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Influence of Exercise on Brown, White and Beige Adipocytes

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Abstract

Obesity results from a chronic positive energy imbalance resulting in hormonal resistance, systemic inflammation, and overall poor metabolic health. Moreover, obesity is strongly associated with co-morbidities such as cardiovascular disease (CVD) and type 2 diabetes. Exercise is established as a way to increase energy expenditure and counteract the metabolic disruption of obesity. Recent research has investigated the ways in which exercise may elicit adaptations in adipose tissue, identifying additional mechanisms for addressing obesity. Adipose tissue has 3 distinct forms of brown (BAT), white (WAT) and beige adipose tissue. BAT is metabolically active, dissipating excess energy in the form of heat, thus responsible for adaptive thermogenesis. WAT stores excess energy in the form of triglycerides and it's accumulation results in obesity. Beige adipose tissue results from morphological adaptations within WAT in response to various stimuli. Beige adipose tissue is more metabolically active than WAT, making it an area of interest for increased energy expenditure. In this review, studies included examine the activation of already present BAT with exercise training interventions. Moreover, included studies investigate exercise induced adaptations to WAT and beige adipose tissue. Exercise as a recommended treatment of obesity is not a novel concept; however, the mechanism by which brown adipose tissue (BAT) is activated and beiging is induced has not been clearly described. The purpose of this review is to discuss the potential mechanisms by which exercise induces responses in adipocytes based off both human and rodent research.

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AI was not used in the creation of this content.

Table of Contents

CHAPTER 1: INTRODUCTION

According to the Center for Disease Control (CDC), in 2020, 41.9% of adults in the United States were classified as obese and approximately 75% are not currently meeting the minimum recommendations for physical activity set by the American College of Sports Medicine (ACSM) [1, 2]. Since 2020 and the outbreak of the Corona Virus Disease 19 (COVID-19), obesity rates are trending upward, and physical activity levels have decreased, furthering the obesity epidemic in the United States [3, 4]. Obesity has been closely linked to increased incidence of cardiovascular disease, hypertension, type 2 diabetes, and metabolic disease, among other comorbidities [5]. It has long been established that exercise offers many health benefits and may result in weight loss [6]. Chronic exercise is known to improve cardiovascular health, metabolic function and support the immune system, offering a counteraction to obesity and obesity related diseases [6, 7]. Adipocytes are in part responsible for energy homeostasis and thermogenic regulation throughout the body, which are both processes disrupted with obesity [8]. Recent research has examined metabolic adipocyte activation from physiological stress created by exercise as a mechanistic target for the treatment of obesity.

Adipose tissue appears in three distinct forms, as energy storing white adipose tissue (WAT), thermogenic brown adipose tissue (BAT) and as inducible beige adipose tissue [9]. WAT is energy storing and widely found throughout the human body, while BAT is metabolically active and is common in certain fat depots. Beige adipocytes share some similarities with the metabolic activity of BAT; however, beige adipocytes are from a different cellular lineage thus making them distinct from BAT [10]. Having large amounts of BAT is considered metabolically favorable as BAT expends excess macronutrient energy by producing heat through thermogenesis rather than storing it as multilocular lipid droplets [11]. Additionally,

within WAT, in a process known as ‘beiging,’ morphological adaptations to a more metabolically active state may also increase energy expenditure [12]. Researchers have recently investigated the activation of existing BAT as well as the possibility of exercise-induced transdifferentiation of WAT to beige adipocytes. Mechanisms by which these changes may occur remain largely unknown, although hypotheses suggest changes through sympathetic nervous system activation and circulating hormones [7, 8, 13]. Current research remains largely in rodents, but translational studies to human adults are increasing in number.

Statement of Problem

Obesity is categorized in populations by the BMI scale and is quantified as >30 kg/m^2, while 18.5-24.9 kg/m^2 is indicative of ‘normal weight’ [14]. Moreover, the overweight categorization on the BMI scale ranges from 25-29.9 kg/m^2. A high BMI is strongly correlated with the development of obesity related co-morbidities, such as insulin resistance and cardiovascular disease [15]. Obesity results when energy intake from food chronically exceeds energy output, creating a positive energy balance. Excess energy accumulates as triglycerides and is stored as lipid droplets in adipocytes [9, 16-18]. Increases in storage leads to either adipocyte hypertrophy or hyperplasia, growth in size and growth in numbers respectively [5, 19-21]. Adipocyte hypertrophy and hyperplasia can result in a chronic systemic inflammatory state which promotes the incidence of metabolic disease [22].

Purpose of Study

As a recommended treatment for obesity, exercise is not a novel concept; however, the mechanism by which BAT is activated and beiging is induced has not been clearly described. The purpose of this review is to discuss the potential mechanisms by which exercise induces responses in adipocytes based off both human and rodent research.

Significance of Study

This review aims for a deeper understanding of the overall effects of exercise and its connection to individuals' health as it relates to obesity. To do so, this review will explore potential mechanisms and associated research methodologies behind the ways BAT is activated and beige adipocytes are proliferated under various stimuli, with a specific focus on aerobic exercise. Previous studies and literature reviews have looked at various stimuli, such as cold and ß-3 adrenergic receptors activation [7, 11, 23-27], considered different mechanisms by which adaptive thermogenesis occurs [8, 13, 28-30], and described the ways in which individuals may benefit from therapeutic intervention [7, 26, 31-33]. While several studies and reviews touch on exercise as a stimulus of adaptive thermogenesis, few have focused on exercise alone and considered the underlying mechanisms by which exercise differs from other stimuli. Moreover, studies of human adults are continually being published on this topic, so the most recent and up to date information will be included and considered for this review.

Limitations and Delimitations

This review recognizes limitations within the field of adipocyte research as it relates to exercise stimuli. First, the bulk of research has primarily been performed on rodents with few translational clinical studies. Of the human studies, small sample sizes and inconsistent data collection methods contribute to confound results. Of the published human studies, sample sizes are limited, yet span varying body compositions and fitness levels. This creates confusion with near significant results being perturbed by large sample variability. Currently, there is no method for measuring activation of BAT during exercise, limiting the understanding of acute exercise induced responses. Additionally, the current gold standard of BAT measurement, PET-CT ^{18}F-FDG, is costly and measures only one contributing variable, local glucose uptake. While

showing potential, this field of research is still new and lacking longitudinal studies that could help describe long term effects of increased adaptive thermogenesis.

