THE EFFECTS OF THE OPTIFAST DIET AND AEROBIC EXERCISE ON INSULIN SENSITIVITY

by

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BACKGROUND: Clinical weight loss (CWL) (5-10%) combined with aerobic exercise improves insulin sensitivity. The OPTIFAST program is a medically supervised diet for weight loss, however, there is minimal data available on the OPTIFAST diet for improvement in insulin sensitivity. METHODS: Twenty-nine sedentary, overweight, and obese adults (Age: 44.8 ± 9.7 yrs; Weight: 95.6 ± 12.8 kg; BMI: 34.2 ± 3.3 kg/m^2) completed a 10-week intervention of supervised aerobic exercise training with an OPTIFAST program to achieve bodyweight loss of ≥7%. The aerobic exercise training consisted of 300 metabolic minutes (MET min) per week and increased by 50 MET min each week until 700 MET min per week was reached. The OPTIFAST diet included meal-replacement products (~800 kcals per day) and weekly classes about nutrition and behavior modification guided by a registered dietician. A 2-hour oral glucose tolerance test (OGTT) was performed, which involved ingestion of 75g of dextrose; serum blood samples were obtained at 0, 30, 60, 90, and 120 minutes and analyzed for glucose and insulin levels. Insulin sensitivity was calculated using the Matsuda Index. A normal score for the Matsuda index is ≥3.

RESULTS: After the intervention, Matsuda Index (3.1, $p<0.001$) and relative VO_{2peak} (2.5 mL/kg/min, $p<0.001$) increased, while weight (-9.1 kg, 9.4%, $p<0.001$), waist circumference (-8.5 cm, $p<0.001$), BMI (-3.2 kg/m^2, $p<0.001$), percent fat mass (-2.1%, $p<0.001$), VAT mass (-0.11 kg, p<0.001), VAT volume (-120.9 cm^3, $p<0.001$), VAT area (-23.2 cm^2, $p<0.001$), and lean mass (-3.5 kg, $p<0.001$) decreased. Changes in insulin sensitivity via the Matsuda Index were associated with changes in percent weight loss (r=-0.59, $p<0.001$), body weight (r=-0.46, $p=0.012$), waist circumference (r=-0.54, $p=0.033$), BMI (r=-0.49, $p=0.007$), VAT mass (r=-0.38, $p=0.041$), VAT volume (r=-0.38, $p=0.040$), and VAT area (r=-0.39, $p=0.039$). No other significant relationships were observed between changes in Matsuda Index with fitness or other body composition measurements (e.g., lean mass and % fat mass). CONCLUSIONS: An OPTIFAST weight loss program combined with aerobic exercise improved insulin sensitivity in overweight and obese adults, with changes in weight and body composition representing important predictors of insulin sensitivity. Future research should investigate the effect of the OPTIFAST diet and aerobic exercise on insulin sensitivity during a weight maintenance period.

The Effects of the OPTIFAST Diet and Aerobic Exercise on Insulin Sensitivity

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List of Abbreviations

1. American Diabetes Association (ADA)
2. Body mass index (BMI)
3. Cardiovascular disease (CVD)
4. Centers for Disease Control (CDC)
5. Dual-energy x-ray absorptiometry (DXA)
6. Electrocardiogram (ECG)
7. Free fatty acids (FFA)
8. Hyperinsulinemic-euglycemic clamp (HEC)
9. Intramyocellular lipids (IMCL)
10. Intravenous glucose tolerance test (IVGTT)
11. National Institute of Health and Nutrition Examinations Survey (NHANES)
12. Oral glucose tolerance test (OGTT)
13. Rating of perceived exertion (RPE)
14. Type II diabetes (T2D)
15. Visceral adipose tissue (VAT)
16. 8-epi-prostaglandin F2ga (PGF2a)

Chapter I: Introduction

Insulin is a hormone that is secreted by beta cells of the pancreas, which regulates the metabolism of carbohydrates, fats, and proteins by promoting the uptake of glucose from the blood into the liver, fat, and skeletal muscle cells. A resistance to insulin results in increased levels of blood glucose. In the state of insulin resistance, cells have an impaired response to insulin. During a state of insulin resistance, the cells of the body do not remove glucose from the bloodstream as effectively with the same amount of insulin, and the beta cells of the pancreas must produce more insulin to remove the same glucose load from the blood. Over time, the progression of insulin resistance can lead to type II diabetes (T2D).[1] Insulin sensitivity describes how sensitive the body is to the effects of insulin. Insulin sensitivity can be improved when mechanisms such as GLUT-4 translocation are improved in the skeletal muscle cells. GLUT-4 translocation is the process by which glucose is removed from the bloodstream when insulin binds to the cell. GLUT-4 translocation can be improved with strategies such as weight loss and exercise. When someone is insulin sensitive it will require less insulin to remove the glucose circulating in the bloodstream compared to an insulin-resistant state[2]. Insulin sensitivity is important because low insulin sensitivity can lead to various health problems such as hyperinsulinemia. Hyperinsulinemia is caused by the body trying to compensate for low sensitivity by producing more insulin. This condition is associated with obesity and T2D.[2]

