscle (IMCL), Insulin Sensitivity Index (ISI), High-density Lipoprotein (HDL), Low-density Lipoprotein (LDL), Diastolic Blood Pressure (DBP), C-reactive Protein (CRP), Tumor Necrosis Factor-a (TNF-a), Bone Mineral Density (BMD), High Glycemic (HG), Low Glycemic (LG), Ad Libitum (AL), Triiodothyronine (T3), Intermittent Energy Restriction (IER), Normal Protein Diet (NPD), High Protein Diet (HPD), Resting Energy Expenditure (REE), Fat-free Mass (FFM), Insulin-like Growth Factor (IGF), Insulin-like Growth Factor Binding Protein (IGFBP), Time-Restricted Feeding (TRF), Normal Diet (ND), Ketogenic Diet (KD), Western Diet (WD), Resistance Training (RT), One-repetition Maximum (1RM), Interleukin (IL), Maximal Aerobic Velocity (MAV), Cross-sectional Area (CSA), Ramadan Fasting (RF), Growth Hormone (GH), Increase (↑), Decrease (↓), Day (d), kilojoules (kJ), kilocalorie (kcal), gram (g), kilogram (kg), hour (h), with (w/), centimeter (cm), milligram (mg).

Table 3

Summary of Weight Loss Studies (Dietary Interventions: ≥ 12 Months)

Publication	Subjects	Duration	Groups	Measures & Prescription	Highlighted Outcome
Racette et al., 2006	48 (18M, 30F) Overweight 50 to 60 years	12 months	CER 20% Exercise 20% Control Health Lifestyle	Weight, body composition by DXA, abdominal adipose tissue by MRI, and energy intake by doubly labeled water; Exercise: Performed at facility (track, cycle ergometers, rowing, ergometers, elliptical machines), health club, homes, or outdoors.	Weight ↓: CER 8 kg (10.7%), EX 6.4 kg (8.4%); Fat mass ↓: CER 77%, EX 87%; Visceral and subcutaneous abdominal adipose tissue ↓ significantly in CER and EX.
Villareal et al., 2006	48 (18M, 30F) Overweight 50 to 60 years	12 months	CER 20% Exercise 20% Control Health Lifestyle	Change in hip and spine BMD, bone markers and hormones.	Weight ↓: CER 8 kg (10.7%), EX 6.4 kg (8.4%); BMD at hip ↓: CER 2.2%; BMD at intertrochanter ↓: CER 2.1%; BMD at spine ↓: CER 2.2%. No BMD ↓ in EX. Body weight change correlated with BMD changes in CER, but not in EX.
Weiss et al., 2006	48 (18M, 30F) Overweight 50 to 60 years	12 months	CER 20% Exercise 20% Control Health Lifestyle	ISI, glucose and insulin via oral glucose tolerance test, adiponectin and TNF-a via fasted serum.	ISI ↑: CER 2, EX 3; Fasting insulin ↓: CER 2.7 U/mL, EX 2.5 U/mL; Fasting glucose ↓: CER 1.4 mg/dL, EX 5.3 mg/dL.
Das et al., 2007	34 (M, F) Overweight 24 to 42 years	12 months	CER 30%: HG LG	Food was provided for first 6 months, then subjects self-administered food for the last 6 months. Measures included energy intake, body weight and fatness, hunger, satiety, and resting metabolic rate.	Weight ↓: LG 7.81%, HG 8.04%; Body fat ↓: LG 17.9%, HG 14.8%; HDL ↑: LG 11.9 mg/dL, HG 13.3 mg/dL; LDL ↓: LG 7.0 mg/dL, HG 7.1 mg/dL; Insulin ↓: LG 21.2 uIU/mL, HG 18.0 uIU/mL; Triacylglycerol ↓: LG 15.2 mg/dL, HG 16.5 mg/dL. Significant ↑ in adiponectin, & ↓ in TNF-a-to-adiponectin ration in CER & EX.
Pittas et al., 2006	34 (M, F) Overweight 24 to 42 years	12 months	CER 30%: HG LG	Food was provided for first 6 months, then subjects self-administered food for the last 6 months. Measures included glucose-insulin dynamics and CRP levels.	Insulin sensitivity ↑: LG 24%, HG 26%; First-phase insulin release ↓: LG 21%, HG 20%; More patients in LG (14 of 16) had a ↓ in CRP, compared to HG (6 of 16).

Table 3. *Summary of Weight Loss Studies (Dietary Interventions: ≥ 12 Months) (continued)*

Publication	Subjects	Duration	Groups	Measures & Prescription	Highlighted Outcome
Ravussin et al., 2015	218 (M, F) BMI (21.9-28) 21 to 51 years	24 months	CER 25% AL	Baseline AL energy intake assessed with doubly labeled water. Resting metabolic rate, core temperature, plasma T3, and TNF-a; and exploratory physiological and psychological measures.	Weight ↓: CER 10.4%; RMR ↓ more in CER than AL at 12 months, but not at 24 months. T3 ↓: CER 25.0 ng/dL, AL 14.1 ng/dL; TNF-a ↓: CER 0.77 pg/mL, AL 0.38 pg/mL. CER had larger decreases in cardiometabolic risk factors, without adverse effects on quality of life.
Villareal et al., 2016	218 (M, F) BMI (21.9-28) 21 to 51 years	24 months	CER 25% AL	Baseline AL energy intake assessed with doubly labeled water. BMD and markers of bone turnover. Others included body composition, bone-active hormones, nutrient intake, and physical activity.	Weight ↓: CER 7.5 kg; Fat mass ↓: 5.3 kg; FFM ↓: CER 2.2 kg; Compared to AL, BMD ↓ in CER: lumbar spine (0.013 g/cm^2), total hip (0.017 g/cm^2), and femoral neck (0.015 g/cm^2). CER had larger ↑ in 25-hydroxyvitamin D, cortisol, and adiponectin and ↓ in leptin and insulin compared to AL. Parathyroid and IGF-1 levels did not differ between groups. CER had lower physical activity.

Note. Male (M), Female (F), Continuous Energy Restriction (CER), CER + Exercise (CERX), Exercise (EX), Dual-energy X-ray Absorptiometry (DXA), Body Mass Index (BMI), Dehydroepiandrosterone Sulfate (DHEAS), Deoxyribonucleic Acid (DNA), Low Calorie Diet (LCD), Magnetic Resonance Imaging (MRI), Cardiovascular Disease (CVD), Visceral Adipose Tissue (VAT), Fat Cell Size (FCS), Ectopic Fat in Liver (IHL) and Muscle (IMCL), Insulin Sensitivity Index (ISI), High-density Lipoprotein (HDL), Low-density Lipoprotein (LDL), Diastolic Blood Pressure (DBP), C-reactive Protein (CRP), Tumor Necrosis Factor-a (TNF-a), Bone Mineral Density (BMD), High Glycemic (HG), Low Glycemic (LG), Ad Libitum (AL), Triiodothyronine (T3), Intermittent Energy Restriction (IER), Normal Protein Diet (NPD), High Protein Diet (HPD), Resting Energy Expenditure (REE), Fat-free Mass (FFM), Insulin-like Growth Factor (IGF), Insulin-like Growth Factor Binding Protein (IGFBP), Time-Restricted Feeding (TRF), Normal Diet (ND), Ketogenic Diet (KD), Western Diet (WD), Resistance Training (RT), One-repetition Maximum (1RM), Interleukin (IL), Maximal Aerobic Velocity (MAV), Cross-sectional Area (CSA), Ramadan Fasting (RF), Growth Hormone (GH), Increase (↑), Decrease (↓), Day (d), kilojoules (kJ), kilocalorie (kcal), gram (g), kilogram (kg), hour (h), with (w/), centimeter (cm), milligram (mg).

Table 4

Summary of Weight Loss Studies (Physical Activity Interventions)

Publication	Subjects	Duration	Groups	Measures & Prescription	Highlighted Outcome
Figueroa et al., 2013	41 (F) Obese 54 years	12 weeks	Diet Diet + Exercise Exercise	Exercise: 4 exercises, at 2 sets of 18-22 repetitions (↑ to 3 sets after 2 weeks), 3 times per week. Workload ↑ to maintain 20 repetitions. Diet: 1,250 kcal/d: 55% carbohydrates, 25% fat, and 20% protein. Body weight, waist circumference, aortic SBP, and muscle mass via DXA measured before and after.	Body weight and waist circumference ↓ similarly between diet and diet + exercise group. Skeletal muscle mass didn't change in diet + exercise but was significantly ↓ in the diet group compared to the exercise alone group. SBP ↓ significantly in all groups.
Swift et al., 2011	155 (F) Obese Postmenopausal w/ elevated BP	6 months	Control Energy expenditure: 4 kcal/kg/week 8 kcal/kg/week 12 kcal/kg/week	Endothelial function was assed via FMD.	FMD ↑: 1.02-1.5% in all exercise groups; FMD ↑ significantly in exercisers with endothelia dysfunction compared to those with normal endothelial function.
Villareal et al., 2017	141 (M, F) Obese > 65 years	6 months	While dieting: RT AT CT Control	Score on PPT, frailty measures, body composition, BMD, physical function, and quality of life. AT: 3 x per week at 60 min. RT: 3 x per week at 60 min, 9 upper- and lower-body exercise, 3 sets of 8-12 reps. Progressed from 65 to 85% 1RM. CT: 3 x per week at 75-90 min. All AT and RT exercises.	PPT ↑: CT 21%, AT 14%, RT 14%; Peak oxygen consumption ↑: CT 17%, AT 18%, RT 8%; Strength ↑: CT 18%, RT 19%, AT 4%; Body weight ↓: CT 9%, AT 9%, RT 9%; FFM ↓: CT 3%, RT 2%, AT 5%; BMD ↓: CT 1%, RT 0.5%, AT 3%.
Kraus et al., 2002	84 (M, F) Overweight w/ dyslipidemia 52.3 years	6 months 8 months	Control 3 Exercise: HHEX LHEX LMEX	HHEX: jogging 20 min/week at 65 to 80% peak oxygen consumption. LHEX: jogging 12 min/week at 65 to 80% peak oxygen consumption. LMEX: walking 12 min/week at 40 to 55% peak oxygen consumption Measure lipoprotein responses to various exercise training protocols.	Minimal weight change was observed; HHEX had the greatest beneficial effect on lipids and lipoproteins than LHEX and LMEX. HHEX provides the maximal benefit in preventing cardiovascular events and death. Improvement in HHEX were related to the amount of physical activity and not related to changes in level of fitness. The amount of exercise was more important for determining lipoprotein responses.

Table 4. *Summary of Weight Loss Studies (Physical Activity Interventions) (continued)*

Publication	Subjects	Duration	Groups	Measures & Prescription	Highlighted Outcome
Willis et al., 2012	119 (M, F) Overweight & Obese 18 to 70 years	8 months	RT AT CT	RT: 3 days per week, 3 sets 8-12 reps. AT: Caloric equivalent of 12 miles per week, 60-80% peak oxygen uptake. CT: Both RT and AT. Measurements: Body composition, cardiopulmonary test, strength.	Fat mass ↓: CT 2.44 kg, AT 1.66 kg, RT 0.26 kg; FFM ↑: CT 0.81 kg, RT 1.09 kg; FFM ↓: AT 0.10 kg; Strength ↑: CT 3810 kg per session, RT 4306 kg per session; Peak oxygen uptake ↑: CT 4.25 ml/kg/min, AT 3.43 ml/kg/min, RT 1.26 ml/kg/min; Waist circumference ↓: CT 1.66 cm^2, AT 1.01 cm^2, RT 0.06 cm^2. AT appears best for reducing fat mass and body mass for time, while RT is needed for increasing lean mass.
Church et al., 2010	262 (M, F) Sedentary w/ type 2 diabetes 30 to 75 years	9 months	RT AT CT Control	RT: 3 time per week, 2 sets of 4 upper body exercises, 3 sets of 3 legs exercises, & 2 sets of 2 abdominal exercises. 10 to 12 repetitions, ↑ once 12 repetitions were completed on 2 consecutive sessions; AT expended 12 kcal/kg/week. CT expended 10 kcal/kg/week and engaged in RT 2 times per week with same variables. Measures included HbA1c and anthropometry data.	Weight ↓: CT 1.5 kg; Fat mass ↓: RT 1.4 kg, CT 1.7 kg; FFM ↑: RT 0.8 kg, and ↓: AT 0.5 kg; HbA1c ↓: CT 0.34%, RT 0.16%, AT 0.24%; Maximum oxygen consumption ↑: CT 1.0 mL/kg per min; Waist circumference ↓: 1.9 to 2.8 cm in all groups compared to control.
Myers et al., 2013	173 (M, F) 57 years	9 months	RT AT CT Control	Analysis of HbAi1c using Short Form-36 Health Survey questionnaire compared across treatment groups and with U.S. national norms.	The QOL physical component subscale and (GH) subscale were improved in all groups compared to control. RT had greatest beneficial change in bodily pain; AT and CT had the greatest beneficial change in physical functioning. CT had greater gains than AT in mental score, vitality, and mental health. Exercise improves QOL, with CT having greater improvements in QOL.

Table 4. *Summary of Weight Loss Studies (Physical Activity Interventions) (continued)*

Publication	Subjects	Duration	Groups	Measures & Prescription	Highlighted Outcome
Villareal et al., 2011	93 (M, F) Obese >65 years	12 months	Diet Diet + Exercise Exercise Control	Exercise: 90 min of aerobic, resistance, and flexibility and balance training. Aerobic: 65% of peak heart rate and ↑ 70 to 85%. Resistance: 1 or 2 sets of 8 to 12 repetitions at 65% 1RM, ↑ to 2 to 3 sets of 6 to 8 repetitions at 80% 1RM. Diet: Consumed a 500 to 750 kcal/d w/ 1 g of protein per kg/d. Diet + Exercise encompassed both. Measures included frailty, body composition, BMD, specific physical functions, and QOL.	Body weight ↓: Diet 10%, Diet + Exercise 9%; Fat mass ↓: Diet 17%, Diet + Exercise 16%, Exercise 5%; FFM ↓: Diet 5%, Diet + Exercise 3%, and ↑: Exercise 2%. BMD at hip ↓: Diet + Exercise 1.1%, Diet 2.6%, and ↑: Exercise 1.5%. Total 1RM ↑: Diet + Exercise 35%, Exercise 34%. VO2peak ↑: Diet + Exercise 17%, Diet 10%, and Exercise 8%; QOL via SF-36 ↑: Diet + Exercise 15%, Diet 14%, Exercise 10%. Combination of weight loss and exercise provides greater improvement in physical function than either intervention alone.