Solidifying the scope of the present review are four delimitations. First, obesity is classified off the BMI parameters set by the CDC [14]. Second, metabolic function was referenced as a culmination of energy expenditure, glucose metabolism, lipid metabolism and hormonal sensitivity [7, 34-36]. Third, beiging was determined by parameters of biochemical expression and metabolic activity [8, 13, 37]. Lastly, study interventions of dietary control and resistance exercise were excluded due to the paucity of research [38].

Basic Assumptions

Several assumptions are made throughout the present review. It is assumed that in conjunction with exercise, an individual's diet will not keep them in a positive energy balance; rather, it is assumed that exercise alone is enough to put an individual into energy balance. Another assumption made is that most obesity comorbidities are reversable in nature and not indicative of a life-long diagnosis. Moreover, it is assumed that regardless of previous medical history, with few exceptions such as cancer diagnosis, an individual has the potential for significant alterations of adaptive thermogenesis. Finally, it is assumed that the available literature, provided by public access or The University of Montana Library, is sufficient in content to draw salient conclusions on the topic of interest.

Section Summary

Obesity is an epidemic within the United States, affecting nearly half of the adult population. Obesity is associated with poor metabolic and cardiovascular health as well as high morbidity rates [5, 15, 39]. Exercise has long been established as an intervention to address obesity and its comorbidities through bouts of increased total body energy expenditure [7, 22,

33]. A developing mechanistic target of adipose tissue by exercise has garnered recent interest as a novel approach for treatment of obesity. It has been proposed that via exercise, adipose tissue may undergo morphological adaptations that in turn increase total body energy expenditure [7, 27, 30, 35, 40]. The purpose of the present review is to parse through the current research on adipose tissue adaptations to exercise, as well as help describe mechanism and methodologies by which these changes may occur.

Definition of Terms

- **White Adipose Tissue (WAT) –** White adipose tissue is a distinct form of adipose tissue found in mammals. WAT is dynamic tissue consisting primarily of adipocytes which store energy in the form of triglycerides. White adipocytes have large unilocular lipid droplets and have few mitochondria [7, 9, 28, 30, 41-43]
- **Brown Adipose Tissue (BAT) –** Brown adipose tissue is a distinct form of adipose tissue found in rodents and humans. BAT is metabolically active, possessing multilocular lipid droplets and an abundance of mitochondria. BAT is in part responsible for energy homeostasis and temperature regulation via adaptive thermogenesis [7, 8, 10, 13, 17, 27, 34, 37, 40, 44-48].
- **Beige Adipose Tissue –** Beige adipose tissue is a distinct form of adipose tissue originating within scWAT depots in both rodents and humans. Beige adipocytes are multilocular and express UCP1 when stimulated. Beige adipocytes are metabolically active, dissipating energy via adaptive thermogenesis [7, 13, 37, 43].
- **Beiging –** Beiging refers to the induction and stimulation of adipocytes within scWAT depots by various stimuli. Beiging in determined by expression of biochemical markers such as UCP1 and PGC1-α [7, 8, 10, 13, 34, 37, 42].

- **Exercise –** Exercise refers to structured and intentional movement that increases energy expenditure, done for the purpose of improving physical fitness [6, 7, 27, 34, 35, 49]
- **Endurance Exercise Training –** Endurance exercise training refers to repetitive bouts of aerobic exercise that elicits physiological adaptations [34, 35, 41, 50-53]
- **Adipokines –** Adipokines are cell signaling molecules released from all forms of adipocytes. Adipokines can interact with other tissues to help regulate various physiological functions such as glucose and lipid metabolism, inflammation, and insulin sensitivity [52, 54-56].
- **Exerkines –** Exerkines are cell signaling molecules released in response to an exercise stimulus from various tissues and organs. Exerkines help mediate the physiological response to exercise and its subsequent adaptations [55, 57, 58].
- **Subcutaneous White Adipose Tissue (scWAT) –** scWAT lays just beneath the skin primarily around the thighs and buttocks, providing insulation and cushioning. Healthy amounts of scWAT is associated with insulin sensitivity and reduced risk of developing type 2 diabetes [13, 28, 32, 41, 43].
- **Visceral Adipose Tissue (vWAT) -**vWAT surrounds vital organs, such as the kidneys, for protection. Excess amount vWAT is referred to as abdominal obesity and is associated with insulin resistance and metabolic disease [13, 28, 43, 59].

Abbreviation of Terms

- **WAT =** White adipose tissue
- **BAT =** Brown adipose tissue
- **scWAT =** Subcutaneous white adipose tissue
- **vWAT =** Visceral white adipose tissue

- **BMI =** Body mass index
- **PET-CT ^{18}F-FDG =** Positron emission tomography – computer tomography ^{18}F-fluorodeoxyglucose
- **FFA =** Free fatty acid
- **ATP =** Adenosine Triphosphate
- **UCP1 =** Uncoupling Protein 1
- **PGC1-α =** Peroxisome proliferator-activated receptor gamma coactivator 1-alpha
- **SNS =** Sympathetic nervous system
- **PRDM16 =** PR domain containing 16
- **IL-6 =** Interleukin 6
- **FGF21 =** Fibroblast growth factor 21
- **Dio2 =** Iodothyronine deiodinase 2
- **CIDEA =** Cell Death Inducing DFFA Like Effector A

CHAPTER 2: REVIEW OF LITERATURE

ADIPOSE TISSUE

Adipose tissue is a versatile and highly variable organ employing several metabolic and endocrine functions throughout the body. Adipose tissue is classified as connective tissue comprised primarily of adipocytes separated into depots throughout the body. White adipose tissue, brown adipose tissue and beige adipose tissue are the three distinctive types of adipocytes established in vivo [10, 18]. Functionally, adipocytes provide insulation and cushioning. Adipose tissue acts as a thermal insulator, helping to maintain body temperature by reducing heat loss. It also serves as a protective cushion around vital organs, such as the kidneys and heart, providing support and reducing the risk of injury [9, 60]. Metabolically, adipocytes store triglycerides for times of energetic need and work to buffer excess energy consumption via the release of heat. Triglycerides are derived from dietary fats and carbohydrates. They are stored in lipid droplets within the adipocytes, serving as a long-term energy reserve [18]. Moreover, adipose tissue serves as a homeostatic regulator of energy production and temperature regulation through hormonal control of several biochemical pathways, mainly lipogenesis, lipolysis, and FA oxidation [8, 13, 20, 57]. As an endocrine organ, adipocytes release adipokines such as adiponectin, interleukin-6 (IL-6), and leptin into circulation [54, 57]. These adipokines are largely responsible for regulating glucose and fatty acid metabolism, insulin sensitivity, blood pressure, and inflammation response. With incidence of obesity, adipocytes lose their capacity to sense, signal and manage energy balance via adipokine insensitivity [7, 8]. Each of the three adipocyte types play individual roles within the overarching structure and function of adipose tissue.