Obesity negatively impacts insulin sensitivity and increases the risk of T2D, in overweight and obese individuals. With approximately a third of the adult U.S. population being obese, the prevalence of T2D is estimated to be 13.0%.[3] Recent research has estimated that if the obesity epidemic continues at the current rate, then 21% of the U.S. population will have T2D by 2050.[4] The prevalence of obesity in T2D is approximately 86.2% of individuals with T2D who

are overweight or obese.[5] Epidemiological studies have linked T2D to obesity and state that insulin resistance precedes T2D. These studies have found a relationship between insulin resistance and weight gain in regions of the body that are associated with visceral adipose tissue.[6] Visceral adipose tissue is more associated with the abdominal region of the body, and the adipocytes found in these locations are the main mediators for insulin resistance associated with increased adiposity. The adipocytes in visceral adipose tissue are the main mediators of insulin resistance in adipose tissue due to the increased levels of free fatty acids, inflammation, and oxidative stress that are seen in increased obesity.[7] Aerobic exercise and weight loss can be lifestyle modifications that can reduce the impact of adipocytes on insulin sensitivity by reducing visceral adipose tissue.[8]

According to the American Diabetes Association (ADA), aerobic exercise has a major role in improving insulin sensitivity in obese adults at risk for T2D, and that a sedentary lifestyle is associated with insulin resistance.[9] The ADA recommends that adults should break up sedentary time with frequent bouts of aerobic exercise to increase insulin sensitivity. An acute bout of low-intensity aerobic exercise may increase insulin sensitivity for approximately 24 hours, indicating that the duration of exercise is more important than intensity.[8] Aerobic exercise may promote improvements in insulin sensitivity due to the improvements in insulin-mediated glucose uptake and mitochondrial function. Insulin sensitivity can be improved with a 5-7% decrease in body weight, but 11-16% weight loss has been shown to produce greater improvements in insulin sensitivity.[10] The ADA recommends calorie-restricted diets, such as the OPTIFAST diet over other forms of weight loss to improve insulin sensitivity. Very low-calorie diets have been observed to be an effective weight-loss treatment, which results in an immediate improvement in insulin sensitivity.[11]

At the present time, there is little evidence available as to the effect of exercise combined with the OPTIFAST diet, which is a common medically supervised diet program. The OPTIWIN study is a very low-calorie diet intervention that uses the OPTIFAST diet which is very effective in weight loss averaging a 10.5% decrease in body weight. However, there were no glycemic or insulin sensitivity variables reported with this study.[12] There is also little research as to whether aerobic exercise combined with the OPTIFAST diet produces greater changes in insulin sensitivity than other combined diet and exercise interventions. By investigating the effects of a combined diet and exercise intervention utilizing the OPTIFAST diet on insulin sensitivity, this study will contribute to the knowledge needed to effectively design interventions of diet and exercise for improving insulin sensitivity in overweight and obese individuals.

Purpose

The primary purpose of this study is to investigate the impact of weight loss via the OPTIFAST diet and aerobic exercise on insulin sensitivity in a population of overweight and obese individuals. Secondly, this study will look to determine the impact of physiological mediators, such as weight loss, body composition, and cardiorespiratory fitness on insulin sensitivity. For the purpose of this study, data from the Prescribed Exercise to Reduce Recidivism After Weight Loss pilot (PREVAIL-p) study will be utilized.

Hypothesis

First, insulin sensitivity via the Matsuda index will be improved following the combined OPTIFAST diet and aerobic exercise intervention. Secondly, changes in body weight, body composition, and cardiorespiratory fitness will serve as predictors for improvements in insulin sensitivity.

Delimitations

The present study will include the use of individuals that are 30-65 years of age and classified as overweight or class 1 or 2 obese. Participants will be chosen from Greenville, NC, and surrounding areas. This intervention will include the supervised OPTIFAST diet and aerobic exercise. The aerobic exercise will be performed at a moderate intensity (50-65% VO_2max) for the intervention. The duration of this combined intervention will be 10 weeks.

Chapter II: Review of Literature

Obesity and T2D represent a growing public health problem in the United States, and they are closely related to insulin resistance.[13] Obesity is associated with the deposition of adipose tissue such as abdominal and visceral fat into insulin-sensitive tissues such as the muscle and the liver, as well as fat-derived cytokines and adipokines. The progressive loss in insulin sensitivity is a key factor in the development of T2D.[14] Similarly, the progression of insulin resistance is also accompanied by an increase in CVD risk factors and metabolic syndrome. CVD and metabolic syndrome precede the onset of T2D and are considered a major factor behind the emerging diabetes epidemic.[15] According to the National Vital Statistics Reports in 2017 T2D was the seventh leading cause of death in the United States and had a mortality rate of 25.7 per 100,000 with approximately 34.1 million adults aged 18 years or older who have T2D.[16] Therefore, interventions to improve insulin sensitivity in obese adults at risk of T2D such as weight loss and exercise have major clinical implications.

The purpose of the present study is to evaluate the effects of a combined diet-induced weight loss from the OPTIFAST diet and aerobic exercise intervention on insulin sensitivity as measured via the Matsuda index and the potential predictors for changes in insulin sensitivity following the intervention. Following the literature review, we will examine the following topics: the impact of obesity and insulin sensitivity, the Matsuda Index, the effect of weight loss on insulin sensitivity, the effect of exercise on insulin sensitivity, and the combined effect of weight loss and exercise on insulin sensitivity.