Note. Male (M), Female (F), Increase (↑), Decrease (↓), Bone Mineral Density (BMD), Quality of Life (QOL), Dual-energy X-ray Absorptiometry (DXA), Fat-free Mass (FFM), One-repetition Maximum (1RM), Resistance Training (RT), Aerobic Training (AT), Concurrent Training (CT), Hemoglobin A1c (HbAi1c), High Volume High Intensity Exercise (HHEX), Low Volume High Intensity Exercise (LHEX), Low Volume Medium Intensity Exercise (LMEX), Blood Pressure (BP), Systolic BP (SBP), Flow-mediated Dilation (FMD), kilojoules (kJ), kilocalorie (kcal), gram (g), kilogram (kg), hour (h), with (w/), minutes (min), United States (U.S.), centimeter (cm), Physical Performance Test (PPT).

2.4. Safety and Ethical Considerations

2.4.1. Introduction

Ethical principles are designed to support autonomy and self-determination, protect vulnerable populations, and promote the welfare and equality of human beings (Gostin, 1991). Ethics are so important in research that codes and policies have been adopted by many professional associations to help guide researchers on ethical behavior (World Medical Association, 2013). These codes address issues of honesty, objectivity, respect for intellectual property, social responsibility, confidentially, non-discrimination, as well as many other areas for the purpose of protecting both the volunteers and researchers of the study (Gostin, 1991). While beneficial, codes and policies do not cover every ethical issue that can occur in research. Thus, most institutions and organizations have developed Institutional Review Boards to ensure the safety of human subjects. The purpose of Institutional Review Boards are to make sure that human rights are not violated, and ethical practices are being utilized throughout the research process (Enfield & Truwit, 2008). Below are several topics, based on the reviewed literature, that require safety and ethical discussion.

2.4.2. Obesity Measurement

Body mass index has emerged as one of the most common and preferred methods for identifying overweight or obese members of the population (Nevill, Stewart, Olds, & Holder, 2006). Despite extensive research on the relationship between stature-adjusted body mass and body fat, some researchers consider BMI to be an inaccurate index of adiposity (Cole, 1991; Nevill et al., 2006). This is because BMI fails to discriminate between body fat and lean mass, and its accuracy changes based on the degree of body fat mass (Freedman & Sherry, 2009; Romero-Corral et al., 2008). In fact, BMI has been shown to misdiagnose overweight and

obesity in health adults and thin children and fail to differentiate between athletes and nonathletes of similar stature (Freedman & Sherry, 2009; Hortobagyi, Israel, & O'Brien, 1994; Nevill et al., 2006). Thus, BMI should not be the only anthropometric data used to describe the biological characteristics of humans (Micozzi & Albanes, 1987). Hypotheses should use multiple anthropometric measurements to test relationships between nutrition, growth, body size, and disease (Micozzi & Albanes, 1987).

2.4.3. Dual-Energy X-Ray Absorptiometry

It is well known that exposure to radiation in high doses at high dose rates is harmful. To protect the safety of workers and patients, dose limits have been imposed to keep radiation exposure to the same order of, or less than, the magnitude of "background" exposures (Baim et al., 2005). For a DXA scan, the dose to the skin (where the beam enters the patient) can be measured easily. This dose, however, does not reflect the full radiation risk to the patient because only a small part of the body is exposed during the DXA scan. To estimate the impact of partial body irradiation, the International Commission on Radiation Protection developed the concept of effective dose (Baim et al., 2005). Effective dose is expressed in units of rem or Sievert (1 uSv = 0.000001 Sv = 0.001 mSv) and is the dose to the whole body that carries the same risk as the partial body dose (Baim et al., 2005). Effective doses allow for comparison between different radiographic examinations and their potential radiation risk, as well as comparisons to background radiation from cosmic rays and naturally occurring radioactive materials in the earth (Baim et al., 2005).

For example, the effective dose of a whole-body DXA, using a Lunar Prodigy, is between 0.37 uSv and 0.60 uSv (0.0004 mSv and 0.0006 mSv) for a scan lasting four and half minutes (Toombs, Ducher, Shepherd, & Souza, 2012). On average, an individual in the U.S. is exposed to

3000 uSv per year (8 uSv per day) of background radiation. Compared to a single day of background radiation, the effective dose of a DXA scan is quite similar and safe. A DXA exam also produces one of the lowest effective doses from commonly used medical x-ray examinations. A conventional chest x-ray, consisting of a posterior-anterior and lateral view, delivers an effective dose of 60 uSv, and a conventional mammogram delivers close to 130 uSv (Baim et al., 2005). Dual-energy x-ray absorptiometry is a low dose procedure that is safe for longitudinal measurements on the progression of bone disease and the efficiency of interventions.

2.4.4. Dietary Weight Loss

It is well known that 3500 calories are equal to one pound of body mass. Weight loss therapy traditionally seeks to achieve a body mass reduction equal to 10% of baseline measurements in six months (National Heart Lung and Blood Institute & National Institute of Diabetes and Digestive and Kidney Diseases, 1998). This is equivalent to an energy deficit between 500 to 1000 calories per day, creating a weight loss of one to two pounds per week (National Heart Lung and Blood Institute & National Institute of Diabetes and Digestive and Kidney Diseases, 1998). It is not recommended to consume less than 1000 calories each day without medical supervision (Guth, 2014). While there is no ideal blend of carbohydrate, protein, and fat during weight loss, it is recommended to consume a balanced diet of 15% to 20% protein, 20% to 35% fat, and the rest from carbohydrates (Guth, 2014; National Heart Lung and Blood Institute & National Institute of Diabetes and Digestive and Kidney Diseases, 1998). Research has shown that consuming more protein (1.2 grams per kilogram body weight) helps preserve a larger portion of fat-free mass during weight loss (Harvie et al., 2013). This is particularly important knowing weight loss, via CER, is associated with reductions of fat-free mass between

10% and 60% (Chaston et al., 2007). It should be noted that long-term, high-protein diets (two to three times the RDA), appear to contribute to urinary calcium loss that may predispose to bone loss (Eisenstein, Roberts, Dallal, & Saltzman, 2002).

2.4.5. Physical Activity

Risk of a sudden cardiac death or acute myocardial infarction is higher in adults compared to adolescents (American College of Sports Medicine, 2017). Research has shown an increased rate in adults performing vigorous exercise and it is higher in most sedentary individuals when they perform unaccustomed or infrequent exercise (American College of Sports Medicine & American Heart Association, 2007). It is recommended for potential participants to be screened for risk factors of cardiovascular, pulmonary, and metabolic diseases, as well as other conditions, to ensure safe and effective exercise (American College of Sports Medicine, 2017). According to American College of Sports Medicine (2017), the purpose of preparticipation health screening is to:

- Identify individuals with medical contraindications for exclusion from exercise programs.
- Recognize persons with significant diseases or conditions that should only be medically supervised when training.
- Detect individuals at increased risk of disease due to age, symptoms, or risk factors who should undergo medical evaluation and testing before beginning an exercise program.
- Recognize the special needs of individuals that may affect exercise training.

Screening procedures and tools must be valid and provide relevant and accurate information about the participants health history, current medical conditions, risk factors, signs or symptoms,

current physical activity or exercise habits, and medications (American College of Sports Medicine, 2017).

Hypertension alone is commonly associated with increased all-cause and cardiovascular mortality (Pescatello et al., 2004). Physical activity, primarily endurance exercise, helps to prevent hypertension and lower blood pressure in adults (Pescatello et al., 2004). Following acute or chronic endurance training, blood pressure has been shown to decrease five to seven mm Hg (Pescatello et al., 2004). In the general population, only two mm Hg reductions in systolic or diastolic blood pressure are needed to decrease the risk of stroke by 14% and 17%, and risk of coronary artery disease by 9% and 6%, respectively (Pescatello et al., 2004). There are no recognized blood pressure cutoff points for exercise participation (Pescatello et al., 2004). With that said, exercise testing may be warranted for men over 45 and women over 55 years planning to engage in vigorous ($\geq$ 60% VO_2 Reserve) exercise (Pescatello et al., 2004). Many patients, however, will be able to begin moderate-intensity (40% to < 60% VO_2 reserve) exercise training without the need of testing (Pescatello et al., 2004). Exercise serves as an ideal method for the prevention, treatment, and control of high blood pressure (Pescatello et al., 2004).

2.4.6. Blood Spot Testing

Dried blood spot tests are an increasingly preferred method for collecting biomarkers in whole blood compared to venipuncture (Ostler, Porter, & Buxton, 2014). Dried blood spot tests are less invasive than venipuncture and are a great, cost-effective alternative. Collecting blood spots are relatively simple, but still need to follow basic safety precautions. Ostler et al. (2014) recommends the following guidelines when conducting dried blood spot tests. Personal protective equipment (e.g., gloves, long pants, etc.) should be worn to protect against infection from blood borne pathogens. Before collection begins, it is important to have approved sharps

and biohazard disposal containers available. To maintain cleanliness, hands should be washed with soap and warm water for 20 seconds before and after physical contact with each participant, and personal protective equipment should be worn when handling sterile or biohazardous material.

Once ready for collection, the participants hands should be warmed with a hand warmer, warm water, or similar, to stimulate blood flow. The selected finger should be cleaned with an alcohol pad and allowed to dry to prevent contamination. Secure each participants arm, below heart level, and have them relax their muscles will help with blood flow. Using a micro-lancet, press firmly against the designated finger perpendicular to the fingerprint, being sure to wipe the first drop of blood away with a sterile gauze pad. Maintain the participants hand below their heart and avoiding squeezing the finger, as it will reduce blood flow. Once drops are collected, the puncture site should be cleaned of any extraneous blood and bandaged to avoid potential contamination. Dispose any sharps into the sharp's container, and biohazards into the appropriate waste barrel.

If a participant is feeling faint or presents signs of perspiration on the face or forehead, blurring vision, drooping eyelids, or nausea stop the procedure. Take care that the patient does not fall and calmly reassure them. Have the participant rest for 10 minutes, resuming the procedure only if the participant consents. If subject does faint, have the participant lie back with feet elevated. Ask them to loosen tight clothing and rest for 10 minutes. Blood collection should not continue. If participant fails to respond after one minute, 911 should be called.

2.5. Conclusion

Obesity is strongly associated with physical dysfunction and many cardiovascular-related disorders (National Heart Lung and Blood Institute, 2013). Contextual elements, including physical and social environment, age, and cultural identity, have been shown to impact healthy behavior and weight status (Williams et al., 2015). In fact, GWAS have been able to account for close to 5% of the individual genetic variation in BMI and adiposity traits caused from these types of factors (Albuquerque et al., 2015; Heymsfield & Wadden, 2017; Pigeyre et al., 2016). While genetics play a role in obesity prevalence, poor regulation of food intake and energy expenditure remains a major cause of increased adiposity. By reducing baseline weight by 5% to 10%, either through reductions in food intake, increases in physical activity, or both, an improvement of many obesity-related risk factors and disease prevention can occur (American College of Cardiology & American Heart Association Task Force on Practice Guidelines, 2014; Apovian et al., 2015; Garvey et al., 2016; Heymsfield & Wadden, 2017).

The primary dietary strategy to reduce adiposity and improve metabolic and hormonal risk factors remains CER, even though it is associated with reductions in fat-free mass and poor compliance (Most et al., 2017). Thus, the efficacy of alternative dietary strategies continues to be researched. Intermittent fasting is one such strategy, and has gained popularity due to its unrestrictive energy intake design (Antoni, Johnston, Collins, et al., 2017; Harvie & Howell, 2017). Studies have shown IF variants, including the KD, to preserve larger portions of fat-free mass than CER, as well as improve muscle strength and endurance when combined with resistance training (Harvie et al., 2013; Mattson et al., 2017; Moro et al., 2016; Soenen et al., 2013; Tinsley et al., 2017). To further support weight loss, aerobic exercise is the most beneficial training method for reducing fat mass and improving cardiorespiratory health (Willis et al., 2012). Though resistance exercise doesn’t significantly reduce fat mass, it does help preserve or

attenuate the loss of muscle mass and strength (Villareal et al., 2017). When combined, aerobic and resistance training leads to greater improvements in overall functional ability and physical performance than either method alone, making concurrent training very beneficial for overall health improvement (Hunter et al., 2004; Villareal et al., 2017; Willis et al., 2012).

Lastly, ethical guidelines for the protection of human subjects in research are well recognized. These have found expression in international guidelines for the conduction of clinical research and have been codified in national statutes and regulations (Gostin, 1991; World Medical Association, 2013). These principals are designed to protect the right of populations to self-determinate, protect vulnerable populations and those that need special justifications, protect the privacy, integrity, and self-esteem of populations, ensure the equitable distribution of benefits and burdens of research, and protect the health and well-being of populations (Gostin, 1991; World Medical Association, 2013).

3. METHODOLOGY

3.1. Purpose

The purpose of this study was to:

1. Determine whether TRF was an effective dietary strategy for reducing fat mass while preserving fat-free mass in combination with aerobic and resistance training.
2. Evaluate potential changes in health-related biomarkers and indicators of muscle health (mass, strength) after eight weeks of TRF and concurrent exercise training.
3. Examine the influence of energy intake and macronutrient distribution on muscle health in TRF and NF throughout the study intervention.

3.2. Participants

The study recruited overweight and obese (determined by BMI between 25.0 and 34.9 kg/m^2) adults between the ages of 35 and 60 years who were not currently following a structured aerobic or resistance training program or dietary plan. Recruitment occurred through email announcements, flyers, and word of mouth. A total of 78 potential subjects were screened for the study. After review, 23 were determined eligible to participate. Participants were excluded if they:

- Did not meet the required BMI or age range.
- Were pregnant or perceived they may become pregnant.
- Currently smoked tobacco, e-cigarettes, or used smokeless tobacco.
- Had current neuromuscular disease, diabetes, uncontrolled high blood pressure, or were being treated for cancer.
- Had a previous heart attack or other chronic heart related conditions not controlled with medicine.

- Had difficulty moving or any musculoskeletal injury that would prevent them from exercise.
- Were currently taking medications that could influence muscle size and strength (e.g., testosterone, growth hormone).
- Had bariatric surgery, a body mass greater than 350 pounds, or were at risk for disordered eating.

3.3. Documentation

The study was registered at clinicaltrials.gov (NCT03823872) and was approved by the North Dakota State University Institutional Review Board (#HE18247; Appendix A). After providing written informed consent (Appendix B) and completing a Physical Activity Readiness Questionnaire (PAR-Q) and health history questionnaire, documents were screened by the research team to determine if participants were healthy and capable of participating in the study. A screening form was completed before each DXA body composition analysis, with female participants providing a urine sample for a pregnancy test. A positive test would deem the participant ineligible and all testing for that subject would be cancelled. Data collection was conducted in the Bentson Bunker Fieldhouse (room 14, 15, and 16) at North Dakota State University, 1301 Centennial Blvd., Fargo, ND 58102. Personal training was conducted in the Wallman Wellness Center at North Dakota State University, 1707 Centennial Blvd., Fargo, ND 58102.