White Adipose Tissue

White adipose tissue (WAT) consists of energy-storing adipocytes characterized by unilocular lipid droplets and few mitochondria. The primary function of WAT is triglyceride storage, insulation, and protection of vital organs [9]. With large lipid droplets and low mitochondrial density, WAT is less metabolically active in comparison to BAT and beige adipocytes [8]. White adipocytes are dynamic in their structure as they can vary greatly in size and number depending on the level of adiposity. To note the variability of size and abundance, WAT contributes ~10-20% of total body weight among lean adults, but in cases of obesity, WAT may contribute up to ~40-70% of total body weight [28]. WAT is dispersed throughout the body and separated into depots. Visceral white adipose tissue (vWAT) surrounds vital organs such as the kidneys, while subcutaneous white adipose tissue (scWAT) lays just beneath the skin primarily around the thighs and buttocks, providing insulation and cushioning [28, 43]. Accumulation of excess vWAT is referred to as abdominal obesity and is associated with insulin resistance and metabolic disease [13, 59]. Alternatively, scWAT is associated with insulin sensitivity and reduced risk of developing type 2 diabetes [13, 32]. WAT depot-specific responses occur because of differing molecular characteristics of vWAT and scWAT. scWAT has been shown to have increased expression of genes associated with glucose and lipid metabolism as well as beiging agents like PGC1-α, which acts as a stimulus for mitochondrial biogenesis [42]. The ability for scWAT to express metabolism genes, specifically beige gene markers, indicates that it has greater capacity to undergo beiging [13]. As previously mentioned, it is characteristic of adipocytes to lose their sensitivity to hormonal stimuli with increasing adiposity in a process known as adipose tissue ‘whitening’ [21]. This dysregulation can result in a spillover of lipids into ectopic locations thus further contributing to hormonal insensitivity,

adipocyte hypertrophy, and contribute to metabolic disease [21, 57]. On the other hand, WAT may be able to undergo 'beiging,' becoming more metabolically active, and elicit the opposite effect of whitening [27, 59]. Beiging will be discussed further but is hypothesized as a potential result of several stimuli including exercise.

Brown Adipose Tissue

Brown adipose tissue (BAT) consists of metabolically active adipocytes characterized by high mitochondrial density, multilocular lipid droplets, and thermogenic activity. The thermogenic properties of BAT can largely be attributed to its mitochondrial density and expression of uncoupling protein 1 (UCP1) [44, 48]. BAT originates in humans from myogenic lineage during the second trimester of embryogenesis [61]. The primary role of BAT is temperature regulation via thermogenic activation. BAT metabolizes lipids via lipolysis to produce heat contributing to non-shivering thermogenesis [48].

While the presence of BAT in rodents and human infants has been well established, recently human adults have been confirmed to possess BAT as well [16, 17, 48, 62]. It was thought that BAT disappeared at an early age, and while age likely is a large player in BAT retention, recent evidence has shown BAT depots in adult humans [45]. Positron emission topography-computer tomography^{18}F-fluorodeoxyglucose (PET-CT ^{18}F-FDG) is considered the gold standard in the detection and identification of BAT [24]. PET-CT ^{18}F-FDG depicts local glucose uptake and is indicative of metabolic activity within the cell. Glucose uptake is determined by standard uptake value in the targeted cell using the radiotracer ^{18}F-FDG, which is injected prior to the scan [63]. Since PET-CT ^{18}F-FDG identifies activity, stimulation is needed for an accurate depiction of the tissue of interest. Given BAT's responsibility of temperature regulation via non-shivering thermogenesis, a common method used for stimulation is mild cold

exposure, whether through room temperature, ice packs, or submersion [24, 26, 27]. Mild cold stimuli activates the sympathetic nervous system which then stimulates β_3-adrenergic receptors on adipocytes [24, 26, 64]. Mild cold exposure is utilized so that non-shivering thermogenesis is activated rather than shivering thermogenesis. It is important to note seasonal differences of BAT activation. BAT is thought to play a role in cold acclimation with cold-induced thermogenesis increasing in colder months [64, 65]. It is critical in the creation of study methodologies to consider the seasonal discrepancies and collect data during the same season for all subjects to avoid confounding BAT activation. Moreover, uncoupling protein 1 (UCP1) expression in metabolically active adipose tissue is considered another criterion for identification [66]. Depots exhibiting UCP1 activity, measured via immunoassays, correspond with glucose uptake depots shown in ^{18}F-FDG PET-CT scans [62]. UCP1 is a critical protein in thermogenic heat production UCP1 uncouples oxidative phosphorylation from ATP synthesis at the electron transport chain. The protons pumped into the mitochondrial intermembrane space are allowed to flow back to the mitochondrial matrix, disrupting the proton gradient needed for ATP synthesis [66]. UCP1 activity results in heat production via non-shivering thermogenesis and its expression is used to indicate the presence of BAT in human adults. BAT's molecular signature expands beyond UCP1 and includes PGC1-α, PRDM16, and Dio2, among others [10]. This molecular signature is used in conjunction with other identification methods to further support BAT identification.

Using medical records from a Boston, MA hospital, a sample of 1972 patients producing 3640 PET-CT scans were retroactively examined. The presence of BAT using PET-CT ^{18}F-FDG was confirmed with the following criteria: tissue section of interest measuring >4mm in diameter, CT density of ~50-250 Hounsfield units, and a max standard uptake value of PET-CT ^{18}F-FDG at 2 g/ml [62]. Results revealed that 7.5% of females and 3.1% of males had cervical