Obesity and T2D Risk

According to the Centers for Disease Control (CDC) data, the prevalence of obesity is 30.5% among United States adults.[3] Further, the National Diabetes Statistic Report estimated

that the prevalence of T2D in U.S. adults is 9.0%. The development of insulin resistance from obesity is an important component in the development of T2D.[1] Thus, improving obesity-induced insulin resistance and reducing T2D prevalence represents a major public health need. Many factors influence obesity and T2D as it relates to insulin sensitivity. Some of these factors include insulin resistance, obesity, and T2D as well as the mechanisms of obesity and T2D that influence insulin resistance. Epidemiological studies have demonstrated that obesity is strongly associated with T2D risk.[2-5] In 2011 approximately 34% of U.S. adults were obese with approximately 11% of people aged 20 years or older who have T2D, with T2D prevalence projected to increase to 21% by 2050.[4] The National Health Interview had 780,694 respondents to their survey about obesity and T2D risk. They found that out of their male respondents 7.6% were underweight while 70.3% were obese. The lifetime diabetes risk in adult women increased from 12.2% in underweight to 74.4% in obese women.[17] To determine the prevalence of overweight and obesity among patients with T2D, 2721 patients with T2D had their BMI measured. The results of this study found that 86.2% of the patients were overweight or obese. In this study 52% of the patients were obese and 8.1% of the patients were morbidly obese. The authors of this study concluded that being overweight or obese substantially increases the lifetime risk of T2D.[5]

Insulin resistance also represents a major risk for developing metabolic syndrome. The metabolic syndrome is defined as the clustering of several risk factors that are associated with insulin resistance such as obesity, T2D, and CVD.[18] According to the National Institute of Health and Nutrition Examination Survey (NHANES), the age-adjusted prevalence of the metabolic syndrome is 23.7% in US adults.[18] According to NHANES overweight and obesity affect more than two-thirds of US adults.[19] A cross-sectional study was conducted in 2015 on 689

participants, aged 18-65 years old to establish the prevalence of metabolic syndrome in overweight and obese adults. The results of this study found that the overall prevalence of overweight and obesity was 63.1%. The prevalence of metabolic syndrome in participants with overweight or obesity was 69.4%. The authors concluded that metabolic syndrome is highly prevalent in overweight and obese populations and that the clustering of metabolic syndrome components increased significantly.[20] Several factors in obesity are associated with insulin resistance including increased adiposity, poor insulin-mediated glucose uptake, and decreased mitochondrial function. Epidemiological data link T2D and obesity, state that insulin resistance is a requisite for T2D, and there is a relationship between insulin resistance and weight gain in regions of the body that are associated with visceral adipose tissue.[1-6] Adipocytes in the viscera are the primary type of adipocyte that causes insulin resistance, but all adipocytes impact insulin resistance no matter their location in the body.[7]

Adiposity

Similar to the epidemiological evidence supporting a link between obesity and T2D, from a mechanistic standpoint, adipocytes have a negative impact on insulin sensitivity. In the state of insulin resistance, the signaling in the adipocyte is impaired leading to a decrease in insulin-mediated glucose uptake.[21] Additionally, several factors that are released by adipocytes (e.g., free fatty acids) which cause inflammation and oxidative stress have been reported to influence insulin signaling with an increase in adiposity, especially in the presence of increased visceral fat.[22]

Free fatty acids (FFA) are secreted by the adipose tissue in response to the storage of adipose tissue in the body. In the case of obesity, plasma FFA levels are increased because of the enlarged adipocytes. Once FFAs are elevated, they will inhibit insulin action, which will further

increase the level of FFA in the blood.[22] According to Boden et al., the reason for the associations between FFA and insulin resistance is not entirely clear; it is known that FFA are a major link between obesity, insulin resistance, and T2D.[23] In a study by Boden et al. rat livers were assessed to determine the acute effects of elevated plasma FFA on insulin action. The authors infused rats with a lipid/heparin solution to increase FFA release. Glucose in the rats that did not receive the lipid/heparin infusion was 93 umol•kg^{-1}•min^{-1} and then rose to 155 umol•kg^{-1}•min^{-1} in rats that received the lipid/heparin infusion. The results suggest that increased levels of FFA in response to increased adipose tissue cause insulin resistance and can cause the inflammation of adipose tissue.[23]

A study on obesity and insulin resistance revealed that low-grade inflammation in white adipose tissue has been found in obese patients. This inflammation of white adipose tissue can lead to insulin resistance, impaired glucose tolerance, and T2D. In obesity white adipose tissue can cause increased production and secretion of a wide range of inflammatory molecules that promote insulin resistance.[24] The increased concentration of inflammatory molecules might interfere with insulin signal transduction which could promote insulin resistance. Insulin is an anti-inflammatory hormone, and insulin resistance interferes with the anti-inflammatory effect which in turn promotes inflammation associated with obesity and T2D.[25] Increased levels of adipose tissue cause oxidative stress in sequence with inflammation which further increases insulin resistance.[25,26]

Oxidative stress is defined as the by-products of metabolism that are involved in the regulation of cellular function. Increased production of these by-products can lead to abnormal changes in intracellular signaling and result in inflammation and insulin resistance.[26] Glucose transport is a cascade of events that starts from the interaction of insulin with its receptor and

ends with intracellular glucose metabolism. Increased adipose tissue causes increased oxidative stress which negatively impacts the glucose transport pathway.[27] To investigate the relationship between oxidate stress with obesity and insulin sensitivity Urakawa et al. investigated 8-epi-prostaglandin F2gα (PGF2α) which is a measure of oxidative stress. In this study, the authors measured insulin levels of 14 obese and 17 nonobese. Plasma concentrations of PGF2α were significantly higher in obese men than in nonobese men ($P<0.05$). The authors found that visceral fat and PGF2α were positively correlated ($r=0.387$, $P<0.05$) and that there was a significant positive correlation between plasma levels of PGF2α and the serum levels of insulin in all men ($r=0.487$, $P<0.01$). The findings of this study suggest that obesity is an important factor of enhanced oxidative stress and that this oxidative stress can trigger insulin resistance.[28]