3.4. Procedures

3.4.1. Informational Presentation

A recruitment presentation was created to inform participants about the purpose of the study, the assessments involved, and the training that would occur during the study. After

reviewing the presentation, participants completed the informed consent and screening questionnaires. Once the informed consent and screening forms were collected, the research team reviewed them to determine eligibility. If eligible, subjects were scheduled for pre-training assessments.

3.4.2. Pre-Training Assessments

The primary assessments for this study were associated with body composition and functional markers to combat elevated levels of adiposity and physical dysfunction. These assessments were separated into two sessions. Session one was conducted in the morning after an overnight fast to assess anthropometrics, blood pressure and heart rate, metabolic and physiological variables, and body composition. Session two was conducted in the afternoon in an unfasted state to assess muscle performance and submaximal cardiorespiratory fitness. Participants were also provided a three-day dietary intake analysis to complete before their first training session. After the pre-training assessments, participants were randomly assigned to a TRF or NF group.

3.4.3. Training Sessions

All subjects were scheduled for an eight-week, standardized concurrent aerobic and resistance training program that began the week following pre-training assessments.

3.4.3.1. Resistance training. Training was standardized for both groups and consisted of three weekly sessions performed on non-consecutive days for eight weeks (24 sessions). The three different weekly sessions were: Session A (chest press, shoulder press, triceps pulldown), Session B (leg press, leg flexion, leg extension), Session C (wide grip latissimus dorsi pulldown, back machine pulley row, bicep curl). The training protocol involved three sets of 12 repetitions with no more than 60 seconds of rest between exercises and sets (Baechle, Earle, & Wathen,

2008). Load was assigned based on a percentage of the participants body mass and was adjusted through trial loads during week one of training, until the goal number of repetitions was achieved (Baechle et al., 2008).

For the first exercise of each session, subjects followed a lift specific warm-up by performing eight repetitions at 40% of their estimated 12RM, followed by a one-minute rest (Miller, 2012). The subjects then completed a second warm-up set of six repetitions at 60% of their estimated 12RM, followed by a two-minute rest (Miller, 2012). Participants began their second week of training attempting to complete three sets of 12 repetitions with their adjusted loads. During each training session, subjects attempted to complete one additional repetition for each set. Once subjects performed three sets of 15 repetitions, on two consecutive training sessions, intensity was increased by adding weight in 2.27- to 9.09-kilogram increments. After adding additional weight, subjects went back to performing three sets of 12 repetitions. The increase in weight ensured subjects maintained appropriate training progression to elicit the desired training response. Certified personal trainers directly supervised all routines to ensure proper form. Subjects were not be allowed to perform other resistance training exercises other than those included in the experimental protocol.

3.4.3.2. Aerobic training. American College of Sports Medicine (2017) has defined 50 to 60 minutes per day to total 300 minutes of moderate, or 150 minutes vigorous, physical activity necessary to promote or maintain weight loss. Our study was designed to help and encourage participants achieve this goal each week. Heart rate reserve (HRR) was used to prescribe appropriate intensities for all aerobic activities. Heart rate maximum was calculated using the Tanaka method (Tanaka, Monahan, & Seals, 2001). The aerobic conditioning program began at a moderate-vigorous intensity (≥55% HRR) and was performed on a treadmill or related

equipment (American College of Sports Medicine, 2017). After completion, subjects were instructed to perform a five-minute cooldown at a low- (<40% HRR) to moderate- (40% to <55% HRR) intensity (American College of Sports Medicine, 2017). Exercise for aerobic training started at total of 75 minutes at week one and increased 75 minutes each week until week five. At weeks five and seven the training intensity was increased (5% to 10%) to maintain the exercise progression while subjects continued to achieve 300 minutes of physical activity per week.

3.4.4. Mid-Training Assessments

Halfway through the intervention (week five) participants blood pressure was assessed and body mass was measured to verify safe weight loss. Safe weight loss was defined as one to two pounds per week, or about two to eight pounds per month. It is common, however, to experience greater weight loss during the start of a new weight loss program, so researchers were responsible for determining whether weight loss was too drastic compared to safe weight loss values.

3.4.5. Post-Training Assessments

Post-training assessments were scheduled within one week of the last training session. The session included all pre-training assessments, except the three-day dietary intake analysis. Once the session was completed, subject received compensation for participating in the study.

3.5. Measures

3.5.1. Anthropometrics

Resting blood pressure and heart rate were collected after five minutes of sitting. Blood pressure was measured with a Diagnostix 703 sphygmomanometer (American Diagnostic Corporation, Hauppauge, NY, USA). Heart rate was counted for one minute at the radial artery

by manual palpation. After resting measures, height was measured using a stadiometer (Seca 213, Chino, CA, USA) and body mass was recorded on an industrial scale (Denver Instrument DA-150, Arvada, CO, USA) with shoes removed. A Baseline measurement tape with Gulick attachment (Fabrication Enterprises, White Plains, NY, USA) was used to measure hip and waist circumference at the widest portion of the hips and at two finger widths above the umbilicus, respectfully.

3.5.2. Saliva

Participant saliva was collected into a single plastic tube via passive drool. The saliva was used to analyze potential changes in hormones (estradiol, progesterone, testosterone, DHEAS, cortisol). Oral hormone users were told to make sure any night dosage was applied at least 12 hours before planned morning collection. Tubes were stored and then shipped to ZRT Laboratory (Beaverton, OR, USA), a CLIA certified diagnostic laboratory.

3.5.3. Dried Blood Spot

Participant whole blood was collected by placing capillary collected blood drops on a blood spot filter card after a finger prick with a safety lancet. The blood spot testing was used to analyze potential changes several health-related biomarkers (insulin, hsCRP, hemoglobin A1c, triglycerides, total cholesterol, HDL, LDL, VLDL). Once dry, the cards were stored and then shipped to ZRT Laboratory (Beaverton, OR, USA), a CLIA certified diagnostic laboratory.

3.5.4. Body Composition

Dual-energy x-ray absorptiometry scans were completed using a Lunar Prodigy, model #8915 (GE Healthcare, Waukesha, WI, USA). A DXA scan is widely considered a gold standard technique for assessing BMD, muscle mass, and body composition. The scan generally takes 10 to 20 minutes. Researchers ensured that participants were wearing appropriate clothing,

removing anything metal or that may interfere with the scan. Participants were asked to lay supine and remain still while the scan was in progress. All DXA scans were reviewed by a radiologist, Dr. Steven Mitchell, to determine whether subjects needed to consult with their physician given unanticipated findings.

3.5.5. Hand Grip Strength

Grip strength was measured in kilograms using a Jamar Hydraulic Hand Dynamometer (Sammons Preston Rolyan, Bolingbrook, IL, USA). Participants were asked to stand with their dominant arm bent to 90 degrees. After a brief countdown, participants squeezed the dynamometer as hard as possible, with encouragement, for three seconds. After a one-minute rest, the test was repeated two additional times. The greatest of three attempts was recorded.

3.5.6. Three-Minute Step

The purpose of the step test was to provide submaximal measures of cardiorespiratory fitness. The test was conducted according to the protocol designed by the YMCA (American College of Sports Medicine, 2017).

3.5.7. Muscle Function

A Biodex Pro4 system dynamometer (Biodex Medical Systems, Shirley, NY) was used to measure the lower body muscle strength and endurance (Ploutz-Snyder, Manini, Ploutz-Snyder, & Wolf, 2002). Isokinetic maximal strength was assessed at 60 degrees per second for the knee extension-flexion and 30 degrees per second for plantar-dorsiflexion. Isokinetic endurance was measured using a 21 repetitions test at 180 degrees per second for the knee extension-flexion and 60 degrees per second for plantar-dorsiflexion. The Biodex dynamometer is highly reliable, safe, and housed in the Health, Nutrition, and Exercise Sciences Department at North Dakota State

University (Drouin, Valovich-McLeod, Shultz, Gansneder, & Perrin, 2004; Feiring, Ellenbecker, & Derscheid, 1990).

3.5.8. Dietary Intake

The TRF group was required to consume all their energy intake within an eight-hour feeding window (1200 and 2000 hours), inducing a fasting window of 16 hours. The NF group maintained their regular dietary habits. Although supervised feeding would be a better-controlled model, the resources required are extensive and expensive (Davy & Davy, 2019). Thus, an ad libitum approach was implemented to examine how energy and macronutrient intake are influenced when feeding patterns are not strictly controlled. All subjects were instructed to complete a three-day dietary intake log at pre-intervention and at weeks one, four, and seven during the intervention to detect any changes in dietary intake. Subjects were asked to document their food intake on two typical days and one atypical day. All dietary instructions were led by a protocol-trained board certified specialist in sports dietetics. The food intake logs were analyzed by registered dietitians using the Food Processor (ESHA, Salem, OR, USA).

3.5.9. Physical Activity

To ensure subjects were meeting the 300-minute physical activity goals, an ActiGraph GT3X+ accelerometer (ActiGraph, Pensacola, FL, USA) was worn at weeks two, five, and eight during the intervention to precisely quantify energy expenditure and the intensity of activities. The accelerometer was worn on the right hip, in line with the right knee, via an elastic band. The accelerometer was worn during waking hours except for water-based activities. A sleep log was given to subjects to record the time they removed the accelerometer for sleep and the time they put it on the following day upon waking.

The GT3X+ accelerometers were processed with epoch durations of 60 seconds. Participants were required to have worn the accelerometer for at least four days, including one weekend day, over a seven day collection period, with a minimum of 10 hours of wear time each day (Aadland & Ylvisåker, 2015; Matthews, Ainsworth, Thompson, & Bassett, 2002; Matthews, Hagströmer, Pober, & Bowles, 2012). To classify physical activity intensity levels, Sasaki, John, and Freedson (2011) cut-points for moderate, hard, and very hard physical activity were used, along with Kozey-Keadle, Libertine, Lyden, Staudenmayer, and Freedson (2011) cut-points for assessing sedentary behavior. The L. Choi et al. (2011) algorithm was used for wear and non-wear time.

3.5.10. Statistical Analysis

Anthropometric measures were described using means and standard deviation or errors. For dependent variables (body composition, cardiometabolic biomarkers, hormones, muscle performance, cardiovascular performance, dietary factors, physical activity), separate 2 (Dietary Plan: TRF and NF) x 2 (Time: Pre- and post-training) ANOVAs with repeated measures were used. An alpha level of 0.05 was used to determine statistical significance. If a significant interaction was found, independent and paired t-tests with Bonferroni corrections were run to compare post-training adaptations. If independent t-tests failed to show the significant interaction effect, delta differences for the variables were calculated, and independent t-tests were used to remove between subject variability. Cohen's d effect sizes were calculated for each group by dividing the difference between W0 and W9 by the pooled standard deviation. All statistical analyses were conducted using SPSS 26 software (IBM Corp., Armonk, NY, USA).

4. TIME-RESTRICTED FEEDING AND CONCURRENT EXERCISE TRAINING DECREASES FAT MASS AND PRESERVES LEAN MASS IN OVERWEIGHT AND OBESE ADULTS

4.1. Abstract

Purpose: The purpose of this study was to determine whether time-restricted feeding (TRF) was an effective dietary strategy for reducing fat mass and preserving fat-free mass while evaluating potential changes in cardiometabolic biomarkers, hormones, muscle performance, and energy and macronutrient intake after eight weeks of aerobic exercise and resistance training in overweight and obese adults. **Methods:** This study was a randomized, controlled trial. Sedentary overweight and obese adults (mean ± SD; age: 44.48 ± 7.28 years; BMI: 29.61 ± 2.62 kg/m^2; females: 85.71%; males: 14.29%) were randomly assigned to a TRF or normal feeding (NF) dietary strategy group. The TRF group consumed all calories between 1200 and 2000 hours, whereas the NF group ate their typical diet. All groups completed eight weeks of aerobic exercise and supervised resistance training. Body composition, muscle performance, energy and macronutrient intake, physical activity, and physiological variables were assessed week zero and week nine. **Results:** A total of 21 participants completed the study (NF: n = 10; TRF: n = 11). A mild energy restriction was seen for the TRF (~300 kcal/day, 14.0%) and NF (~250 kcal/d, 11.0%) groups between baseline and week seven. Losses of total body mass were significantly greater for TRF (3.3%) relative to NF (0.2%), of which TRF had significantly greater losses of fat mass (9.0%) compared to NF (3.3%) despite similar reductions in energy intake. Lean mass increased across the intervention for both TRF (0.6%) and NF (1.9%), with no group differences. **Conclusion:** These data support the use of TRF and concurrent exercise training as a short-term dietary strategy for reducing fat mass and preserving lean mass in overweight and obese adults.

4.2. Introduction

Intermittent fasting is a broad term that encompasses a variety of increasingly popular dietary regimens in which individuals cycle between food intake and prolonged periods of little or no energy intake (Mattson et al., 2017). There are many variants of IF, including TRF, alternate day fasting, alternate day modified fasting or the "5:2" diet, and periodic fasting (Anson et al., 2003; Harvie & Howell, 2017). The appeal of this dietary strategy is that individuals do not need to restrict energy intake every day, or at all, such as with CER, to attain weight loss and metabolic benefits (Antoni, Johnston, Steele, et al., 2017; Harvie & Howell, 2017). This is important considering CER is associated with poor compliance and appears to accelerate the return of pre-deprivation body mass levels once the restraints over feeding are removed (Anastasiou et al., 2015; Borer, 2013). More seriously, CER is known for weight loss consisting of 10% to 60% fat-free mass, which suggests a large proportion of metabolically active skeletal muscle tissue is lost instead of adipose tissue (Chaston et al., 2007). Intermittent fasting, on the other hand, has shown high levels of compliance and does not appear to lead to a compensatory over-consumption on the non-dieting days (Gabel et al., 2018; Harvie et al., 2011, 2013). In fact, recent studies in young men and women have found that TRF combined with resistance training results in the retention of lean mass, loss of fat mass, and improvement in muscle performance (Moro et al., 2016; Tinsley et al., 2017, 2019).

This is important, as obesity prevalence and incidences of physical dysfunction (i.e., sarcopenia and dynapenia) continue to rise in the U.S. population, along with obesity-related conditions (e.g., cardiovascular disease, stroke, type 2 diabetes, and certain types of cancers; Buford et al., 2010; Hales et al., 2017; National Heart Lung and Blood Institute, 2013). These conditions represent major health problems and are some of the leading causes of preventable

death in the U.S (National Heart Lung and Blood Institute, 2013). Sarcopenia, the age-related loss of muscle mass, alone negatively affects strength, balance, and stability; leading to an increased risk of falls and impaired ability to perform activities of daily living such as walking, personal care, cooking, and chores (Tinetti et al., 2006, 1988). The most alarming consequence of decreased muscle strength is its ability to predict future mortality in middle-aged and older adults (Cooper et al., 2010). Concurrent training appears to be the optimal exercise method for improving overall functional ability and physical performance when compared to aerobic or resistance training alone; making it ideal for attenuating age-related declines in muscle mass and strength and maintaining ability to perform activities of daily living (Hunter et al., 2004; Villareal et al., 2017; Willis et al., 2012).