supraclavicular or superior mediastinal BAT depots. The authors consider this to be an underestimation of BAT prevalence since the adipocytes would have been inactive at the time of the scans without any intentional stimulus like cold. Additional predictors of having high BAT mass were also proposed by the authors, including age, BMI, fasting glucose, smoking status, medications being taken, and reason for hospital visit [62]. Another study examined UCP1 presence in perithyroid cervical adipose tissue among 35 patients undergoing thyroid surgery (n=27 females, n=8 males) [16]. Ten patients were identified as having UCP1 positive adipocytes (UCP1+). Within the UCP1+ group, the collected tissue exhibited classic BAT morphology and was organized into distinct depots. Sympathetic innervation among the UCP1+ group was ten times denser than in the UCP1- tissue. Notably, the sample utilized for this study captured a wide range of ages (18-82 years) and BMIs (18-37 kg/m^2). The younger and leaner individuals were more likely to be UCP1+ ($p<0.001$ and $p<0.03$ respectively) [16]. While unable to separate these variables based off this study alone, BMI and age are reinforced as strong predictors for the presence of BAT. Interestingly, the white adipocytes of the UCP1- group were nearly twice the size of the UCP1+. This further differentiates the adipocyte types and associates certain iterations of WAT with the presence or absence of BAT and vice versa. A different study examined five healthy subjects and the activation of BAT via cold-induced glucose uptake [17]. In mouse studies, cold and β_{3-} adrenergic stimulation is established as a mechanistic target for BAT activation but has not yet been solidified in human adults [23, 67]. Participants underwent two ^{18}F-FDG PET-CT scans; one scan was performed at a thermoneutral temperature. The second scan was also done at a thermoneutral temperature, except in this trial participants would alternate putting their feet into ice water for five minutes in and five minutes out. Results from the cold induction trial showed a 15x increase in UCP1 activity, significant increases in β_{3-}

adrenergic receptors, significant upregulation of Dio2, and significant enhancement of PGC1-α and PRDM16 [17]. Moreover, three of the subjects underwent tissue biopsies of their supraclavicular fat depots and displayed UCP1 expression at levels 1000x higher than WAT. These studies help solidify the presence of BAT in human adults and exhibit a molecular signature characteristic of BAT.

Together this suggests BAT is metabolically active tissue found in a portion of human adults. Many factors contribute to the likelihood that an individual possesses BAT including age, BMI, sex, use of ß-blockers, and fasting glucose levels [62]. Supraclavicular and paraspinal depots are the largest and most active in those possessing BAT [46] In addition to these primary depots, brown adipose tissue can also be found in smaller amounts in other areas of the body, such as the axillary region, mediastinum, and the perirenal region. However, these secondary depots are less well-defined and have a lower density of brown fat cells compared to the supraclavicular and paraspinal depots [10, 17, 20, 44, 47, 62]. BAT is identified using ^{18}F-FDG PET-CT scans, histological analysis and immunochemical assays [24, 37, 44, 66]. Due to the enhanced metabolic function of BAT compared to WAT, activation and retention are key targets for potential therapeutic interventions.

Beige Adipose Tissue

Beige adipocytes. also known as brite (brown-in-white) or recruitable brown adipocytes, are a distinct type of fat cells that possess thermogenic properties similar to BAT. The molecular signature of beige adipocytes differs greatly from WAT yet shares many similarities with the signature of BAT. Beige adipocytes are largely identified by the chemical markers of UCP1, PGC1-α, PRDM16, Tmem26, CIDEA and Cd137 [10, 13, 37]. Beige adipocytes also differ from BAT since they require stimulation for their molecular presence to be known, while BAT

continually expresses its chemical markers even in dormancy [10, 13, 21, 37, 40]. These markers vary in their degree of expression and do not always correspond with BAT's responses to certain stimuli [10, 37, 43]. It is important to note the distinction in origins between beige and BAT despite their similarities. Beige adipocytes originate within WAT depots as a response to various stimuli, including cold exposure, exercise, and hormonal signaling [37, 43]. Given the previously described discrepancy in specific WAT depot responses to certain stimuli, beige adipocyte depots are more likely to be found in scWAT [10, 13, 21, 28]. Furthermore, beige adipocytes do not have the potential to become brown adipocytes; however, beige can undergo whitening, or 'de-beiging' process with stimulus withdrawal [10, 37]. Evidence of beiging can be seen in as little as 2 weeks of systematic cold exposure and it's reversal takes approximately 5 weeks of exposure to warm temperatures [68]. The presence of beige adipocytes has garnered significant interest due to their potential role in increased energy expenditure and metabolic regulation.

Section Summary

Three distinct adipocytes have been identified in human adults, and their varying functions allow for better understanding of adaptive thermogenesis and it's physiological potential. WAT is characterized by large unilocular lipid droplets and limited metabolic activity [9, 43]. In cases of obesity, there is WAT accumulation and overflow into ectopic sites creating an environment of high inflammation and hormonal resistance [33, 36]. High concentration of WAT is associated with insulin resistance and metabolic dysfunction, conversely high concentrations of BAT is associated with hormonal sensitivity and increased total body energy expenditure [7]. BAT is characterized by multilocular lipid droplets and high metabolic activity. BAT functions as a homeostatic regulator of core temperature, utilizing its unique expression of UCP1 and dense mitochondrial network [7, 17, 69]. Both rodents and human adults possess

BAT, although there are several factors linked with the likelihood of BAT presence including age, BMI, sex, and metabolic health status [16, 17, 45]. Activation of pre-existing BAT is a large area of interest in terms of therapeutic targets for treatment of obesity of obesity related diseases, such as type 2 diabetes mellitus [7, 26, 33]. Another therapeutic target is set on beige adipocytes and the beiging of scWAT. Beige adipocytes are found within scWAT depots and are identified by UCP1 expression upon stimulation [8, 10, 37]. BAT and beige adipocytes possess similar elevated metabolic properties yet are distinct. Beige adipocytes are thought to originate in response to various stimuli from scWAT in a process of beiging [8, 13, 37]. With beiging, scWAT decreases lipid droplet size, increases sympathetic innervation, and expresses metabolic factors like UCP1 [27, 30]. WAT, BAT, and beige adipose tissue are distinct in their characteristics and functions. Moreover, the distinct tissues are potential targets for therapeutic intervention whose mechanistic adaptations with exercise training are discussed further in the present review.

EXERCISE AND ADIPOSE TISSUE

BAT Activation During Exercise

The influence of exercise on BAT activity has produced conflicting results in several research studies and a mechanism for activation has yet to be confirmed. Exercise is a heat-producing action that increases an individual's core temperature, a highly regulated variable [70]. Since BAT acts as a homeostatic regulator of heat production in vivo, it seems counterintuitive that it would become active with exercise. BAT is even thought to potentially be hypoactive during exercise; however, BAT is predominantly controlled via SNS stimulation and corresponding catecholamine release associated with exercise [47, 48, 62]. Exercise-induced release of catecholamines, such as norepinephrine, binds to β3 adrenergic receptors on adipocytes stimulating the adenylate cyclase pathway resulting in the mobilization of glucose and FFAs [67]. Cold-induced and β3 adrenergic receptor stimulation by the SNS, has been shown in rodents to increase UCP1 expression, mitochondrial biogenesis, and glucose uptake in BAT [26, 27, 48, 71]. Alternatively, several other rodent studies found hypoactivity in BAT after five-, six- and nine-week exercise running programs [50, 53, 72, 73]. The role of SNS stimulation of BAT during exercise remains unclear but demonstrates a potential link for increased metabolic activity. It is possible that BAT is hypoactive in its SNS response during exercise to regulate the increasing temperatures that accompany exercise [13, 27].