However, obesity is an important determinant of the risk of developing insulin resistance and T2D, abdominal adiposity is the major reason why the risk of developing insulin resistance and T2D is so prevalent.[29] For example, Brochu et al. in postmenopausal women observed that despite these women having a high accumulation of body fat their metabolic profiles were normal. This study evaluated 43 obese postmenopausal women aged 50-71. Since the menopausal transition and the aging process causes an increase in fat mass and a decrease in lean mass, the authors recorded body fat percentage as the measure for obesity rather than BMI. They determined group placement by glucose disposal rate (M value) cut point of 8.0 mg/min*kg during a glucose clamp procedure. Women who were above the cut-point were put into the high insulin sensitivity group (MNO group) and women who were below the cut-point were put in the low insulin sensitivity group (MAO group). The results found that the MNO group had 49.6% less visceral adipose tissue than the MAO group. The results of this study support the evidence that despite the high level of body fat, decreased abdominal adiposity can result in high levels of

insulin sensitivity.[13] The above data suggest that obesity caused by visceral adipose tissue increases the level of FFA in the blood, which is associated with an increase in inflammation and oxidative stress; this can then lead to insulin resistance.[7] Despite the changes in insulin resistance due to visceral adipose tissue, physical activity has been shown to decrease the amount of adipose tissue in the abdominal region of the body due to the redistribution of the body's adipose tissue.[8]

Physical Activity and Insulin Sensitivity

Physical activity has a major role in improving insulin sensitivity in obese adults at risk for T2D. Similar to obesity, a sedentary lifestyle is associated with insulin resistance. In 2016 the American Diabetes Association (ADA) published a position statement that physical activity and exercise should be recommended for all individuals with insulin resistance.[8] Behavior change strategies can be utilized to promote the adoption and maintenance of lifetime physical activity such that all adults should decrease their total amount of sedentary time by breaking up sitting time with frequent bouts of activity if insulin-resistant individuals meet the recommended amount of aerobic exercise.[8] According to the ADA acute bouts of aerobic exercise can increase glucose uptake in the muscle fivefold through insulin-independent mechanisms such as the increase of GLUT-4 translocation. In insulin-independent mechanisms, glucose uptake remains for about 2 hours and in insulin-dependent mechanisms, glucose uptake remains for about 48 hours after exercise if exercise is prolonged.[8] Improvements in insulin action may result for 24 hours following a bout of aerobic exercise lasting approximately 20 minutes. Insulin action in obese, insulin-resistant adults lasts for at least 24 hours following a low-intensity bout of aerobic exercise lasting about 60 minutes.[8] The ADA used the FITT principle of exercise prescriptions to determine their recommendations for promoting insulin sensitivity. Insulin-resistant individuals

should aerobically exercise 3-7 days/week, with no more than two consecutive days without exercise, and engage in resistance exercise a minimum of 2 nonconsecutive days/week, but preferably 3 days/week. Insulin-resistant individuals should engage in moderate to vigorous activity for both aerobic and resistance exercise. Insulin-resistant populations should do prolonged, rhythmic exercise for aerobic exercise. Both aerobic and resistance exercises should be focused on major muscle groups. Insulin-resistant individuals should aerobically exercise for at least 150 min/week at moderate to vigorous intensity and they should do 8-10 exercises with 1-3 sets of 10-15 repetitions for resistance exercise. Exercise may promote an improvement in insulin sensitivity via improved insulin-mediated glucose uptake and mitochondrial function.[8]

Insulin Mediated Glucose Uptake

In skeletal muscle and adipose tissue, insulin promotes membrane trafficking of the glucose transporter GLUT-4 from storage vesicles to the plasma membrane. This facilitation of GLUT-4 from storage to the plasma membrane promotes the uptake of glucose from the bloodstream.[30] According to Laakso et al. in insulin-resistant individuals, glucose uptake was found to be significantly decreased indicating a reduction in responsiveness to insulin.[31] A study by Yeni-Komahian et al. with 490 healthy nondiabetic volunteers to quantitatively measure insulin-mediated glucose uptake by determining the steady-state plasma glucose concentration. Participants consumed a 75-gram glucose load and measured their steady-state plasma glucose after the infusion. The results of this study show that steady-state plasma glucose concentration was more than sixfold higher in the upper 10% of this insulin resistance population compared to the lowest 10% of the population.[32] Also, it was demonstrated that obese subjects demonstrated a decrease in glucose transport (Laakso et al., 1990). In the study by Laasko et al. the authors evaluated six healthy lean men and six healthy obese men to explain the relationship between

insulin's effects to stimulate glucose uptake and the alteration of this relationship in obese individuals. The results of this study showed that in obese subjects the whole-body glucose uptake curve and maximal whole-body glucose uptake were lower than in lean subjects which may be due to abnormalities in the mitochondria's ability to produce ATP ($P<0.01$).[31]