While diet and exercise improve many health consequences of obesity and attenuate declines in muscle mass and strength, dietary strategies are not always followed nor manageable for long-term use (Beavers et al., 2015). Fortunately, the highly compliant IF regimes have shown promise to deliver benefits similar to CER in terms of weight loss and cardiometabolic health (Anton et al., 2018; Barnosky et al., 2014; Harris et al., 2018; Harvie et al., 2013; Mattson et al., 2017; Rothschild et al., 2014; Rynders et al., 2019). While TRF has become an increasingly popular IF strategy, there are still a limited number of studies observing its effects on body composition and metabolic health with and without exercise (Rynders et al., 2019). Thus, more controlled trials on TRF involving exercise are needed to validate the dietary strategy on its ability to preserve fat-free mass during weight loss and reduce disease risk in adults (Anton et al., 2018; Barnosky et al., 2014; Bhutani, Klempel, Kroeger, Trepanowski, & Varady, 2013; Moro et al., 2016; Tinsley et al., 2017, 2019).

The purpose of this study was to determine whether TRF was an effective dietary strategy for reducing fat mass and preserving fat-free mass while evaluating potential changes in cardiometabolic biomarkers, hormones, muscle performance, and energy and macronutrient intake after eight weeks of aerobic and resistance exercise training in sedentary, overweight and obese adults.

4.3. Methods

4.3.1. Overview

The study was registered at clinicaltrials.gov (NCT03823872) and was approved by the North Dakota State University Institutional Review Board (#HE18247). After providing written informed consent and a completing the PAR-Q and health history questionnaire, documents were screened by the research team to determine whether participants were healthy and capable of participating in the study (Warburton, Jamnik, Bredin, Shephard, & Gledhill, 2017). The primary outcomes for this study were fat mass, fat-free mass, and body fat percentage and functional markers to combat elevated levels of adiposity and physical dysfunction. Secondary outcome measures included metrics of muscle performance, blood and saliva markers, blood pressure, physical activity level, and nutritional intake. Data collected occurred from October 2018 to December 2019 at North Dakota State University in Fargo, North Dakota, USA.

4.3.2. Participants

Sedentary, overweight and obese female and male participants, determined by a BMI between 25.0 and 34.9 kg/m^2, between the ages of 35 and 60 years were recruited via email announcements, flyers, and word of mouth. Sedentary was defined as someone who was not currently following a structured aerobic or resistance training program or dietary plan. After providing written informed consent, participants were screened and then excluded if they were

pregnant, trying to become pregnant, currently smoking tobacco, using e-cigarettes or smokeless tobacco, had previous injuries that would prevent them from exercising, taking medications that could influence muscle size and strength (e.g., testosterone, growth hormone), had uncontrolled chronic heart related conditions, or any major signs of cardiovascular, pulmonary, metabolic disease or have two or major coronary risks factors, or other reasons needing medical clearance. Of 78 screened participants, 23 were determined eligible to participate in the study and were randomly assigned to a TRF group or a NF group. During the study, two participants dropped out due to unrelated reasons (i.e., dental complication, back injury). A total of 21 participants completed the study (Figure 1).

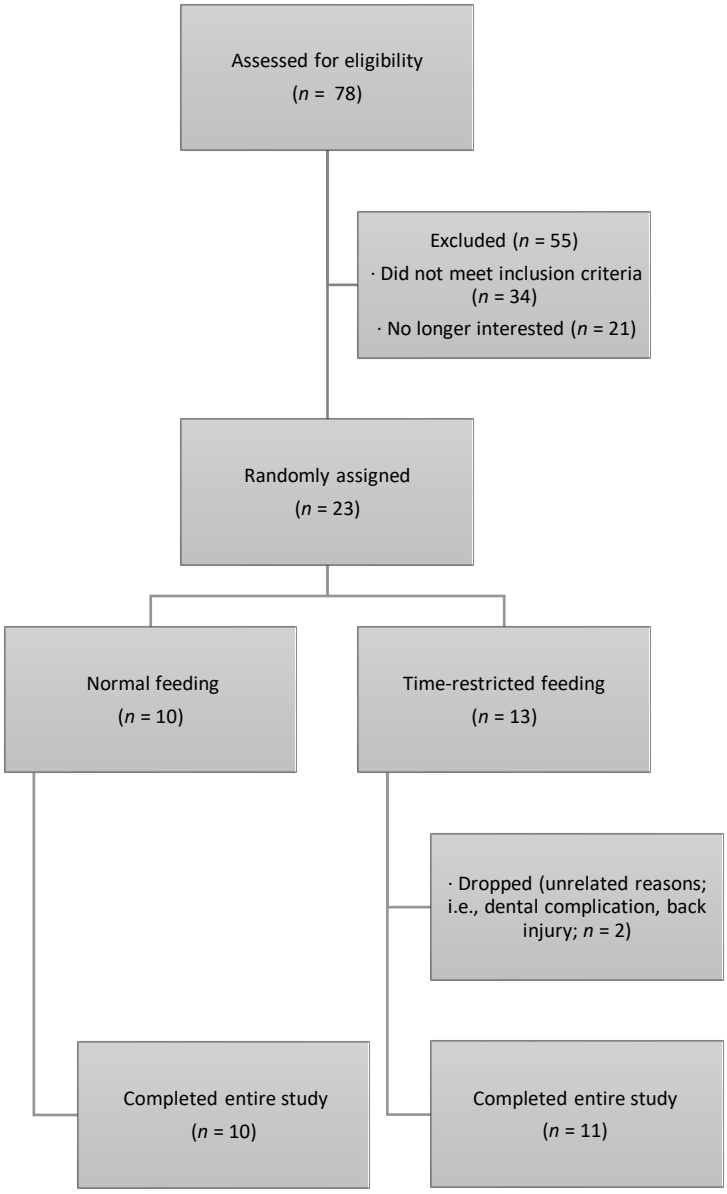

Figure 1. Subject Screening and Completion Flowchart.

4.3.3. Dietary Strategy and Nutrition Monitoring

Although supervised feeding would be a better-controlled model, detailed meal plans are not a common dietary habit in the general population and the resources required are extensive and expensive (Davy & Davy, 2019). Thus, an ad libitum approach was implemented to examine how energy and macronutrient intake are influenced when feeding patterns are not strictly controlled. The TRF participants were required to consume all their calories between 1200 and

2000 hours each day, inducing a fasting window of 16 hours, while the NF participants were required to maintain their regular dietary habits. Compliance to dietary strategy was reviewed three times a week at resistance training sessions by personal trainers. If a participant indicated energy consumption outside the feeding window, it was marked as noncompliant. Dietary intake was measured by three-day dietary records, which were analyzed using the Food Processor software (ESHA, Salem, OR, USA) by registered dietitians (Prentice et al., 2011; Thompson & Byers, 1994). All dietary instructions were led by a protocol-trained, board certified specialist in sports dietetics via a previously recorded instructional video, and intake was analyzed on two typical days and one atypical day at W0, W1, W4, and W7. Participants in TRF were discouraged from consuming any beverages other than water, black coffee, or tea during the 16-hour fasting window.

4.3.4. Resistance Training Program

Resistance training was standardized for both groups and consisted of three different workouts, performed on non-consecutive days, each week for eight weeks. The three resistance training routines were: Workout A (chest press, shoulder press, triceps pulldown), workout B (leg press, leg flexion, leg extension), workout C (wide grip latissimus dorsi pulldown, back machine pulley row, bicep curl). The training protocol involved three sets of 12 repetitions with no more than 60 seconds of rest between exercises and sets (Baechle et al., 2008). Load was assigned based on a percentage of the participants body mass and was adjusted through trial loads during W1 of training, until the goal number of repetitions was achieved (Baechle et al., 2008).

For the first exercise of each workout, subjects followed a lift specific warm-up by performing eight repetitions at 40% of their estimated 12RM, followed by a one-minute rest, and

then a second warm-up set of six repetitions at 60% of their estimated 12RM, followed by a two-minute rest (Miller, 2012). Participants began W2 of training attempting to complete three sets of 12 repetitions with their adjusted loads. During subsequent training sessions each week, subjects attempted to complete one additional repetition for each set. Once subjects performed three sets of 15 repetitions, on two consecutive training sessions, intensity was increased by adding weight in 2.27- to 9.09-kilogram increments. After adding additional weight, subjects went back to performing three sets of 12 repetitions. The increase in weight ensured subjects maintained appropriate training progression to elicit the desired training response.

Resistance training sessions were performed during the eight-hour feeding window, at the participants convenience to match work schedules. All subjects in the TRF group trained between 1300 and 1900 hours to ensure adequate time for energy intake before and after resistance training. Certified personal trainers supervised all routines to ensure proper form and safety. Subjects were discouraged from performing any other resistance training exercises outside of their weekly sessions.

4.3.5. Aerobic Training Program and Physical Activity Monitoring

The American College of Sports Medicine (2009) has defined 50 to 60 minutes per day to total 300 minutes of moderate, or 150 minutes vigorous, physical activity necessary to promote or maintain weight loss. The current study was designed to help and encourage participants achieve this goal each week. Heart rate maximum was calculated using the Tanaka method (Tanaka et al., 2001) and HRR was used to prescribe aerobic training intensities. The training protocol began at a moderate-to-vigorous (≥55% HRR) intensity and was performed on a treadmill or related aerobic conditioning equipment (American College of Sports Medicine, 2017). After completion, subjects were instructed to perform a five-minute cooldown at a low

(<40% HRR) to moderate (40% to 55% HRR) intensity (American College of Sports Medicine, 2017). Participants were instructed to perform a minimum of 75 minutes of moderate-to-vigorous aerobic activity at W1, which increased 75 minutes each subsequent week until W5. At W5 and W7 training intensity was increased (5% to 10%), depending upon participants conditioning, to maintain exercise progression.

To ensure subjects were meeting the 300-minute physical activity goal, an ActiGraph GT3X+ accelerometer (ActiGraph, Pensacola, FL) was worn at W2, W5, and W8 to precisely quantify the intensity of their activities. The accelerometer was worn on the right hip, in line with the right knee, via an elastic band. The accelerometer was worn during waking hours except for water-based activities. A sleep log was provided to subjects to record the time they removed the accelerometer for sleep and the time they put the device on the following day upon waking.

The GT3X+ accelerometers were processed with epoch durations of 60 seconds. Participants were required to have worn the accelerometer for at least four days, including one weekend day, over a seven day collection period, with a minimum of 10 hours of wear time each day (Aadland & Ylvisåker, 2015; Matthews et al., 2002, 2012). To classify physical activity, Sasaki, John, and Freedson (2011) cut-points for moderate, vigorous, and very vigorous physical activity were used, along with Kozey-Keadle, Libertine, Lyden, Staudenmayer, and Freedson (2011) cut-points for assessing sedentary behavior. The L. Choi et al. (2011) algorithm was used for wear and non-wear time validation.

4.3.6. Overview of Lab Assessments

The primary assessments for this study were associated with body composition and functional markers to combat elevated levels of adiposity and physical dysfunction. These assessments were conducted by trained research assistants during two separate sessions at both

W0 and W9. Session one was conducted in the morning after a 12-hour overnight fast to assess anthropometrics, resting blood pressure and resting heart rate, metabolic and physiological variables, and body composition. Session two was conducted in the afternoon in a nonfasted state to assess muscle performance and submaximal cardiorespiratory fitness. After pre-training assessments, participants were randomly assigned to a TRF group or a NF group.

4.3.7. Anthropometric and Hemodynamic Assessments

Resting blood pressure and heart rate were collected after five minutes of sitting. Blood pressure was measured with a Diagnostix 703 sphygmomanometer (American Diagnostic Corporation, Hauppauge, NY, USA). Heart rate was counted for one minute at the radial artery by manual palpation. After resting measures, height was measured using a stadiometer (Seca 213, Chino, CA, USA) and body mass was recorded on an industrial scale (Denver Instrument DA-150, Arvada, CO, USA) with shoes removed. A Baseline measurement tape with Gulick attachment (Fabrication Enterprises, White Plains, NY, USA) was used to measure hip and waist circumference at the widest portion of the hips and at two finger widths above the umbilicus, respectfully.

4.3.8. Metabolic and Physiological Assessments

Blood and saliva were collected between 0600 and 0900 hours and was emphasized to be within one hour of waking. Collection procedures for each test where conducted as outlined by ZRT Laboratory (Beaverton, OR, USA), a CLIA certified diagnostic laboratory. Once blood was dry and immediately after saliva was collected, samples were frozen at -80°C until ready to be shipped. Results of the laboratory analyses were provided to the study investigators.

Participant whole blood was collected by placing capillary collected blood drops on a blood spot filter card following a finger prick with a safety lancet. The blood spot testing was

used to analyze potential changes of several health-related biomarkers (insulin, hsCRP, hemoglobin A1c, triglycerides, total cholesterol, HDL, LDL, VLDL). Dried blood spot testing has shown strong correlation with conventional serum tests, making it a reliable and convenient tool for screening cardiometabolic risk factors (Kapur, Kapur, & Zava, 2008).

Participant saliva was collected into a single plastic tube via passive drool. The saliva was used to analyze potential changes in hormones (estradiol, progesterone, testosterone, DHEAS, cortisol). Oral hormone users were told to make sure any night dosage was applied at least 12 hours before planned morning collection. While saliva has not yet become a mainstream sample source for hormone analysis, it has been proven to be reliable and in some cases superior to other body fluids for hormone analysis (Gröschl, 2008).

4.3.9. Body Composition Assessment

Measurements of body composition were taken via DXA. Scans were performed on a Lunar Prodigy, model #8915 (GE Healthcare, Waukesha, WI, USA), with enCORE software. Quality assurance was established each morning prior to a scan using a quality control block. Participants were positioned according to manufacturer's recommendations. Female participants were screened for pregnancy with a urinary human chorionic gonadotropin test (ClinicalGuard, Atlanta, GA, USA) to confirm that each participant was not pregnant before scanning.

4.3.10. Muscle and Aerobic Performance Assessments

All subjects completed a low to moderate warmup on a stationary bike for five minutes before testing. Hand grip strength was measured in kilograms using a Jamar Hydraulic Hand Dynamometer (Sammons Preston Rolyan, Bolingbrook, IL, USA). Participants were asked to stand with their dominant arm bent at 90 degrees. After a three second countdown, participants squeezed the dynamometer as hard as possible, with encouragement, for an additional three

seconds, followed by one-minute of rest. The test was repeated two more times and the greatest of three attempts was recorded.

To observe potential changes in cardiorespiratory fitness due to aerobic conditioning throughout the study, a three-minute step test was conducted according to the protocol designed by the YMCA (American College of Sports Medicine, 2017).