Another proposed mechanism by which BAT is activated during exercise is through exercise-induced secreted factors independent of SNS stimulation. These secreted factors, known as exerkines, include but are not limited to, IL-6, cardiac natriuretic peptides, and fibroblast growth factor-21 (FGF21). IL-6 is released from working skeletal muscle in response to low glycogen stores thus increasing lipolysis within BAT and stimulating

gluconeogenesis in the liver [13, 51, 69]. Cardiac natriuretic peptides released from cardiac tissue during exercise due to increasing heart rate and the stretching of cardiomyocytes. Acute exercise increases the response of cardiac natriuretic peptides and upregulates lipolysis, as well as UCP1 expression and mitochondrial biogenesis within BAT [40, 74]. FGF-21 is an endocrine factor released in both humans and rodents in response to exercise. FGF-21 is in part responsible for adiponectin release, thus exerting endocrinal and autocrinal regulation over insulin sensitivity, glucose metabolism, and lipolysis [25, 26, 75]. Potential BAT activation during exercise is a multi-faceted mechanism in need of further research.

BAT Activity in Endurance Trained Humans

Physiological responses to exercise vary greatly depending on modality, intensity, and environment, among other factors. Exercise bouts of long duration and low intensity shift towards using FFA as the primary fuel source over glucose [76, 77]. BAT's thermogenic regulation in times of energetic demand, signals for the hydrolysis of triglycerides into glycerol and three FFA, in a process known as lipolysis. The active muscle then uptakes circulating FFA and puts it through ß-oxidation for energy production. Moreover, endurance trained muscle has a greater capacity to oxidize fats [78]. Given this metabolic influence, it appears that aerobic exercise would elicit a greater response in BAT activity.

In humans, a study compared endurance-trained male cyclists with BMI and age-matched sedentary males (each group n=12) [51]. Both groups were exposed to a mild cold stimulus, from cool ice packs, for 2 hours and had ^{18}F-FDG PET-CT scans done. Interestingly, the endurance-trained subjects showed significantly less mean and maximal glucose uptake into BAT compared to their untrained, sedentary counterparts [50, 51]. Another cross-sectional study compared cold-induced BAT activity of aerobically trained female athletes with non-

athletes (athlete n=16, non-athlete n=8) [79]. Between the two groups, there was no difference in age and BMI; however, the athlete group did have a significantly lower core temperature, lower heart rate, and lower total body fat mass. Cold-induced BAT activity of cervical-thoracic depots was measured using ^{18}F-FDG PET-CT scans. There was no significant difference in the number of subjects with detectable BAT between groups. Of those with detectable BAT, the non-athlete group displayed significantly higher BAT volumes than the athlete group. Although trending towards reduced activity in the athlete group, no significant difference in cold-induced glucose uptake was found [79]. Profound limitations were noted by the authors as their sample size was small with 24 females and data collection was conducted throughout the year, creating possible interreference by seasonal ambient temperatures [32, 79]. A third study followed participants through a 2-week, 6 sessions/week, high interval intensity training (HIIT) or moderate intensity continuous training (MICT) training programs [80]. Healthy yet sedentary middle-aged men (n=28) were randomly assigned to HIIT or MICT training. Prior to training the participants were further described as having high BAT (n=6) or low BAT (n=12). At baseline, the high BAT group had greater insulin sensitivity and HDL cholesterol as well as lower total body adiposity and leptin concentration. Following the training program, the high BAT group had significantly decreased insulin-stimulated-glucose uptake whereas the low BAT measured no change in insulin-stimulated glucose uptake. No significant differences were noted between HIIT and MICT modalities [80]. An additional study examined activation of BAT in 34 obese individuals before and after a 16-week combined endurance and resistance exercise training program [81]. Following the combined training intervention, subjects displayed increased BAT activity in cold-induced PET-CT ^{18}F-FDG scans. Another study examined tissue specific insulin-stimulated glucose uptake among 61 men over an 11-week

aerobic training program [82]. Participants were randomly assigned to high dose exercise (600kcal/day), moderate dose exercise (300kcal/day), or a non-exercise control. Results showed aerobic training significantly increased insulin-stimulated glucose uptake in skeletal muscle and no change in uptake in brown adipocytes [82]. These studies suggest that endurance training lowers metabolic activity in brown adipocytes, reinforcing the hypoactivity of BAT with exercise.

Section Summary

Activation of already present BAT with exercise is thought to be stimulated through SNS and SNS-independent mechanisms. SNS stimulated release of catecholamines with exercise is hypothesized to work with the ß-3 adrenergic receptors on adipocytes to upregulate lipolysis. Evidence from rodent and human studies has demonstrated that cold-induced ß-3 adrenergic receptor stimulation activates BAT metabolic activity; however, minimal evidence points towards exercise stimulating these receptors in a similar manner [13, 38, 41, 50, 67]. SNS-independent activation refers to the release of exerkines from various tissues, including skeletal muscle and adipocytes. IL-6, cardiac natriuretic peptides, and FGF-21 are thought to activate pre-existing BAT during exercise by regulating real time glucose metabolism, lipolysis, and insulin sensitivity [21, 39, 54, 61, 62]. Due to the lack of methodology of measuring BAT activity during exercise, these mechanisms of activation remain largely ideas and areas of interest.

Despite the lack of measurement during an exercise bout, several studies have investigated the effects of endurance training on BAT activity in both human and rodent subjects. Human studies have shown mixed results; however, it is likely that short term endurance exercise training actually decreases the metabolic activity of BAT in both healthy

and obese populations [31, 60, 61, 66, 67, 68]. Hypoactivity is marked by a decrease of insulin-stimulated-glucose uptake into already present BAT after short term endurance training [31, 60, 61, 66, 67]. The response of already present BAT, during exercise and with endurance training, requires further investigation to determine its role in overall metabolic activity on both immediate and long-term timelines.