Mitochondrial Dysfunction

Mitochondrial dysfunction can be caused by high levels of intramyocellular lipids (IMCL), a low oxidative capacity (low ATP production). The combination of high IMCLs and a low oxidative capacity are key components in the development of insulin resistance in the skeletal muscle.[33] However, many studies have determined that high IMCL levels do not influence insulin sensitivity directly, but rather represent a marker of increased fatty acid metabolites, which in turn affect insulin sensitivity.[34] Turner and Heilbronn stated that previous studies had found abnormalities in markers of mitochondrial metabolism in various insulin-resistant individuals. Despite the correlation between mitochondrial dysfunction and insulin resistance, some studies had found that they could not decipher whether mitochondrial dysfunction was a primary cause of insulin resistance or a consequence of insulin resistance.[35]

Reduced mitochondrial function may be one of the reasons for insulin resistance in muscle and improving mitochondrial function may be linked to improvement in insulin sensitivity.[43] A four-month combined diet and aerobic exercise intervention were assessed to determine whether mitochondrial function is a component in improving insulin sensitivity in the adult population at risk for T2D. The results show that insulin sensitivity increased by 21% ($P<0.05$) and that there were significant increases in skeletal muscle mitochondrial density ($P<0.01$). The authors concluded that lifestyle modifications such as diet and aerobic exercise may be a key component in the improvement of insulin sensitivity.[43]

Insulin Sensitivity and Weight Loss

Current treatment guidelines recommend weight loss to improve metabolic function such as insulin sensitivity. The ADA recommends that moderate weight loss of 5-7% can improve insulin sensitivity in the obese population.[8] Magkos et al. studied whether 5% weight loss could improve insulin sensitivity and the effects of progressive weight loss greater than 5% on insulin sensitivity. The authors randomized 40 participants to a weight maintenance group or a diet-induced weight-loss group. The results obtained from this study demonstrate that 5% weight loss increases insulin-stimulated glucose uptake by ~25% in people who were obese with some degree of insulin resistance, but 5% weight loss did not improve insulin sensitivity in people with T2D. The authors also found that 11-16% weight loss was associated with a 2-fold increase in insulin sensitivity.[10] A study by Clamp et al. randomized women into four groups; reduced-overweight/obese (n=15), stable low weight (n=19), relapsed-overweight/obese (n=11), and obese stable weight (n=11). The objective of this study was to show that weight loss improves insulin sensitivity. The authors administered a 75-gram OGTT and used the Matsuda index to calculate insulin sensitivity. The results of this study showed that the reduced-overweight group had an insulin sensitivity score of 0.85, the low stable weight group had an insulin sensitivity score of 1.86, the relapsed-overweight/obese group had an insulin sensitivity score of 2.36, and the obese stable weight group had an insulin sensitivity score of 3.10. Based on these results the authors concluded that successful weight loss shows enhanced insulin sensitivity.[36] These findings suggest that even moderate weight loss can lead to enhanced insulin sensitivity, but higher amounts of weight loss led to significant increases in insulin sensitivity. Despite methods of weight loss such as bariatric surgery, the ADA recommends calorie restriction as the best method to induce weight loss associated with insulin sensitivity improvements.[8]

Calorie Restriction and Insulin Sensitivity

It is well established that calorie-induced weight loss improves insulin sensitivity in obese individuals.[37] In obese individuals, it was determined that an 800 kcal or less per day diet was needed to induce improvements in insulin sensitivity in obese and morbidly obese individuals.[38] A study by Svendsen et al. evaluated the effect of a very low-calorie diet (500-600 kcal per day) on insulin metabolism. The authors used 17 overweight women (BMI>28 kg/m^2) and assessed their insulin metabolism by an OGTT and calculated insulin sensitivity by the Matsuda index. During this study, the subjects lost on average 11% of their baseline weight. Based on the Matsuda index calculations insulin sensitivity increased significantly ($P<0.05$). The authors concluded that a very low-calorie diet is an effective weight-loss treatment, and as a result, it can have an immediate effect on insulin sensitivity.[11] A study by Jazet et al. evaluated ten obese patients with T2D, eight women and two men. The participants were told to discontinue all oral blood glucose-lowering medication. The participants underwent a very low-energy diet to lose 50% of their excess body weight. The author's results determined that a very low-energy diet was efficient to improve insulin sensitivity with the loss of 50% of excess body weight. These effects occurred even though the participants had been taken off their glucose-lowering medication (including insulin) and they were still obese at the end of the study. Meal replacement diets have been known to dramatically decrease weight and thus improve insulin sensitivity.[39]

The OPTIFAST Diet

The OPTIFAST diet is a low-calorie diet that is a medically supervised weight loss program that uses meal replacement to lose weight two times more compared to a reduced-calorie food-based diet.[40] The OPTIFAST diet has been known to reduce blood glucose by

improving insulin sensitivity and reducing weight. The OPTIFAST diet includes about five meal replacements per day at about 150-160 kcals per meal replacement averaging 800 kcals per day.[40] A study by Ard et al. aimed to determine the effectiveness of the OPTIFAST program compared with a food-based dietary plan for weight loss. This study used 273 participants that were randomized into a group using the OPTIFAST diet and a group using a food-based dietary plan. At the end of the trial, the OPTIFAST group lost 10.5% compared to 5.5% for the food-based diet. The body fat mass lost was higher in the OPTIFAST group versus the food-based diet group (9.7 kg and 3.5 kg respectively). Since the OPTIFAST group lost more weight and body fat mass it is related to improvements in both blood glucose and insulin sensitivity. Data on the OPTIFAST diet showed significant improvements in weight loss, but limited data is evaluating the effect of the OPTIFAST diet on insulin sensitivity directly. Data from studies utilizing the OPTIFAST diet also does not show how aerobic exercise may improve insulin sensitivity more than with the diet alone.[12]