A Biodex Pro4 system dynamometer (Biodex Medical Systems, Shirley, NY, USA) was used to measure lower body muscle strength and endurance of the right leg (Ploutz-Snyder et al., 2002). Isokinetic maximal strength was assessed at 60 degrees per second for the knee extension-flexion and 30 degrees per second for plantar-dorsiflexion. Isokinetic endurance was measured using a 21 repetitions test at 180 degrees per second for the knee extension-flexion and 60 degrees per second for plantar-dorsiflexion.

4.3.11. Statistical Analysis

Anthropometric measures were described using means and standard deviation or errors. For dependent variables (body composition, cardiometabolic biomarkers, hormones, muscle performance, cardiovascular performance, dietary factors, physical activity), separate 2 (Dietary Plan: TRF and NF) x 2 (Time: Pre- and post-training) ANOVAs with repeated measures were used. An alpha level of 0.05 was used to determine statistical significance. If a significant interaction was found, independent and paired t-tests with Bonferroni corrections were run to compare post-training adaptations. If independent t-tests failed to show the significant interaction effect, delta differences for the variables were calculated, and independent t-tests were used to remove between subject variability. Cohen's d effect sizes were calculated for each group by dividing the difference between W0 and W9 by the pooled standard deviation. All statistical analyses were conducted using SPSS 26 software (IBM Corp., Armonk, NY, USA).

4.4. Results

4.4.1. Participants

A total of 21 participants (NF: n = 10; TRF: n = 11) completed the study. The NF group was composed of nine female participants and one male participant, while the TRF group contained nine female participants and two male participants. No baseline differences were present between the two groups (Table 5).

Table 5

Participant Characteristics at Baseline

	NF (n = 10)	**TRF (n = 11)**	***P* (group)**
Age (years)	43.90 ± 1.93	45.00 ± 2.55	0.739
Body Mass (kg)	82.93 ± 3.25	82.00 ± 2.58	0.823
Height (cm)	167.78 ± 3.44	165.71 ± 1.98	0.599
BMI (kg/m^2)	29.41 ± 0.81	29.80 ± 0.84	0.742
Hip Circumference (cm)	108.36 ± 2.94	109.17 ± 1.60	0.806
Waist Circumference (cm)	95.32 ± 2.99	98.03 ± 1.89	0.445

Note. Data are presented as mean ± SE. *P* values are from one-way ANOVA. Body Mass Index (BMI), Normal Feeding (NF), Time-Restricted Feeding (TRF).

A time x group effect $F(1,19) = 6.524$, $p = 0.019$ was observed for BMI. Post-hoc tests for BMI showed a significant decrease W0 to W9 for TRF $t(10) = 3.512$, $p = 0.006$. Group differences in BMI from W0 to W9 were calculated, and an independent t-test showed a significant $t(19) = -2.554$, $p = 0.019$ decrease in TRF (mean ± SE; -0.99 ± 0.28) relative to NF (mean ± SE; -0.11 ± 0.19). A time x group effect $F(1,19) = 5.914$, $p = 0.025$ was observed for body mass. Post-hoc tests for body mass showed a significant decrease W0 to W9 for TRF $t(10) = 3.789$, $p = 0.004$. Group differences in body mass from W0 to W9 were calculated, and an independent t-test showed a significant $t(19) = -2.432$, $p = 0.014$ decrease in TRF (mean ± SE; -2.51 ± 0.66) relative to NF (mean ± SE; -0.43. ± 0.52). Of anthropometric data, a time effect $F(1,19) = 6.703$, $p = 0.018$ was observed for waist circumference. Anthropometric data are found in Table 6.

4.4.2. Physical Activity Monitoring

There was a significant time effect $F(2,38) = 10.202$, $p < 0.001$ observed for step count across the intervention. There was also a significant time effect $F(2,38) = 4.379$, $p = 0.019$ observed for moderate-to-vigorous physical activity. Average time spent in moderate-to-vigorous physical activity across the intervention was above 300 minutes for both groups, indicating an achievement of weekly physical activity goals (Figure 2). Physical activity data are found in Table 7.

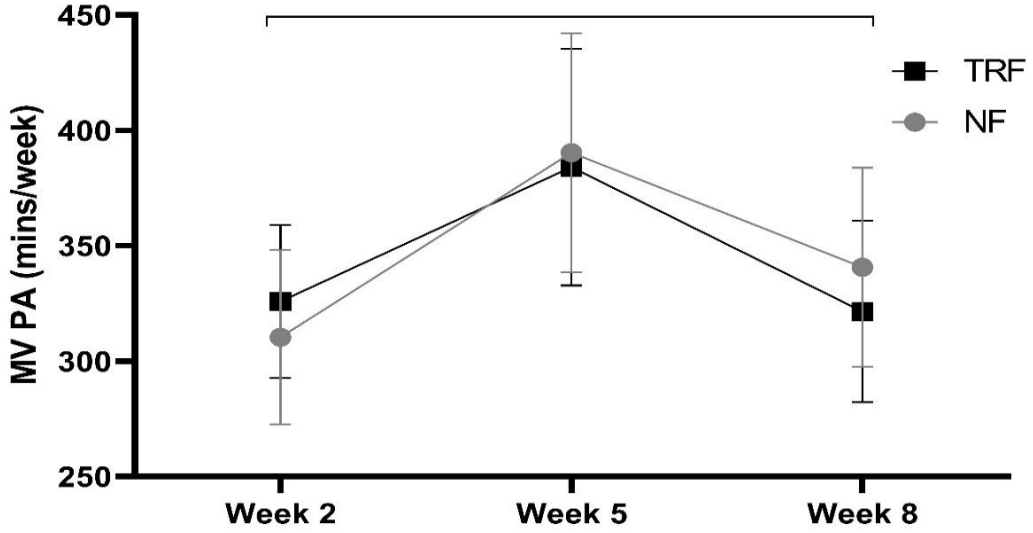

Figure 2. Average Time Spent in Moderate-to-Vigorous Physical Activity. Results display (TRF: n = 11; NF: n = 10) average minutes (mean ± SE) at W2, W5, and W8. Brackets indicate a significant change within groups (i.e., time main effects), with no significant differences between groups. Moderate-to-Vigorous (MV); Physical Activity (PA); Time-Restricted Feeding (TRF); Normal Feeding (NF).

4.4.3. Dietary Intake

A significant time effect $F(3,57) = 5.146$, $p = 0.003$ was observed for energy intake across W0, W1, W4, and W7. Significant time effects $F(3,57) = 6.854$, $p = 0.001$ and $F(3,57) = 6.723$, $p = 0.001$ were observed for carbohydrate intake in both g/day and g/kg/day, respectfully, across the same period. Dietary data are found in Table 8.

4.4.4. Body Composition

A time x group effect $F(1,19) = 5.824$, $p = 0.026$ was observed for tissue (fat %). Post-hoc tests for tissue (fat %) showed a significant decrease W0 to W9 for NF $t(9) = 3.902$, $p = 0.004$ and TRF $t(10) = 6.430$, $p < 0.001$. Group differences in tissue (fat %) from W0 to W9 were calculated, and an independent t-test showed a significant $t(19) = -2.413$, $p = 0.026$ decrease in TRF (mean ± SE; -2.49 ± 0.39) relative to NF (mean ± SE; -1.26 ± 0.32).

A time x group effect $F(1,19) = 5.803$, $p = 0.026$ was observed for region (fat %). Post-hoc tests for region (fat %) showed a significant decrease W0 to W9 for NF $t(9) = 3.929$, $p = 0.003$ and TRF $t(10) = 6.301$, $p < 0.001$. Group differences in region (fat %) from W0 to W9 were calculated, and an independent t-test showed a significant $t(19) = -2.409$, $p = 0.026$ decrease in TRF (mean ± SE; -2.43 ± 0.39) relative to NF (mean ± SE; -1.22 ± 0.31).

A time x group effect $F(1,19) = 5.602$, $p = 0.029$ was observed for region (lean %). Post-hoc tests for region (lean %) showed a significant decrease W0 to W9 for NF $t(9) = -3.852$, $p = 0.004$ and TRF $t(10) = -6.442$, $p < 0.001$. Group differences in region (lean %) from W0 to W9 were calculated, and an independent t-test showed a significant $t(19) = 2.367$, $p = 0.029$ increase in TRF (mean ± SE; 2.36 ± 0.37) relative to NF (mean ± SE; 1.21 ± 0.31).

A time x group effect $F(1,19) = 13.378$, $p = 0.002$ was observed for fat mass (kg). Post-hoc tests for fat mass (kg) showed a significant decrease W0 to W9 for NF $t(9) = 3.215$, $p = 0.011$ and TRF $t(10) = 7.758$, $p < 0.001$. Group differences in fat mass (kg) from W0 to W9 were calculated, and an independent t-test showed a significant $t(19) = -3.661$, $p = 0.002$ decrease in TRF (mean ± SE; -2.95 ± 0.38) relative to NF (mean ± SE; -1.08 ± 0.34).

A time x group effect $F(1,19) = 9.511$ $p = 0.006$ was observed for tissue mass (kg). Post-hoc tests for tissue mass (kg) showed a significant decrease W0 to W9 for TRF $t(10) = 4.242$, $p =$

0.002. Group differences in tissue mass (kg) from W0 to W9 were calculated, and an independent t-test showed a significant $t(19) = -3.083$, $p = 0.006$ decrease in TRF (mean ± SE; -2.64 ± 0.62) relative to NF (mean ± SE; -0.16 ± 0.49).

A time x group effect $F(1,19) = 9.668$ $p = 0.006$ was observed for total body mass (kg). Post-hoc tests for total mass (kg) showed a significant decrease W0 to W9 for TRF $t(10) = 4.284$, $p = 0.002$. Group differences in total mass (kg) from W0 to W9 were calculated, and an independent t-test showed a significant $t(19) = -3.112$, $p = 0.006$ decrease in TRF (mean ± SE; -2.66 ± 0.62) relative to NF (mean ± SE; -0.18 ± 0.48).

A significant time effect $F(1,19) = 4.578$, $p = 0.046$ was observed for lean mass (kg) W0 to W9. A significant time effect $F(1,19) = 14.973$, $p = 0.001$ was also observed for visceral fat mass (kg). Interestingly, TRF visceral fat mass (0.25) decreased almost twice as much relative to NF (0.14) from W0 to W9. Body composition changes are found in Figure 3. Body composition data are found in Table 9.

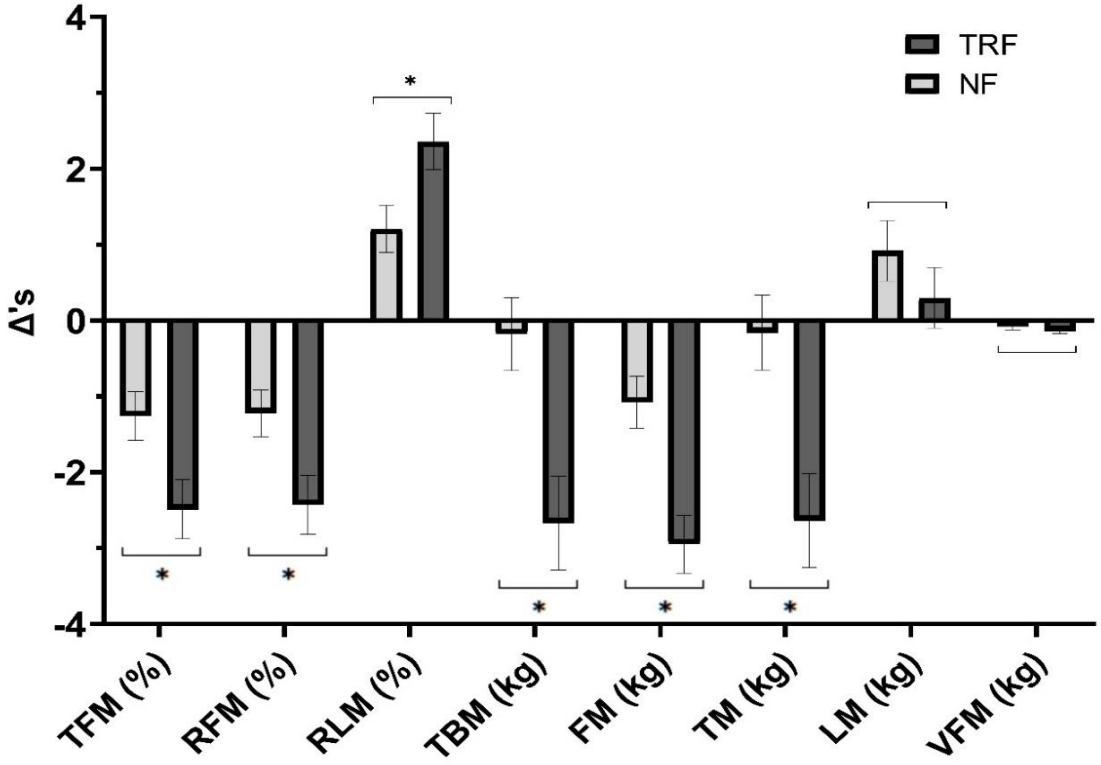

Figure 3. Body Composition Changes. Results display (TRF: n = 11; NF: n = 10) delta differences (mean ± SE) between W0 and W9. Asterisk with brackets indicate a significant difference in TRF relative to NF (i.e., interaction effect). Brackets indicate a significant change within groups (i.e., time main effects), with no significant differences between groups. Tissue Fat Mass (TFM); Region Fat Mass (RFM); Region Lean Mass (RLM); Total Body Mass (TBM); Fat Mass (FM); Tissue Mass (TM); Lean Mass (LM); Visceral Fat Mass (VM); Time-Restricted Feeding (TRF); Normal Feeding (NF).

4.4.5. Muscle Performance

A significant time effect was observed for knee flexor strength peak torque $F(1,19) = 21.949$, $p < 0.001$. A significant time effect was also observed for knee flexor endurance total work $F(1,19) = 10.137$, $p = 0.005$. Significant time effects $F(1,19) = 4.724$, $p = 0.043$ and $F(1,19) = 13.153$, $p = 0.002$ were observed for dorsiflexion strength peak torque and endurance total work, respectfully. Interestingly, a significant time x group effect $F(1,19) = 7.241$, $p = 0.014$ was observed for knee extensor strength peak torque. However, post-hoc tests for knee extensor strength peak torque revealed no significant changes for the TRF or NF group. Group

differences in knee extensor strength peak torque from W0 to W9 were calculated, and an independent t-test showed a significant $t(19) = -2.691$, $p = 0.014$ increase in NF (mean ± SE; 18.54 ± 8.59) relative to TRF (mean ± SE; -6.65 ± 4.34). Muscle performance data are found in Table 10.

4.4.6. Cardiorespiratory Performance and Hemodynamics

A significant time effect $F(1,19) = 73.307$, $p < 0.001$ was observed for resting heart rate. A significant time effect $F(1,19) = 26.555$, $p < 0.001$ was observed for step heart rate (i.e., heart rate one-minute after step test completion). Interestingly, TRF step heart rate (22.72) decreased almost twice as much as relative to NF (13.50) from W0 to W9. Cardiorespiratory performance and hemodynamics are found in Table 11.