WAT Activation and 'Beiging' in Response to Exercise

Exercise is known to enact changes within WAT, although the mechanism by which these changes occur remains unestablished. WAT is a tissue with plasticity, therefore many stimuli can elicit responses in its activity and morphology [49, 83]. Exercise training results in changes in WAT, including reduction of adiposity and lipid content as well as decreased risk factors for metabolic disease [49]. 'Beiging' refers to a morphological adaptation of WAT to a more metabolically active state, similar to that of BAT. Beiging has collected interest as a potential target in the treatment of obesity with the thought that induction would increase total body energy expenditure. Basal metabolic rate is hypothesized to increase with BAT and beige adipose tissue activity, in addition to energy expenditure from exercise itself contributing to increased total expenditure [8, 40, 47]. In rodents, the presence and inducibility of beige adipocytes via exercise has been well documented ; however, in human studies, there remains controversy over exercise-induced beiging. Despite conflicting study results, changes in adipocyte gene expression, mitochondrial biogenesis, and exerkines action remain areas of interest in determining the influence exercise has on WAT [7, 27, 30, 49, 54]. Depot specific changes between vWAT and scWAT have been noted as having intrinsic differences, so for the purpose of this review scWAT will predominately be discussed.

Mitochondrial biogenesis has been reported to be an exercise-induced reaction in both rodents and humans. Rodent studies with endurance training interventions of varying modalities (swimming, treadmill running, and voluntary wheel running) showed an increase in mitochondrial respiration in scWAT [41, 42, 84, 85]. Activity was determined by the presence of mitochondrial markers PGC1-α and cytochrome-c expression. Some studies done in humans regarding mitochondrial biogenesis within scWAT have shared similar results to those

performed with rodents [86, 87]. One study had 24 obese women (BMI 33.1 ± 2.9 kg/m^2) undergo taurine-supplementation (n=8), taurine-supplementation with a combined resistance and endurance exercise program (n=8) or an exercise program only (n=8) [86]. The taurine groups were supplemented with 3g taurine, 2 hours prior to their workout. Workouts were 3 times a week, for 55 mins a session, over the course of 8 weeks. The training sessions involved 1 of 15 resistance exercises for 30 seconds, alternating with 30 seconds of jogging. Participants worked at 75-90% of their HRmax throughout the training sessions, After 8 weeks of training, taurine supplementation alone did not affect mitochondrial action in scWAT, but the two exercise groups had significant increases in mRNA expression of CIDEA and PRDM-16 [86]. Moreover, the taurine-supplementation and exercise group had additional mRNA expression of UCP1, PGC1-α in scWAT [86]. Conclusions from this study show exercise training upregulates the expression of mitochondrial gene markers in obese women, indicating increased mitochondrial respiration in scWAT [86]. Another study implemented a 4-week intensive exercise program on 60 Caucasian males and females [87]. Subjects were separated based on an OGTT into normal glucose tolerance (n=9 males, n=11 females), impaired glucose tolerance (n=9 males, n=11 females), and type 2 diabetes (n=11 males, n=9 females). The four-week intensive program consisted of 60-minute sessions, 3 times a week. Sessions were broken down into 10-minute warm-up, 20-minutes of running or cycling, 20-minutes of swimming and a 10-minute cool-down. Additionally, subjects performed a VO_{2max} test at the start and end of the four weeks. Results showed VO_{2max} test improvements across all subjects as well as increased PGC1-α expression by approximately 3-fold in scWAT following endurance training [87]. Taken together, these studies indicate that exercise training can elicit increased mRNA expression of chemical markers associated with mitochondrial biogenesis in scWAT.

Exerkines influence on Beiging scWAT

Exerkines are cytokines released by several organs with exercise that may contribute to the beiging of scWAT [58]. It has been proposed that the cross-talk between skeletal muscle myokines and adipocyte adipokines, are the key regulator in exercise induced beiging of scWAT [27]. Exercise induced adaptations in exerkines have been found to upregulate the expression of important chemical markers associated with beiging in scWAT, mainly UCP1 and PGC1-α mRNA [27, 30]. Although several rodent studies demonstrate the action of cross-talk, translation to human has yielded conflicting outcomes [19, 27, 30, 34, 35, 41, 42, 49, 54, 56, 58, 74, 77, 80, 82, 87, 88]. For the purposes of this review, irisin, IL-6 , leptin, and adiponectin will be considered despite several other exerkines potential influence [27].

Irisin is secreted with exercise stimulated gene expression of PGC1-α, previously noted as an important protein in mitochondrial biogenesis and the subsequent beiging of scWAT [25]. PGC1-α stimulates the release of FNDC5 from skeletal muscle upon contraction. Following the release, FNDC5 is cleaved and produces irisin which is released into circulation [25]. In rodents, studies clearly demonstrate exercise-induced increases in plasma irisin concentrations and successive expression of mRNA UCP1 [89, 90]. Evidence from rodent studies also demonstrate increased glucose uptake into skeletal muscle and increased insulin sensitivity [89, 90]. Importantly, in FNDC-5 knockout mice, these adaptations were lost, and in fact metabolic function was decreased without the presence of the irisin precursor [91]. However, the exercise-induced response of irisin in humans has been hotly debated in previous years. Human studies have not shown such conclusive results as those drawn from rodents. For example, a 12-week endurance exercise intervention on 33 non-diabetic subjects (n=13 ‘normal’ weight, n=10 overweight, n=10 obese) found no significant changes in irisin levels in

the ‘normal’ weight or obese groups [59]. However, a significant increase was found in the overweight group [59]. Furthermore, results showed increased genomic expression of beige markers, but no metabolic improvement with insulin resistance. On the other hand, another study found that 15 subjects (n=5 male, n = 10 female) with obesity displayed increases in irisin serum levels following training [92]. Subjects underwent a training protocol in which they biked on a cycle ergometer for 45 minutes at 60-70% of VO_{2Peak} 3x/week for 8 weeks [92]. No additional beiging markers were investigated with this study. Together these studies produce conflicting data regarding irisin responses to exercise training in humans. In humans, in remains unclear whether irisin serum levels change in response to endurance training, but in rodents irisin is associated with beiging of scWAT.

Leptin, adiponectin, and IL-6 are exerkines commonly studied together as they help regulate glucose and lipid metabolism and are impaired with obesity. Leptin is a satiety hormone responsible for long term energy balance and is predominately released as an adipokine from WAT. With obesity leptin resistance can develop, leading to impaired hormonal signaling and disruptions in energy balance [93]. Adiponectin is another adipokine responsible for glucose and lipid metabolism and insulin sensitivity [94]. With exercise training, adiponectin has produced conflicting results with some studies noting a significant increase in circulating adiponectin and some showing no changes or even decreased levels [59, 95, 96]. In rodent studies adiponectin is associated with beiging markers after cold stimulation [95, 96]. Moreover, adiponectin KO mice show resistance for cold-induced beiging markers [94]. Leptin and adiponectin are inversely correlated with one another in relation to adiposity. Higher leptin levels are correlated with BMI while high adiponectin levels are inversely correlated with BMI [96, 97]. Lastly, IL-6 acts as an anti-inflammatory agent released from

skeletal muscle upon contraction and in response to low blood glucose levels [88, 98]. While IL-6 is predominately released from skeletal muscle, it is simultaneously expressed in WAT during exercise [98]. In rodent studies, IL-6 stimulates beige markers UCP1 and PGC1-α, in cases of high cell turnover like such as with burns [99].