Exercise and Weight Loss on Insulin Sensitivity

The ADA recommended in 2016 that a structured lifestyle intervention to prevent or delay the onset of T2D in insulin-resistant populations should include at least 150 minutes/week of physical activity and dietary changes resulting in 5-7% weight loss.[8] Physical inactivity and overweight or obesity are common denominators in T2D, prediabetes, and insulin resistance. Lifestyle modifications such as weight loss and physical activity have been seen to prevent T2D and decrease CVD mortality in insulin-resistant populations.[41] A study with 23 obese men and women was investigated to observe the effects of calorie restriction combined with weight loss on insulin sensitivity. The participants were either randomized into a 12-week aerobic exercise group with a normal caloric intake (n=11) or a 12-week aerobic exercise group with a reduced-

calorie diet (n=12). The main finding of this study was that the 12-week aerobic exercise group with a reduced-calorie diet improved insulin sensitivity more than the 12-week aerobic exercise group with a normal caloric intake.[42]

These findings suggest that combined lifestyle modifications of aerobic exercise and calorie restriction are more beneficial to improving insulin sensitivity rather than weight loss and exercise alone. The exact amount of diet and exercise to achieve the greatest improvements is not known. However, the ADA recommends that obese insulin-resistant adults should meet the recommended aerobic activity guidelines of 150 min/week combined with 5-7% weight loss.[8] Future studies should look at the effects of different weight loss methods combined with aerobic exercise to improve insulin sensitivity the most.

Mediators of Insulin Sensitivity

Changes in weight, body composition, and cardiorespiratory fitness may serve as mediators for improvement in insulin sensitivity. Weight gain is associated with the deterioration of metabolic health and the increase of insulin resistance, whereas weight loss improves insulin sensitivity.[36] Body composition plays a large role in insulin sensitivity because BMI and android fat are positively correlated to visceral fat, which increases the metabolic risk for insulin resistance.[44] Current research has shown that unfit individuals have higher odds of having markers for insulin resistance.[45] Clarke et al. states that fitness may be protective against markers of insulin resistance and that the association between weight, body composition, cardiorespiratory fitness, and insulin resistance has not been studied in a large population of healthy adults.[45]

In a study by Houmard et al., insulin action was evaluated in 11 morbidly obese participants who underwent gastric bypass surgery. The intervention produced significant weight

loss from a mean of 142.3 kg before the surgery to a mean of 79.6 kg following the surgery. Fasting insulin was decreased by approximately 84% and insulin sensitivity increased by approximately 360% utilizing the minimal model. This study evaluated morbidly obese patients who underwent gastric bypass instead of class 1 or 2 obese patients who lost weight from a diet intervention; however, it suggests that if there is significant weight loss, significant improvement in insulin sensitivity may occur.[46]

A study by Kang et al. evaluated 287 male and 278 female participants using dual-energy x-ray absorptiometry (DXA) to evaluate the amount of android and gynoid fat area. The researchers also evaluated waist circumference and BMI. They found that as waist circumference, BMI, android, and gynoid fat area increased, visceral adipose tissue increased. They found that android fat was most associated with increased amounts of visceral adipose tissue and that it is a pathogenic fat depot in insulin resistance or metabolic syndrome. Visceral adipose tissue or central obesity is associated with insulin resistance and metabolic syndrome, suggesting that if visceral adipose tissue is decreased the liver and the working muscles may become more insulin sensitive.[44]

According to the ADA exercise-induced improvements in cardiorespiratory fitness is a mechanism by which insulin resistance is improved, but it is not clear whether the change in cardiorespiratory fitness measured by VO_2 peak is a predictor of the individual's ability to manage glucose in the blood.[47] A study by Clarke et al., stated that cardiorespiratory fitness may be protective against insulin resistance, but this has not been studied in a large population of healthy adults. The authors studied 19,263 women and 48,433 men who were enrolled at the Cooper Clinic. The participants had no history of cardiovascular disease or diabetes. After exercise testing, individuals with normal weight and poor fitness had a 2.2-fold higher odds of

insulin resistance in women (p=0.001) and 2.8-fold higher odds in men (p<0.001). The obese group and unfit group had the highest odds ratio for insulin resistance with the women being 20.3 (p<0.001) and 12.9 for unfit, obese men (p<0.001). This data suggests that no matter the gender unfit individuals have a higher risk for insulin resistance. It will take further research to understand the relationship between cardiorespiratory fitness and insulin sensitivity, but this data suggests that insulin sensitivity may improve due to the decrease of insulin resistance.[45]

Weight loss, body composition, and cardiorespiratory fitness may be predictors of insulin sensitivity, but these predictors have not been studied together or how they may impact the overall change in insulin sensitivity following a diet and aerobic exercise program.