4.4.7. Metabolic and Physiological Variables

No significant time effects were observed in blood or saliva markers. It is important to note that triglycerides, LDL, and VLDL were excluded from analysis due to an unknown contaminate on the blood spot cards from the manufacturer that interfered with the enzymes used to detect triglycerides, causing the triglyceride values to be two to three times higher than normal. Both LDL and VLDL were impacted as triglyceride values were required for these calculations. Resting cardiometabolic and hormonal data are found in Table 12.

Table 6

Anthropometrics

	Group	W0	W9	Δ	ES (d)	*P* (group)	*P* (time)	*P* (I)
Body Mass (kg)	NF	82.93 ± 3.25	82.50 ± 3.49	-0.43	-0.04	0.641	**0.003**	**0.025**
	TRF	82.00 ± 2.58	79.49 ± 2.54	-2.51	-0.30			
BMI (kg/m^2)	NF	29.41 ± 0.81	29.30 ± 0.88	-0.11	-0.04	0.966	**0.005**	**0.019**
	TRF	29.80 ± 0.84	28.81 ± 0.83	-0.99	-0.36			
Hip Circumference (cm)	NF	108.36 ± 2.94	108.94 ± 2.65	0.58	0.07	0.886	0.328	0.079
	TRF	109.17 ± 1.60	107.22 ± 1.74	-1.95	-0.35			
Waist Circumference (cm)	NF	95.32 ± 2.99	92.31 ± 3.03	-3.01	-0.32	0.626	**0.018**	0.493
	TRF	98.03 ± 1.89	92.79 ± 2.20	-5.24	-0.77			

Note. Data are presented as mean ± SE. *P* values are from repeated-measures ANOVA. Body Mass Index (BMI), Effect Size (ES), Interaction (I), Normal Feeding (NF), Time-Restricted Feeding (TRF).

Table 7

Physical Activity

	Group	W2	W5	W8	*P* (group)	*P* (time)	*P* (I)
Sedentary Time (min/d)	NF	2984.90 ± 183.84	2992.20 ± 191.57	2767.10 ± 294.79	0.648	0.464	0.252
	TRF	2905.36 ± 232.89	2653.45 ± 164.29	2839.18 ± 112.75			
Light PA (min/day)	NF	2429.20 ± 197.79	2559.30 ± 200.11	2295.50 ± 264.43	0.455	0.439	0.251
	TRF	2314.55 ± 101.20	2199.82 ± 157.44	2245.91 ± 115.95			
MV PA (min/day)	NF	310.40 ± 37.90	390.30 ± 51.69	340.70 ± 43.15	0.952	**0.019**	0.782
	TRF	325.82 ± 33.19	384.09 ± 51.30	321.55 ± 39.32			
Steps (#/day)	NF	7540.90 ± 782.06	8781.34 ± 842.02	8038.80 ± 685.90	0.686	< **0.001**	0.299
	TRF	8116.20 ± 828.09	9772.56 ± 1185.84	7929.34 ± 835.08			

Note. Data are presented as mean ± SE. *P* values are from repeated-measures ANOVA. Interaction (I), Physical Activity (PA), Moderate-to-Vigorous (MV), Normal Feeding (NF), Time-Restricted Feeding (TRF).

Table 8

Dietary Intake

	Group	W0	W1	W4	W7	Δ	*P* (group)	*P* (time)	*P* (I)
Energy (kcal)	NF	2227 ± 177	1985 ± 158	1921 ± 158	1974 ± 245	-253	0.467	**0.003**	0.510
	TRF	2112 ± 179	1640 ± 159	1856 ± 208	1806 ± 180	-306			
Protein									
(g)	NF	76 ± 8	71 ± 6	76 ± 9	70 ± 10	-6	0.899	0.088	0.611
	TRF	83 ± 9	68 ± 6	73 ± 8	73 ± 7	-10			
(%)	NF	14 ± 1	14 ± 1	16 ± 1	14 ± 1	0	0.106	0.208	0.347
	TRF	16 ± 1	17 ± 1	16 ± 1	16 ± 1	0			
(g/kg)	NF	0.9 ± 0.1	0.8 ± 0.1	0.9 ± 0.1	0.8 ± 0.1	-0.1	0.624	0.111	0.532
	TRF	1.0 ± 0.1	0.8 ± 0.1	0.9 ± 0.1	0.9 ± 0.1	-0.1			
Carbohydrate									
(g)	NF	266 ± 18	241 ± 19	236 ± 19	235 ± 26	-31	0.209	**0.001**	0.240
	TRF	255 ± 29	177 ± 24	202 ± 22	190 ± 28	-65			
(%)	NF	49 ± 4	50 ± 3	50 ± 3	49 ± 3	0	0.107	0.336	0.316
	TRF	48 ± 3	43 ± 3	44 ± 3	41 ± 2	-7			
(g/kg)	NF	3.2 ± 0.2	2.9 ± 0.2	2.9 ± 0.2	2.8 ± 0.2	-0.4	0.230	**0.001**	0.215
	TRF	3.1 ± 0.3	2.2 ± 0.3	2.5 ± 0.3	2.4 ± 0.3	-0.7			
Fat									
(g)	NF	83 ± 10	76 ± 9	71 ± 8	77 ± 11	-6	0.961	0.407	0.602
	TRF	82 ± 9	68 ± 7	79 ± 13	81 ± 8	-1			
(%)	NF	33 ± 3	34 ± 2	33 ± 2	34 ± 2	1	0.056	0.299	0.785
	TRF	35 ± 2	37 ± 2	37 ± 2	41 ± 1	6			
(g/kg)	NF	1.00 ± 0.12	0.91 ± 0.10	0.84 ± 0.07	0.91 ± 0.10	-0.1	0.719	0.316	0.493
	TRF	1.0 ± 0.1	0.8 ± 0.1	1.0 ± 0.2	1.0 ± 0.1	0.0			

Note. Data are presented as mean ± SE. *P* values are from repeated-measures ANOVA. Interaction (I), Normal Feeding (NF), Time-Restricted Feeding (TRF). Percentage of energy intake (%).

Table 9

Body Composition

	Group	W0	W9	Δ	ES (d)	*P* (group)	*P* (time)	*P* (I)
Tissue (Fat %)	NF	40.81 ± 1.94	39.55 ± 2.04	-1.26	-0.20	0.902	< **0.001**	**0.026**
	TRF	41.10 ± 1.64	38.61 ± 1.83	-2.49	-0.43			
Region (Fat %)	NF	39.56 ± 1.93	38.34 ± 2.02	-1.22	-0.20	0.887	< **0.001**	**0.026**
	TRF	39.79 ± 1.62	37.36 ± 1.81	-2.43	-0.43			
Region (Lean %)	NF	57.33 ± 1.81	58.53 ± 1.91	1.20	0.20	0.917	< **0.001**	**0.029**
	TRF	57.01 ± 1.53	59.36 ± 1.71	2.35	0.44			
Tissue Mass (kg)	NF	80.09 ± 3.23	79.92 ± 3.41	-0.17	-0.02	0.612	**0.002**	**0.006**
	TRF	79.21 ± 2.46	76.58 ± 2.53	-2.63	-0.32			
Fat Mass (kg)	NF	32.81 ± 2.40	31.73 ± 2.46	-1.08	-0.14	0.746	< **0.001**	**0.002**
	TRF	32.71 ± 1.98	29.76 ± 2.07	-2.95	-0.44			
Lean Mass (kg)	NF	47.28 ± 2.26	48.19 ± 2.49	0.91	0.12	0.707	**0.046**	0.292
	TRF	46.52 ± 1.58	46.82 ± 1.63	0.30	0.06			
Total Body Mass (kg)	NF	82.67 ± 3.31	82.49 ± 3.48	-0.18	-0.02	0.624	**0.002**	**0.006**
	TRF	81.83 ± 2.53	79.16 ± 2.58	-2.67	-0.32			
Visceral Fat Mass (kg)	NF	1.07 ± 0.17	1.00 ± 0.15	-0.07	-0.14	0.700	**0.001**	0.261
	TRF	1.01 ± 0.18	0.87 ± 0.16	-0.14	-0.25			
BMC (kg)	NF	2.58 ± 0.13	2.57 ± 0.12	-0.01	-0.03	0.915	0.119	0.221
	TRF	2.60 ± 0.11	2.58 ± 0.11	-0.02	-0.05			
BMD (g/cm^2)	NF	1.23 ± 0.04	1.24 ± 0.04	0.01	0.09	0.751	0.387	0.161
	TRF	1.26 ± 0.04	1.25 ± 0.04	-0.01	-0.10			

Note. Data are presented as mean ± SE. *P* values are from repeated-measures ANOVA. Bone Mineral Content (BMC), Bone Mineral Density (BMD), Effect Size (ES), Interaction (I), Normal Feeding (NF), Time-Restricted Feeding (TRF).

Table 10

Muscle Performance

	Group	W0	W9	Δ	ES (d)	*P* (group)	*P* (time)	*P* (I)
Hand Grip (kg)	NF	42.90 ± 3.70	44.30 ± 3.68	1.40	0.12	0.601	0.573	0.341
	TRF	41.36 ± 2.81	41.00 ± 2.95	-0.36	-0.04			
KE STR PT (Nm)	NF	137.74 ± 7.36	156.28 ± 6.81	18.54	0.83	0.523	0.220	**0.014**
	TRF	140.13 ± 15.12	133.47 ± 13.18	-6.66	-0.14			
KF STR PT (Nm)	NF	81.86 ± 6.08	100.36 ± 5.47	18.50	1.01	0.677	< **0.001**	0.636
	TRF	79.92 ± 7.70	94.89 ± 7.20	14.97	0.61			
KE END TW (J)	NF	1456.39 ± 121.37	1467.26 ± 152.35	10.87	0.02	0.265	0.383	0.301
	TRF	1313.84 ± 144.05	1189.72 ± 126.13	-124.12	-0.28			
KF END TW (J)	NF	1108.58 ± 127.64	1306.51 ± 97.90	197.93	0.55	0.993	**0.005**	0.773
	TRF	1087.26 ± 119.88	1325.25 ± 78.82	237.99	0.71			
PF STR PT (Nm)	NF	85.76 ± 6.21	82.83 ± 5.03	-2.93	-0.16	0.109	0.952	0.379
	TRF	67.52 ± 6.30	70.87 ± 8.72	3.35	0.13			
DF STR PT (Nm)	NF	19.60 ± 2.75	25.28 ± 2.17	5.68	0.72	0.740	**0.043**	0.870
	TRF	20.88 ± 2.87	25.75 ± 2.16	4.87	0.58			
PF END TW (J)	NF	759.52 ± 79.67	698.26 ± 81.53	-61.26	-0.24	0.231	0.082	0.802
	TRF	627.55 ± 84.04	546.53 ± 93.91	-81.02	-0.27			
DF END TW (J)	NF	110.19 ± 33.98	231.15 ± 30.35	120.96	1.19	0.730	**0.002**	0.159
	TRF	160.75 ± 45.45	212.05 ± 29.88	51.30	0.40			

Note. Data are presented as mean ± SE. *P* values are from repeated-measures ANOVA. Effect Size (ES), Interaction (I), Knee Extensor (KE), Strength (STR), Peak Torque (PT), Endurance (END), Total Work (TW), Plantar Flexion (PF), Dorsiflexion (DF), Normal Feeding (NF), Time-Restricted Feeding (TRF).

Table 11

Cardiorespiratory Performance and Hemodynamics

	Group	W2	W9	Δ	ES (d)	*P* (group)	*P* (time)	*P* (I)
Systolic BP	NF	119.80 ± 2.34	118.20 ± 2.79	-1.60	-0.20	0.921	0.150	0.388
	TRF	121.82 ± 2.58	115.64 ± 2.81	-6.18	-0.69			
Diastolic BP	NF	83.00 ± 1.24	78.60 ± 1.89	-4.40	-0.87	0.820	0.107	0.168
	TRF	80.55 ± 1.60	80.18 ± 1.82	-0.37	-0.07			
Resting HR	NF	74.60 ± 2.40	68.90 ± 2.58	-5.70	-0.72	0.654	< **0.001**	0.064
	TRF	74.82 ± 1.74	65.73 ± 2.24	-9.09	-1.21			
Step HR	NF	125.10 ± 6.43	111.60 ± 7.14	-13.50	-0.63	0.346	< **0.001**	0.205
	TRF	122.27 ± 4.53	99.55 ± 5.79	-22.72	-1.32			

Note. Data are presented as mean ± SE. *P* values are from repeated-measures ANOVA. Blood Pressure (BP), Effect Size (ES), Interaction (I), Heart Rate (HR), Normal Feeding (NF), Time-Restricted Feeding (TRF).

Table 12

Resting Cardiometabolic and Hormonal Profiles

	Group	W0	W9	Δ	ES (d)	*P* (group)	*P* (time)	*P* (I)
Insulin (µIU/mL)	NF	13.09 ± 2.17	10.48 ± 0.73	-2.61	-0.51	0.361	0.092	0.934
	TRF	11.28 ± 1.41	8.91 ±1.79	-2.37	-0.44			
hsCRP (mg/L)	NF	1.01 ± 0.30	1.28 ± 0.29	0.27	0.29	0.114	0.694	0.197
	TRF	2.91 ±0.93	2.41 ± 0.81	-0.50	-0.17			
HbA1c (%)	NF	4.70 ± 0.17	4.32 ± 0.17	-0.38	-0.70	0.816	0.055	0.142
	TRF	4.60 ± 0.20	4.55 ± 0.25	-0.05	-0.07			
Cholesterol (mg/dL)	NF	200.40 ± 12.20	199.20 ± 12.02	-1.20	-0.01	0.800	0.804	0.655
	TRF	201.64 ± 12.13	205.82 ± 9.89	4.18	0.11			
HDL (mg/dL)	NF	54.60 ± 6.45	54.60 ± 4.22	0.00	0.00	0.966	0.589	0.859
	TRF	54.82 ± 3.01	53.91 ± 2.87	-0.91	0.43			
Estradiol (pg/mL)	NF	0.81 ± 0.20	0.92 ± 0.17	0.11	0.19	0.683	0.264	0.801
	TRF	0.71 ± 0.10	0.88 ± 0.11	0.17	0.48			
Progesterone (pg/mL)	NF	24.20 ± 10.42	17.00 ± 5.69	-7.20	-0.27	0.646	0.759	0.678
	TRF	24.27 ± 9.74	25.36 ± 10.59	1.09	0.03			
Testosterone (pg/mL)	NF	30.80 ± 8.60	26.10 ± 7.19	-4.70	-0.19	0.625	0.128	0.334
	TRF	34.09 ± 7.03	33.00 ± 6.63	-1.09	-0.05			
DHEAS (ng/mL)	NF	4.48 ± 1.10	4.07 ± 0.68	-0.41	-0.14	0.286	0.541	0.105
	TRF	5.37 ± 0.93	6.25 ± 1.26	0.88	0.24			
Cortisol (ng/mL)	NF	5.67 ± 0.79	5.18 ± 0.47	-0.49	-0.20	0.785	0.956	0.374
	TRF	4.93 ± 0.88	5.48 ± 0.53	0.55	0.23			

Note. Data are presented as mean ± SE. *P* values are from repeated-measures ANOVA. Effect Size (ES), Interaction (I), High-Sensitivity C-Reactive Protein (hsCRP), Hemoglobin A1c (HbA1c), High-Density Lipoprotein Cholesterol (HDL), Dehydroepiandrosterone Sulfate (DHEAS), Normal Feeding (NF), Time-Restricted Feeding (TRF).