In the previously described study by Otero-Diaz, 33 sedentary adults participated in 12-week cycling endurance exercise program (3x/week at 70-80% HR_{max}) [59]. From baseline to post intervention measurements, leptin and adiponectin were reduced significantly ($p<0.054$ and $p<0.001$ respectively) while acute IL-6 were significantly increased ($p<0.001$) following a single exercise bout [59]. Interestingly, there was no significant change in resting circulating IL-6 post intervention, indicating that IL-6 likely plays a transient role in the beiging of scWAT, if contributing at all. Expression of beige markers, UCP1 and TBX1, were significantly increased following exercise intervention; however, there was no metabolic improvement reported [59]. This study suggests that the influence of exerkines on the beiging of scWAT is a part of a greater mechanism with complex interplay between systems. Another study had 110 subjects (n=35 male, n=75 female) undergo a 24-week mixed endurance and resistance exercise program (150min/week and ~80min/week respectively) [58]. The participants were placed in non-exercise control, vigorous intensity (75min/week at 60% HR reserve and 75min/week at 80% HR reserves) or moderate intensity (150min/week at 80% HR reserve) groups. No matter the group, leptin, adiponectin, and IL-6 were not significantly changed in resting plasma levels following the training protocol [58]. Leptin showed a decreasing trend in resting plasma levels as well as significant decreases after acute bouts, in accordance with previous research. Together these studies indicate that cross-talk by leptin, adiponectin and IL-6 are not likely the mechanistic link between exercise and beiging of

scWAT [58]. Despite these negative results, it remains possible that these exerkines are part of a bigger mechanism controlling skeletal muscle and scWAT cross-talk and ultimately beiging of scWAT.

Section Summary

WAT in high amounts is associated with obesity and its comorbidities, exercise is known to alter WAT levels as well as its morphology. WAT is hypothesized to have the capacity to undergo beiging, where in scWAT depots, adipocytes display metabolic activity similar to BAT [8, 39, 50, 70, 72]. Genomic expression, mitochondrial respiration and exerkine expression are thought to culminate in beiging in scWAT. Both human and rodent studies have reported mixed results on the process of beiging. With an endurance exercise training stimulus, mitochondrial respiration is increased as measured by mRNA expression of PGC1-α, PRDM16, CIDEA, and UCP1 [69, 71, 72, 73, 74, 75]. Cross-talk between skeletal muscle and scWAT is hypothesized as being a key link in beiging of scWAT with an exercise stimulus [12, 27, 30, 59, 96]. In rodents, proposed cross-talk has shown promising results, but the translation to clinical studies have not shown the same results [59, 90, 100]. The response of exerkines irisin, adiponectin, and IL-6, as they relate to beiging in humans remains unclear and requires more research. Alternatively, leptin is reduced from circulation, resulting in greater metabolic activity of scWAT, indicative of beiging [55, 90, 100].

CONCLUSION

Adipose tissue is dynamic in its ability for various stimuli to elicit morphological and metabolic adaptations. BAT is metabolically active, dissipating energy in the form of heat through adaptive thermogenesis [10, 17, 46]. Alternatively, WAT is energy storing, holding excess energy in the form of triglycerides. Accumulation of WAT qualifies as obesity with a BMI >29.9 $kg.m^2$ [28, 43]. Beige adipose tissue is inducible and displays metabolic activity within WAT depots [8, 10, 37, 43]. Exercise interventions result in unique adaptations in each of the distinct adipose tissue forms.

Exercise does not appear to activate already present BAT in humans, rather, it appears to become hypoactive. BAT is predominantly in charge of temperature regulation throughout the body, so logically it follows that with heat producing exercise BAT would become hypoactive [35, 47, 86]. Despite this logic, in rodents it appears that BAT is primarily activated through SNS stimulation and SNS independent cytokines [27, 40, 50, 70]. Translation of rodent BAT activation does not appear to correspond with BAT activation in humans. Endurance trained indviduals display significantly less metabolic activity from BAT than their sedentary counterparts in response to SNS stimulation via cold stimulus [51, 79]. Moreover, with an endurance training intervention, individuals displayed either significant decreases or no changes in metabolic activity within BAT [80]. Unsurprisingly, with endurance training intervention, insulin-stimulated-glucose uptake into skeletal muscle was significantly increased, but there was not an uptake difference into BAT [82]. While endurance exercise may not result in activation of BAT, it does not disclude metabolic benefits of posessing BAT.

Exercise induced adaptations to WAT have been established as physiologically beneficial as it applies to increased energy expenditure and incidence of obesity With exercise

WAT decreases in volume, primarily via reduction in lipid droplet size, and deinfluences the several negative metabolic affects associated with obesity [21, 42]. Further adaptations occur with subsequent beiging of scWAT, induced via exercise [8, 10, 13]. With endurance exercise interventions, mitochondrial biogenesis and altered genomic expression result in beiging of scWAT [27, 30]. Following exercise training intervention, induction of beige depots displayed smaller and multilocular lipid droplets as well as greater concentration of mitochondria [44, 86, 87]. Beige adipose tissue appears to have similar training adaptations to skeletal muscle which can be seen with structural and metabolic remodeling [27, 30]. The analogous training adaptations support the idea of adipose tissue and skeltal muscle cross-talk, especially with the tissues following similar adaptive timelines. Studies analyzing potential cross-talk via exerkines have produced conflicting results; however, a lack of standardized measurement methodologies may largely contribute to variance in results [59, 89, 90, 100]. Nonetheless, with exercise training in humans, beiging induces morphological and metabolic changes within scWAT.