The Matsuda Index

The Matsuda index was developed by Matsuda and DeFronzo is a surrogate measure of insulin sensitivity created from the hyperinsulinemic-euglycemic clamp (HEC).[48] The Matsuda index is based on the oral glucose tolerance test (OGTT), which measures the body's response to glucose. OGTT data is obtained after the participant ingests a 75g load of glucose. The participant then has their blood drawn at 0, 30, 60, 90, and 120-time points and is analyzed for plasma glucose concentration. The Matsuda denotes whole-body insulin sensitivity that represents the hepatic and peripheral tissues and considers insulin sensitivity in the basal state and after the ingestion of a glucose load. This index was strongly correlated with the direct measure of insulin sensitivity derived from the HEC (r=0.73, P<0.0001).[48] According to Matsuda and DeFronzo, the Matsuda index based on OGTT samples can effectively be used to define insulin sensitivity in individuals with impaired glucose homeostasis.

The Matsuda index is calculated by taking the square root of (fasting plasma glucose times fasting plasma insulin) times (mean OGTT glucose concentration times mean OGTT

insulin concentration) and then dividing it by 10,000. Matsuda and DeFronzo derived 10,000 to represent a constant that allows one to obtain numbers ranging from 0 to 12. The square-root conversion was used to correct the nonlinear distribution of values. The fasting plasma glucose and insulin were recorded using blood drawn at the basal state before the glucose load was ingested. The mean OGTT glucose and insulin concentrations were estimated to be the difference between the oral glucose load and the glucose remaining in the glucose space as indicated by the difference between the fasting plasma glucose and 2-hour plasma glucose concentrations. The glucose space was calculated as 0.19 times body weight. The estimated glucose uptake was divided by the mean plasma glucose concentration from 0 to 120 minutes to adjust for the influence of different plasma glucose levels. The Matsuda index does not have a normal range for assessing insulin sensitivity, but it describes someone to have insulin resistance with a score of less than or equal to 3.[48]

The HEC is the gold standard for measuring insulin sensitivity. However, a major disadvantage of the technique is that it is time-consuming and expensive in comparison to using OGTT data. This led to various indices of insulin sensitivity including the Matsuda index the use of data from OGTT data.[49] According to Radikova, the Matsuda index was strongly correlated with the HEC. In subjects with normal glucose tolerance, the correlation coefficient was ($r=0.66$ $P<0.0001$), in subjects with impaired glucose tolerance the correlation coefficient, was ($r=0.60$ $P<0.0005$). However, in subjects with T2D the correlation was weaker ($r=0.54$, $P<0.0001$).[50] The Matsuda index may be potentially useful for identifying insulin resistance for weight loss and exercise because of the much greater costs of the HEC.[51]

While the HEC is considered the gold standard for measuring insulin sensitivity, the Matsuda index has been associated with other measures of insulin sensitivity such as the

intravenous glucose tolerance test (IVGTT) which is an estimation of insulin sensitivity and is equivalent to the HEC.[52] The IVGTT has surrogate measures of insulin sensitivity similar to that of the OGTT. The correlation between the HEC and IVGTT was shown to have a correlation coefficient of ($r=0.88$ $P<0.001$) meaning that the correlation of insulin sensitivity from measurements based on IVGTT data is stronger than that of OGTT data. However, the IVGTT is more time-consuming than the OGTT suggesting that OGTT data may be more convenient for study staff and study participants.[52] Even though the Matsuda Index is a reliable method for measuring whole-body insulin sensitivity it does have limitations that may affect studies involving obesity.

Based on a study by Elsedfy et al. obesity was shown to have an impact on the Matsuda index measurements. Out of 23 obese subjects, 21 were found to be insulin resistant. While HOMA-IR identified 7 out of 23 subjects, the Cederholm index identified 4 out of 23 subjects, and FGIR identified 2 out of 23 subjects to be insulin resistant. This data suggests that the Matsuda index overestimated insulin resistance in obese individuals.[53] However, the Matsuda Index was found to be better at identifying insulin sensitivity compared to other indices based on OGTT data.[48]

Summary

While it has been shown that the combined interventions of aerobic exercise and diet-induced weight loss improve insulin sensitivity, one gap in the literature is that the exact methods of diet (OPTIFAST) and the amount of exercise needed to improve insulin sensitivity via the Matsuda index is not known. This is important as OPTIFAST is a popular diet used in many medically supervised weight loss programs. Many studies have investigated improvements in mediators such as exercise duration, weight loss, body composition, and cardiorespiratory fitness

as it related to insulin sensitivity, but it is not known how the OPTIFAST diet will impact these mediators' effect on insulin sensitivity via the Matsuda index. These mediators have been observed to have an impact on specific clinical populations such as T2D patients, adolescents, and adults, but the impact of the OPTIFAST diet on these mediators is not as consistent. It is also not known whether greater insulin resistance at baseline precedes a higher risk for T2D.

Chapter III: Methods

The purpose of this study was to investigate the effects of the OPTIFAST diet and aerobic exercise intervention on the Matsuda index for insulin sensitivity and to assess the changes in physiologic mediators of insulin sensitivity following the completion of the intervention. The data for this study was obtained from the Prescribed Exercise to Reduce Recidivism After Weight Loss pilot (PREVAIL-P) study. The primary purpose of the PREVAIL study was to evaluate the effect of aerobic exercise on weight maintenance following 7-10% weight loss. The PREVAIL methodology was approved by the East Carolina University Institutional Review Board.