4.5. Discussion

The purpose of our investigation was to examine the effects of ad libitum TRF and concurrent exercise training on body composition, cardiometabolic biomarkers, hormones, muscle performance, and energy and macronutrient intake. The primary findings of this study were that eight weeks of TRF (i.e., consuming all energy intake between 1200 and 2000 hours daily) and concurrent exercise training reduced total body mass, BMI, and fat mass more significantly than NF and the same concurrent exercise training in sedentary, overweight and obese adults. Secondary findings were that concurrent exercise training significantly increased lean mass and muscle performance for TRF and NF, while demonstrating a significant improvement in knee extensor strength peak torque for NF relative to TRF.

Our findings showed a mild, yet significant energy restriction for both the TRF, ~300 kcal/day (14%), and NF, ~250 kcal/d (11%), groups between baseline and W7. Despite these similar reductions in energy intake, our study demonstrated a 3.3% loss of total body mass for TRF relative to a 0.2% loss in NF. These reductions in total body mass are similar to previous studies on TRF in middle-aged and younger individuals (Anton et al., 2019, 2018; Gabel et al., 2018). Interestingly, losses of fat mass for TRF (9.0%) were nearly three times greater than the NF group (3.3%); suggesting that TRF may have a greater impact on the loss of fat mass than mild energy restriction alone, considering that energy and macronutrient intake were not significantly different between the two groups. Studies have indicated that weight loss associated with TRF was resultant of subsequent reductions in energy intake (Gabel et al., 2018; Gill & Panda, 2015). Considering our results display this energy restriction in both groups, it is likely that this unintentional reduction was induced by the concurrent exercise training or awareness of recording their food intake.

It has been suggested that chronic exercise balances hunger responses with improved satiety following meal consumption, altering the sensitivity of the appetite control system (King et al., 2009). Studies have supported this, demonstrating reductions in appetite and ad libitum energy intake when a meal with high-energy density was consumed in individuals participating in structured exercise (Caudwell et al., 2013; Martins, Kulseng, Rehfeld, King, & Blundell, 2013; Martins, Truby, & Morgan, 2007). However, findings on appetite suppression and reduced energy intake following chronic exercise are limited and mixed, making it challenging to identify exact reasons for reductions in energy intake (Dorling et al., 2018). We speculate that the variation between balancing meal timing while adapting to a new exercise program is the most likely contributor to the mild energy restriction seen in this study.

The preservation of lean mass while following IF has produced mixed results, as regimes tend to incorporate or induce deficits in energy intake (Catenacci et al., 2016; Tinsley & La Bounty, 2015). Recent studies, however, have demonstrated the ability of TRF and resistance exercise to at least preserve lean mass and muscle performance (Moro et al., 2016; Tinsley et al., 2017, 2019). Considering the participants in our study were not accustomed to structured resistance exercise, muscle endurance was selected as our training method (Baechle et al., 2008). Our primary objective was to preserve lean mass, with a secondary objective to improve muscle performance. Both groups completed 100% of their resistance training workouts and experienced lean mass increases of 0.6% in TRF and 1.9% in NF. When considering losses of fat mass among groups, the percentage of regional lean mass increased more significantly for TRF (2.4%) relative to NF (1.2%). Additional benefits were observed for knee flexor and ankle dorsiflexor muscle performance across time, while knee extensor and ankle plantar flexor muscle performance was maintained. Curiously, a significant interaction effect for knee extensor

strength peak torque was observed that showed an increase in NF (13.5%) relative to TRF (-4.8%). We are not able to explain why a drop in knee extensor peak torque occurred in the TRF group. However, since post-hoc tests revealed no significant changes for TRF or NF from W0 to W9, we believe this interaction is simply a minor increase in NF and decrease in TRF across the intervention. Nevertheless, our study supports the use of resistance exercise as a method for increasing lean mass and at least maintaining muscle performance (i.e., strength and endurance), even while under a mild energy restriction (Figueroa et al., 2013; Haskell et al., 2007; Villareal et al., 2017, 2011; Willis et al., 2012; Winett & Carpinelli, 2001). These findings are particularly important due to the loss of muscle mass associated with aging and in response to energy restriction, which can lead to the loss of functional independence later in life (Buford et al., 2010; Chaston et al., 2007; Tinetti et al., 2006, 1988).

Average time spent in moderate-to-vigorous physical activity across the intervention was above 300 minutes for both groups. While this indicates an achievement of weekly physical activity goals, the addition of aerobic exercise did not appear to further enhance weight loss or improve indicators of cardiometabolic health, other than heart rate, relative to studies on aerobic exercise alone (Church et al., 2010, 2007; Kodama et al., 2007; Kraus et al., 2002; Myers et al., 2013; Swift et al., 2011, 2014). In fact, many of the cardiometabolic effects observed in IF remained relatively unaffected by TRF in this study (Harris et al., 2018; Mattson et al., 2017; Rothschild et al., 2014; Rynders et al., 2019; Seimon et al., 2015; Tinsley & La Bounty, 2015). For example, studies on IF, specifically TRF and alternate day fasting, have shown comparable reductions to CER in total cholesterol, LDL, triglycerides, and fasting glucose and insulin, with few eliciting increases in HDL (Catenacci et al., 2016; Gabel et al., 2018; Hutchison et al., 2019; Schübel et al., 2018; Trepanowski et al., 2017; Varady, Bhutani, Klempel, & Kroeger, 2011).

Many of the participants in the present study were metabolically healthy at baseline with all variables at or within the normal range. Research has shown that physiological markers in metabolically healthy, obese adults remain relatively unaffected by IF and other dietary regimes, but further investigation is needed to verify whether individuals with more adverse metabolic profiles receive greater benefits when following IF regimes (Gabel et al., 2018; Hoddy et al., 2014; Janiszewski & Ross, 2010; Rynders et al., 2019; Trepanowski et al., 2017).

The present study also explored the effects of TRF and concurrent exercise training on anabolic and catabolic hormone concentrations. Recent investigations on TRF and resistance training have indicated no change in biological markers in young women and counterintuitive reductions in anabolic hormones (i.e., testosterone and IGF-1) in resistance-trained men after eight-week interventions (Moro et al., 2016; Tinsley et al., 2019). After a 12-week resistance training intervention in overweight and obese adults, Roberts, Croymans, Aziz, Butch, and Lee (2013) saw no decrease in total testosterone, but a decrease in basal testosterone attributed to increased concentrations of sex hormone-binding globulin. Roberts et al. (2013) also found decreases in basal cortisol, which they attributed to an improvement in metabolic profile, specifically basal insulin, even though the obese participants were metabolically healthy before the intervention. It is still unclear whether obese individuals need to perform resistance training at similar intensities as lean individuals to stimulate these anabolic and catabolic hormones (O'Leary & Hackney, 2014). We speculate that the unchanged hormonal profiles in the present study were due to the primarily female and metabolically healthy adult population.

This study has several limitations. First, adherence to TRF and dietary intake were assessed by self-report. While our study showed adherence rates greater than six days per week, it is possible that participants feigned compliance at assessments. Similarly, estimates of nutrient

intake may be inaccurate as the faults of using self-reported dietary intake logs are well-recognized (Lichtman et al., 1992; Ortega, Perez-Rodrigo, & Lopez-Sobaler, 2015; Sawaya et al., 1996). Second, the inability to have complete control over the dietary intake of each group, as the resources required are extensive (Davy & Davy, 2019). Third, the duration of our study was only eight weeks. Longer studies are required to determine the degree of weight loss and cardiometabolic improvement that can be achieved with TRF and concurrent exercise training.

4.6. Conclusion

In summary, these findings suggest that an eight-hour TRF window with concurrent exercise training greatly reduces fat mass relative to a NF control group and preserves lean mass in sedentary, overweight and obese adults. While no changes in physiological variables were seen in this study, TRF and concurrent exercise training appear to improve resting heart rate and heart rate recovery after exercise greater than NF. These data support the use of TRF and concurrent exercise training as a short-term dietary strategy for reducing fat mass and preserving lean mass in sedentary, overweight and obese adults.

4.7. Funding

The project described was supported by the National Institute of General Medical Sciences, 1U54GM115458. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

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APPENDIX A. IRB APPROVAL LETTER

NDSU NORTH DAKOTA STATE UNIVERSITY

June 6, 2018

Dr. Kyle Hackney
Department of Health, Nutrition & Exercise Sciences

IRB Approval of Protocol #HE18247, "Effects of eight weeks of concurrent exercise training and time-restricted feeding (16/8) on body composition, muscle endurance, metabolism, cardiovascular risk factors, and dietary intake in overweight, sedentary males and females"
Co-investigator(s) and research team: Christopher Kotarsky, Sherri Stastny, Shannon David, Steven Mitchell

Approval expires: 5/10/2019 Continuing Review Report Due: 4/1/2019

Research site(s): NDSU Funding agency: NIH through UNMC
Review Type: Full Board, meeting date – 5/11/2018
Risk Level: A minor increase over minimal risk
IRB approval is based on original submission, with revised: protocol materials (received 6/4/2018). Please utilize the stamped consent which accompanies this letter.

Additional approval is required:
o prior to implementation of any proposed changes to the protocol (Protocol Amendment Request Form).
o for continuation of the project beyond the approval period (Continuing Review/Completion Report Form). A reminder is typically sent two months prior to the expiration date; timely submission of the report is your responsibility. To avoid a lapse in approval, suspension of recruitment, and/or data collection, a report must be received, and the protocol reviewed and approved prior to the expiration date.

A report is required for:
o any research-related injuries, adverse events, or other unanticipated problems involving risks to participants or others within 72 hours of known occurrence (Report of Unanticipated Problem or Serious Adverse Event Form).
o any significant new findings that may affect risks to participants.
o closure of the project (Continuing Review/Completion Report Form).

Research records are subject to random or directed audits at any time to verify compliance with IRB regulations and NDSU policies.

Thank you for cooperating with NDSU IRB procedures, and best wishes for a successful study.

Sincerely,
Kristy Shirley
Kristy Shirley, CIP
Research Compliance Administrator

For more information regarding IRB Office submissions and guidelines, please consult www.ndsu.edu/irb. This Institution has an approved FederalWide Assurance with the Department of Health and Human Services: FWA00002439.

INSTITUTIONAL REVIEW BOARD
NDSU Dept 4000 | PO Box 6050 | Fargo ND 58108-6050 | 701.231.8995 | Fax 701.231.8098 | ndsu.edu/irb
Shipping address: Research 1, 1735 NDSU Research Park Drive, Fargo ND 58102

APPENDIX B. INFORMED CONSENT

NDSU NORTH DAKOTA STATE UNIVERSITY

Health, Nutrition, & Exercise Sciences (HNES)
NDSU Dept. 2620; PO Box 6050
Fargo, ND 58108-6050
701.231.7479

Effects of eight weeks of concurrent exercise training and time-restricted feeding (16/8) on body composition, muscle strength and endurance, metabolism, cardiovascular risk factors, and dietary intake in overweight, males and females.

This study is being conducted by:
Christopher Kotarsky, MS, North Dakota State University. Phone: 216.956.5412. Email: christopher.kotarsky@ndsu.edu
Kyle Hackney, PhD, Assistant Professor in HNES, North Dakota State University. Phone: 701.231.6706. Email: kyle.hackney@ndsu.edu
Sherri Stastny, PhD, Professor in HNES, North Dakota State University, Phone: 701.231.7479. Email: sherri.stastny@ndsu.edu

Key Information about this study:

This consent form is designed to inform you about the study you are being asked to participate in. Here you will find a summary about the study; however, you can find more detailed information later in the form.

Inclusion Criteria:

- Are male or female between the ages of 35-60 years.
- Are classified as overweight/obese, determined by body mass index between 25.0-34.9 kg/m^2.
- Are otherwise generally healthy and mobile.
- Available for testing and training sessions, each lasting roughly one-two hours.

Exclusion Criteria:

- Are pregnant or perceive you may be pregnant. A urine screen will be used to rule out pregnancy before bone mineral density scan is performed.
- Currently smoke tobacco, e-cigarettes, or use smokeless tobacco.
- Have been told by a doctor that you have neuromuscular disease, diabetes, high blood pressure, or are being treated for cancer.
- Have previously had a heart attack or other chronic heart related conditions that are not controlled with medicine.
- Have difficulty moving without assistive devices or walking one-quarter mile.
- Are taking medications that influence muscle size (testosterone, growth hormone, etc.).
- Have had bariatric surgery.
- Have a body mass greater than 350lbs.
- At risk for disordered eating based on self-report.

Institutional Review Board
North Dakota State University
PROTOCOL #: HE18247
APPROVED: 5/10/2019
EXPIRES: 5/9/2020

Risks:

- Muscle soreness due to exercise testing and training may occur during the study.
- A detailed outline of the risks associated with this study is listed below.

Benefits:

- Improvements in muscular strength and endurance, as well as cardiorespiratory fitness, may occur as a result of the concurrent training used in this study.

Time Commitment:

- The whole study will last **10-12 weeks** and involve at least **29 contact hours** with research staff and trainers.

Compensation:

- You will receive a total of $200 in compensation after the completion of post-training assessments.

Privacy Concerns:

- Face-to-face meetings will be completed at the Bentson Bunker Field house on NDSU campus (BBFH lower level, Human Performance Lab and Room 14, 15 and 16). Even though the first session is a group situation, you will be allowed privacy for questions regarding yourself (such as questions about your health and eligibility). After instruction and screening forms are completed, and eligibility is verified, you will be asked to read and sign an informed consent. You will be encouraged to ask questions and then schedule an appointment for testing. All tests will be completed with two members of the team present in rooms with closed doors and windows. You will be assigned a number 01-40 , and only numbers, no names, are used on testing forms. Health information will be kept confidential and locked in an office. All paper copy information will be shredded once data is transferred to a secure server.

Why am I being asked to take part in this study?