It appears paradoxical that exercise training interventions would induce metabolically active tissue while simultaneously displaying hypoactivity of already present metabolic tissue. BAT is shown to be hypoactive with SNS stimulation in trained individuals, while exercise training induces metabolic adaptations of beige adipocytes [26, 71, 82]. Exercise training adaptations improve whole body temperature regulation through blood redistribution to the skin and more effective sweat production [101]. It is not a stretch to think that BAT would respond similarly with training, as core tempertaure fluctuations are ameliorated and thermogenic regulation is needed to a lesser degree with exercise training [101, 102]. In relation to induction of beige adipose tissue from scWAT in response to exercise, it appears

scWAT demonstrates training adaptations similar to skeletal muscles [8, 13]. With exercise training, skeletal muscle undergoes structural and metabolic remodeling, such as mitochondrial biogenesis [103]. As exercise creates an energetic demand for fat oxidation, the large pools of triglycerides contained in WAT are an ideal source for fuel [104]. As a result scWAT undergoes beiging resulting in structural and metabolic adaptations. This implies that beige adipocytes result from use and depletion of a fuel source. Moreover, the metabolic activity follows suit with relative skeletal muscle training adaptations, indicating intertissue cross-talk. Despite the similar thermogenic properties of beige and BAT, it appears the distinct tissues respond inversely and independent from one another following an exercise training intervention. Exercise induced changes to adipose tissue is an area in need of more scientific investigation; howver, it appears that as a target for obesity treatment, induction of beige adipose shows the greatest potential.

CHAPTER 3: METHODS

Research Design

The present research is formatted in accordance with the University of Montana's graduate school professional paper. The aim of this professional paper is to examine published research and draw salient conclusions on thermogenic activity of adipocytes in response to exercise stimuli as a potential therapeutic target for obesity. The applied methodology, described below, and present literature review, culminate as the author's basis for proposed contributions to the field of obesity research.

Methodology and Research Procedure

Peer-reviewed articles accessed online via Google Scholar and PubMed were utilized in the primary research stages. A variety of key words and phrases utilized on the databases include, but were not limited to adipocytes, brown adipose tissue, browning, white adipose tissue, beige adipose tissue, exercise, physical activity, obesity, metabolic disorders, adipocyte activation, brown adipose tissue in humans, transdifferentiation, UCP1, and adipokines. Moreover, grey literature from government agencies helped establish relevant and foundational statistics, demographics as well as prudent health recommendations. Publication date parameters were set to reflect research from 2000 to 2023. The range of utilized papers had two exceptions outside the set parameters, with papers from 1987 and 1998 which were included for their foundational information. The author reviewed and collected literature, using the described methods, from winter of 2023 through summer of 2023. The initial research stages yielded too large a variety of publications, so the author refined their search to reflect more apropos literature. Further selection of relevant literature stemmed primarily from the initial literature search and leads resulting from that initial search, to better serve the aims of the present professional paper.

Additional search criteria eliminated most rodent studies, with few exceptions to help fill gaps in human research and offer potential next steps for future research. Examined studies instead focused on lean individuals and obese individuals. Research focused on lean individuals helped to describe presence and potential benefits of BAT, while studies including obese individuals helped to describe potential mechanisms of thermogenic activity alterations via an exercise stimulus. Ultimately, primary source peer-reviewed papers, applicable reviews, and grey literature, all contributed to the conclusions drawn in the professional paper.

Research Findings

Using the previously described procedures, the research findings and subsequent evidence was used to form the basis of this paper. Key words and phrases were used in various combinations yielding numerous results summarized and shown in Table 1. Table 1 is not an exhaustive list and does not account for titles resulting from multiple search terms.

Key Word and Phrases	Search Results (n)
(brown adipose tissue) AND (exercise)	593
(brown adipose tissue) AND (endurance exercise training)	51
(white adipose tissue) AND (browning/beiging)	46
(skeletal muscle crosstalk) AND (adipose tissue)	3
(exercise) AND (brown adipose tissue activation)	22
(exercise) AND (beige adipocyte)	1
PubMed filters: Full Text, Randomized Control Trial, Clinical Trial	

Table 1. Summary of PubMed search results from key words and phrases applicable to the present paper's topic. This table is based off results taken in August of 2023.

The author used study titles and abstracts to determine whether they were applicable to the scope of this paper and warranted further reading. The studies utilized were categorized based off

species, population, and intervention method. Studies included were aerobic exercise intervention based and directly examined the activation or inducibility of adipose tissue. Moreover, studies that looked at the activation of BAT had inclusion criteria of healthy and active subjects. Studies that examined scWAT and beiging had inclusion criteria of obese subjects in at least one of the study groups. Studies not included were those that contained resistance based interventions or dietary interventions. One study was not included in its entirety due to its lack of accessibility, but access of the abstract allowed it to still be considered [81]. Ultimately, 10 review papers were considered, and 25 primary studies were included. Eleven studies used rodents and 14 studies had adult humans as subjects. Human study interventions included in the present paper were from exercise and cold stimuli (n= 7 and n= 7 respectively). The exercise training intervention studies performed on humans are described in Table 2.

Section Summary

The present professional paper and its conclusions are drawn from published peer reviewed literature accessed through online databases. Studies utilized focused on a mix of populations and fitness levels, an expansion of the original intent of author as there remains a gap in literature to be able to select for particular samples. Kristin I. Stanford and Aaron M. Cypress are critical contributing authors to the area of metabolism as it applies to adipose tissue. Exercise intervention studies focused primarily on endurance exercise training with a few considering acute and resistance interventions. After this search of the literature, the author was able to culminate evidence into conclusions for future research purposes.

Table 2. Description of exercise training interventions including modality, duration, frequency, intensity, and population

Author	Exercise Modality	Intervention Duration	Intervention Frequency	Intensity	Population
Motiani, 2010	HIIT or MICT	2 weeks	6 sessions/ week	High intensity interval training	Healthy yet sedentary middle-aged males (n=28)
Reichkendler, 2013	aerobic exercise	11 weeks	High dose (600kcal/day) Moderate dose (300kcal/day)	50-70% VO_{2peak} (4 sessions/week) and >70% VO_{2peak} (3 sessions/week)	Males (n=61)
Carvahalo, 2021	resistance and endurance exercise	8 weeks	3 sessions/ week for 55mins/session	75-90% Hrmax	Obese Females (n=24)
Ruschke, 2010	running or cycling	4 weeks	3 sessions/ week for 60mins/session	50-70% VO_{2max}	Caucasian Males (n=29) and Females (n=31)
Otero-Diaz, 2018	cycling	12 weeks	3 sessions/week	70-80% HR_{max}	Males and Females (n=33)
Inoue, 2020	cycling	8 weeks	3 sessions/week for 45mins/session	60-70% VO_{2peak}	Males (n=5) and Females (n=10)
Mendez-Gutierrez, 2023	resistance and endurance exercise	24 weeks	150 min/week endurance ~80 min/week resistance	Vigorous = 75 min/ week at 60% HR reserve and 75 min/week at 80% HR reserve Moderate=150min/week at 60% HR reserve	Males (n=35) and Females (n=75)

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