Time-restricted feeding is an increasingly popular dietary approach because it does not require a restriction on energy intake (amount of food consumed). Instead, time-restricted feeding reduces the time window of energy intake (example: 12:00pm-8:00pm). The purpose of this study is to (1) determine whether time-restricted feeding is an effective dietary strategy for reducing fat mass while preserving fat-free mass in combination with aerobic and resistance training, (2) evaluate potential changes in health-related biomarkers and indicators of muscle health (mass, strength) after 8 weeks of resistance training with time-restricted feeding, and (3) examine the influence of caloric intake and macronutrient distribution on muscle health in time-restricted feeding and normal feeding pre-to-post-resistance training.

What will I be asked to do?

I. **Screening/Instruction Session (1.5 hours)**
You will be asked to attend a discussion about the study and then, if you are still interested, fill out forms to see if you are eligible to participate. You will be asked to complete several screening forms to determine your overall health including a physical activity and health history questionnaire. These questionnaires are used to determine if you are healthy enough for the study.

II. **Pre-Assessment Session (Week 1: 2-3 hours)**
You will then be asked to schedule one or two testing session(s) to complete the following:

A. **Anthropometric Data**: Height, weight, and waist and hip circumference. You will be asked to stand on a digital scale, stand next to a wall with a tape measure device, and have your waist and hip size measured via a tape measure.

B. **Dried Blood Spot Testing:** Your blood will be collected by placing blood drops on a filter card after a finger prick with a lancet. The blood spot testing will be used to test potential changes several health-related biomarkers [insulin, high-sensitivity C-reactive protein (Hs-CRP), hemoglobin A1c, triglycerides, cholesterol, HDL, LDL, very LDL] due to dietary strategy and aerobic and resistance training.

C. **Saliva Testing:** Saliva will be collected by having you perform a passive drool into a plastic tube. The saliva will be used to test potential changes in hormones [estradiol (E2), progesterone (Pg), testosterone, dehydroepiandrosterone sulfate (DS), cortisol (C)] due to dietary strategy and aerobic and resistance training.

D. **Muscle Testing:** You will perform 3 tests to determine your hand strength and leg strength. Your hand strength will be measured by squeezing a hand-held device as hard as possible. You will then be seated in a specialized chair and asked to extend and curl your legs as hard as possible. Next, the chair will be repositioned, and you will perform a third test to flex and extend your ankle (like you are pushing on a gas pedal) as hard as possible.

E. **Bone Mineral Density Test:** A bone mineral density test will be completed while you relax on a table. Strong bones are important for your health. A bone mineral density test is the best way to measure your bone health. It compares your bone density, or mass, to that of a healthy person who is the same age and sex as you are. The test can provide a snapshot of your bone health. The test can identify osteoporosis, determine your risk for fractures (broken bones), and measure your response to osteoporosis treatment. The most widely recognized bone mineral density test is called a central dual-energy x-ray absorptiometry, or central DXA test.

   Female participants will be asked to provide a urine sample before the DXA procedure to rule out pregnancy. We ask that you dress in shorts and a T-shirt. For this procedure, two Velcro straps will be placed on your lower limbs to help keep the lower body in correct position during the scan. Once positioning is complete the trained researchers will guide you through the procedure. You will be asked to remain still as the scanning arm moves from the top of your head to the feet and back to the head. This takes approximately 5-12 minutes depending on height and weight. When the scan is complete, the Velcro straps will be removed, and you will be assisted off the DXA table.

F. **3-Minute Step Test:** Prior to cardiovascular and muscle testing, you will undergo a 5-minute warm-up on a stationary bike. The purpose of this step test is to provide us with measures of cardiorespiratory fitness. You will be asked to step up and down on a 12" surface for 3 minutes.

G. **Load Assignment:** The purpose of this testing is to help determine your appropriate training weight during the eight weeks of resistance training.

H. **Dietary Intake:** You will be instructed to complete a 3-day dietary intake log, which will include demographic and dietary habit questions, pre-intervention and at weeks one, four, and seven during the intervention to detect any changes in dietary intake. You will be asked to document food intake on 2 typical days and 1 untypical day.

III. **Training Sessions (Weeks 2-9: 3 times per week, 1 hour per session)**

After pre-training assessments, you will be randomly assigned to a time-restricted feeding group or a normal feeding group. The time-restricted feeding group will be required to consume all their energy (food) in an 8-hour feeding window (12:00pm to 8:00pm), inducing a fasting window of 16 hours. The normal feeding group will maintain their typical dietary habits, and consume their energy (food) at any time throughout the day. Exercise training for both groups will be completed within feeding windows, and last eight weeks. Halfway through the intervention (week 5) blood pressure will be measured and body mass will be assessed.

A. **Resistance Training:** Training will be standardized for both groups, and consist of 3 weekly sessions performed on non-consecutive days for 8 weeks (24 sessions). The resistance training program will consist of 3 different weekly sessions: Session A (chest press, military press, tricep pressdown), Session B (leg press, leg curl, leg extension), Session C (wide grip lat pulldown, back machine pulley row, bicep curl). Before training begins, you will complete a 5-minute warm-up on a treadmill or related equipment.

Resistance training will involve 3 sets of 12-15 repetitions, at a moderate intensity, with 30 seconds of rest between exercises and sets. For the first exercise of each session, you will follow a lift specific warm-up by performing 8 repetitions, followed by a 1-minute rest. You will then complete a second warm-up of 6 repetitions, followed by a 2-minute rest. Training sequence will begin at 3 sets of 12 repetitions, at a moderate intensity, to train in the desired repetition range for muscle endurance.

During each training session, you will attempt to complete one additional repetition for each set. Once you perform 3 sets of 15 repetitions, on two consecutive training sessions, intensity will be increased by adding weight in 5-pound increments. After adding additional weight, you will go back to performing 3 sets of 12 repetitions. A verbal cadence of two seconds during the eccentric phase and two seconds during the concentric phase will be used to avoid any discrepancies in lifting velocity in both training groups. Certified personal trainers will directly supervise all routines to ensure proper form. Resistance training exercises, other than those included in the experimental protocol will not be allowed.

B. **Aerobic Training:** After each resistance training session, you will complete an aerobic conditioning program at a moderate-vigorous intensity on a treadmill or related equipment. After completion, you will perform a 5-minute cooldown at a low-to-moderate intensity. Exercise duration for aerobic training will start at 15 minutes, and increase 5 minutes every week during weeks 2-4. At weeks 5 and 7 the training intensity will be increased to maintain exercise progression.

The American College of Sports Medicine has defined 50-60 min·d-1 to total 300 minutes moderate, or 150 minutes vigorous, physical activity necessary to promote or maintain weight loss. Our study will help you achieve a portion of this goal each week. We encourage you to complete the remaining physical activity on your own time. To ensure you are meeting this goal, physical activity will be monitored at weeks two, five, and eight during the intervention using an Actigraph GT9X (AG) accelerometer (Actigraph, Pensacola, FL), worn on the non-dominant wrist, to precisely quantify energy expenditure and the intensity of activities.

IV. **Post-training Assessment Session (Week 10: 2 hours)**
Post-training assessments will be scheduled within one week of last training session. This session(s) will include all pre-training assessments, expect dietary intake and load assignment. Once completed, you will receive final compensation for participating in the study.

Where is the study going to take place, and how long will it take?

The screening/instruction session will take **one hour**. If you agree to be a part of the study, pre-training assessments will be required for collection of demographic information (such as height and weight), muscle testing, bone and body composition testing, and blood spot and saliva testing (**two-three hours**). Once the pre-assessments are complete, you will begin the training intervention 3 times per week for 8 weeks (**one hour per session**). After training is completed, post-training assessments will be scheduled (**two hours**). The whole study will last **10-12 weeks**, with at least **29 contact hours** with research staff and trainers.

All meeting will be scheduled at a time that works for you and will be at the Bentson Bunker Fieldhouse on the NDSU campus (BBFH lower level, Human Performance Lab and Room 14, 15 and 16) or Wallman Wellness Center on the NDSU campus.

What are the risks and discomforts?

The study team has minimized the known risks by studying a group of healthy participants. It is not possible to identify all potential risks in research procedures, but the researcher(s) have taken reasonable safeguards to minimize any known risks to you.

- Low dose radiation exposure. The full body DXA scan is not capable of producing high doses of radiation. For example, if you had 625 full body DXA scans in one year you would still only be exposed to ~25% of the limit for radiation exposures are in the United States from natural sources that are in the environment. However, it is still considered good practice to test for pregnancy for all females of child bearing age, before a scan is completed. Therefore, all subjects will be asked to provide a urine sample/pregnancy screen test upon arrival for testing. Any positive pregnancy test would deem any further testing halted.
- Exercise related discomforts (low-moderate risk of occurring)
    - Muscle soreness and cramping.
    - Lightheadedness or an adverse cardiovascular response.
    - Repetitive stress injuries to muscle, tendon, ligaments, or bone.
    - We will provide you with a warm-up prior to assessing muscle strength and we use very safe equipment for testing.
- Infection at the site of the finger stick blood draw (low risk of occuring).

- We will use standard precautions to protect against infection including cleaning the site with alcohol and covering the site with a bandaid following the blood draw.
- Breach of privacy and/or confidentialiy of health information (low risk of occuring).
- Discomfort during assessments (low risk of occuring).
- Loss of health information from questionnaires (low risk of issue).
  - All assessments will be completed with only the study team present in rooms with closed doors and windows. We will keep health information confidential and locked in an office. We will shred all personal health information once the study is completed.
- Equipment malfunction (very low risk of occurring).
  - Pinching or injury from hardware or software failures.
  - All equipment will be examined prior to testing to reduce a risk of a malfunction.

What are the expected benefits of this research?

Individual Benefits: You may experience body composition, cardiovascular, and muscle strength and endurance improvements following the 8 weeks of resistance and aerobic training. You will be provided with a summary of your own data once the study is completed if you wish. This will also include averages of nutritional intake, physical activity, muscle endurance and strength, body and bone composition, and health-related biomarkers and hormone levels.

Societal Benefits: We will develop educational materials intended for the public after learning more about time-restricted feeding and concurrent exercise training at the end of this study. These educational materials will include physical activity interactions with dietary intake. Our study distinguishes itself by incorporating both an aerobic and resistance training intervention with time-restricted feeding in overweight, minimally physically active, middle-aged males and females, who are at a greater risk of cardiovascular disease and physical dysfunction. Our research may show that time-restricted feeding, in combination with concurrent training, effectively reduces fat mass while preserving fat-free mass. This is important because time-restricted feeding does not require a restrictive energy intake, which is associated with poor compliance and muscle loss. Thus, time-restricted feeding may be an ideal dietary approach for reversing risk factors associated with obesity and attenuating age-related declines in muscle mass and strength.

Do I have to take part in this study?

Your participation in this research is your choice. If you decide to participate in the study, you may change your mind and stop participating at any time without penalty or loss of benefits to which you are already entitled.

What are the alternatives to being in this study?

Instead of being in this research, you may choose not to participate.

Who will have access to my information?

We will keep private all research records that identify you. Your information will be combined with information from other people taking part in the study. When we write about the study, we will write about the combined information that we have gathered. We may publish the results of the study; however, we will keep your name and other identifying information private. We will make every effort to prevent anyone who is not on the research team from knowing that you gave us information, or what that information is. For example, your name will be kept separate from your research records and these two things will be stored in different places under password protection. If you withdraw before the research is over, your information will be retained in the research record. We will not collect additional information about you.

Certificate of Confidentiality

The Department of Health and Human Services (HHS) has issued a Certificate of Confidentiality to further protect your privacy. With this Certificate, the investigators may not disclose research information that may identify you in any Federal, State, or local civil, criminal, administrative, legislative, or other proceedings, unless you have consented for this use. Research information protected by this Certificate cannot be disclosed to anyone else who is not connected with the research unless:

1. there is a law that requires disclosure (such as to report child abuse or communicable diseases but not for legal proceedings);
2. you have consented to the disclosure, including for your medical treatment; or
3. the research information is used for other scientific research, as allowed by federal regulations protecting research subjects.

Disclosure is required, however, for audit or program evaluation requested by the agency that is funding this project or for information that is required by the Food and Drug Administration (FDA).

You should understand that a Confidentiality Certificate does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this research. If you want your research information released to an insurer, medical care provider, or any other person not connected with the research, you must provide consent to allow the researchers to release it. This means that you and your family must also actively protect your own privacy.

How will my blood and saliva samples be used?

Collected samples will be sent to ZRT labs for analysis of cardiovascular profiles and hormones. After analysis (3 months) they will be destroyed. They will not be used or distributed for future research, even if de-identified.

Can my participation in the study end early?
If you fail to participate in all scheduled sessions, you may be removed from the study.

Will I receive any compensation for participating in the study?
After completion of all post-training assessments, you will receive $200 in compensation. You will receive $100 after the first 4 weeks and $100 after all data collection sessions are complete at the end of the study.

What happens if I am injured because of the study? [include if applicable]
In general, exercise training is very safe and healthy for you. However, if you are injured during this study, you should contact Kyle Hackney at 701.231.6706. Some minor treatment for the injury will be available including first aid, emergency treatment, and follow-up care as needed. Payment for this treatment must be provided by you and your third party payer (such as health insurance). This does not mean that you are releasing or waiving any legal right you might have against the researcher or NDSU because of your participation in this research.

What if I have questions?
Before you decide whether you'd like to participate in this study, please ask any questions that come to mind now. Later, if you have questions about the study, you can contact Kyle Hackney at 701.231.6706 or kyle.hackney@ndsu.edu, or Christopher Kotarsky at 216.956.5412 or christopher.kotarsky@ndsu.edu.

What are my rights as a research participant?
You have rights as a research participant. All research with human participants is reviewed by a committee called the *Institutional Review Board (IRB)* which works to protect your rights and welfare. If you have questions about your rights, an unresolved question, a concern or complaint about this research you may contact the IRB office at 701.231.8995, toll-free at 855-800-6717 or via email (ndsu.irb@ndsu.edu).

Documentation of Informed Consent:

You are freely making a decision whether to be in this research study. Signing this form means that

1. you have read and understood this consent form
2. you have had your questions answered, and
3. you have decided to be in the study.

You will be given a copy of this consent form to keep.

_____ _____

Your signature Date

_____ _____

Your printed name Date

_____ _____

Person conducting informed consent discussion signature Date

_____

Printed name of person conducting informed consent discussion

Documentation of DXA Consent:

You understand that the bone mineral density (DXA) examination is an X-Ray procedure that involves radiological isotopes_____ (initials)

_____ _____

Signature of researcher explaining study Date

_____

Printed name of researcher explaining study

Documentation of Release of Images:

You have the choice to allow all DXA scan images obtained during this study to be used by the research team in outreach materials, publications, manuscripts, poster presentations, PowerPoint presentations, and University websites. Images will only be used in a professional context when describing the study. Your name will never be associated with the images unless we obtain further permission from you later.

Yes _____

No _____

_____ _____

Your signature Date

_____

Your printed name