Participants

Thirty-nine participants were recruited from the Pitt County, North Carolina area through emails sent to East Carolina University (ECU) employees, newspaper advertisements, Facebook advertisements, from a study website, or weight loss meetings at Vidant Health. Eligibility was based on age, and overweight or obesity class. To be eligible for the study, both men and women were between 30-65 years of age, and overweight (BMI: 25-29.9 kg/m^2) or class 1 (BMI: 30.0-34.9 kg/m^2) or class 2 (BMI: 35.0-39.9 kg/m^2) obese. Exclusion criteria included a diagnosis of either type 1 or type 2 diabetes or a fasting glucose of >125 mg/dL, cardiovascular disease, systolic blood pressure >160 mmHg and or diastolic blood pressure >100 mmHg, pregnancy or plans to become pregnant, taking medications or procedures that could influence weight loss or regain such as hypo/hyperthyroidism or bariatric surgery, other medical conditions that include neuromuscular, gastrointestinal, respiratory, neurological, major psychiatric conditions, no contraindications to exercise, and must have been medication stable for three months prior to the start of the study.

Participant Screening

Participant screening began with a web screen in which the participants answered questions including height and weight, medical history, and study-related questions. The study staff then reviewed the web screen to determine if the participant was preliminarily eligible (e.g., age, BMI, CVD risk) for the study based on inclusion and exclusion criteria. Preliminarily eligible participants would be contacted by study staff to schedule a phone interview where basic information such as height, weight, medical information, exercise habits, and participant feasibility was confirmed from the web screen. The phone interview also included basic information about the study to determine participant eligibility. If staff determined the participant was still eligible, then an orientation was scheduled to further assess eligibility, discuss any important information, and answer any questions. At the orientation, additional information was obtained including medical history questionnaire, study surveys, and potential barriers to completing the study. Also, at this visit height, weight, and resting blood pressure was obtained. Following the orientation, participants returned for a blood draw for a comprehensive metabolic panel blood draw which included hepatic, renal, hematological, endocrine, and metabolic function. The blood panel was reviewed by the study physician for medical clearance. Following the blood draw the participant was scheduled for two clinical visits and completed a calendar for expected availability for exercise sessions. Following the completion of the participant screening process, the participant underwent baseline testing to obtain primary and secondary outcome measurements. Figure 1 shows a flow chart displaying participant screening and visits.

Primary Outcome

The primary outcome of this study was the change in insulin sensitivity via the Matsuda index from baseline to the completion of the combined intervention of the OPTIFAST diet and

aerobic exercise. Insulin sensitivity was determined from the measurements of insulin and glucose from and OGTT using the Matsuda index.[48] All measurements obtained from the OGTT were performed in the morning while being fasted for at least 12 hours. Insulin sensitivity was measured at baseline and the completion of the study (10 weeks) utilizing the Matsuda index.

Secondary Outcomes

The secondary outcome measures that were assessed are glucose, insulin, weight change, body composition, and cardiorespiratory fitness. The rationale for these outcome measures was that they may have an impact on insulin sensitivity. These measures were assessed in two visits at baseline and completion of the study (10 weeks). During the first visit, we assessed weight, body composition (DXA), and cardiorespiratory fitness. During the second visit, we assessed glucose and insulin from an OGTT. Figure 3 displays the list of outcome visits for baseline and follow-up.

Outcome Measure Visit 1

Weight was assessed using a level beam scale (Health O Meter Professional, McCook, IL) rounded to the nearest tenth of a kilogram with the participant only wearing a hospital gown. All weight measurements were taken during a 12-hour fasted state. Body composition was measured using dual-energy x-ray absorptiometry (DXA) (Hologic, Horizon A Marlborough, MA) to calculate total fat mass, lean mass, and visceral fat (APEX version 5.6.0.5). During the DXA scan participants were positioned on the table in a supine position with arms by their side, thumbs facing up, and toes in a pigeon-toed position. While the scan was taking place, the participants were instructed to remain still in this position for the duration of the scan. After completion of the DXA scan, body composition analysis was performed using skeletal landmarks identified by the manufacturer. Waist circumference was also measured using a

Gulick tape measure recorded in centimeters. Cardiorespiratory fitness was measured by the modified Balke protocol (Trackmaster 425, Carefusion, Newton Kansas) with respiratory gases (VO_2, VCO_2) and ventilation measured using a TrueOne 2400 Metabolic Cart (Parvo Medics, Salt Lake City, Utah). During the fitness test a resting heart rate, blood pressure, and electrocardiogram (ECG) were recorded during the test. During the first two minutes of the test, the speed was 2.0 mph with a 0% grade. The speed then increased to 3.0 mph and the grade was increased by 2.5% every two minutes until the end of the test. The study physician reviewed the ECG report from baseline prior to starting the study. Cardiorespiratory fitness was reported in relative VO_2peak (mL/kg/min), absolute VO_2peak (L/min), and estimated METS.

Outcome Measure Visit 2

The OGTT was conducted using a catheter placed in the antecubital vein and remained there throughout the two-hour test. Following a fasting blood sample, participants ingested a 75-gram glucose beverage. Additional blood samples were drawn at 30, 60, 90, and 120 minutes following the glucose beverage. The blood samples were then stored at -80°C until analyzed for insulin and glucose concentrations. Insulin sensitivity was calculated using the Matsuda Index. The Matsuda index was calculated by taking the square root of (fasting plasma glucose times fasting plasma insulin) times (mean OGTT glucose concentration times mean OGTT insulin concentration) and then dividing it by 10,000.[48] The mathematical calculation of the Matsuda index is shown in Figure 2. The OGTT occurred in the morning in a fasted state (12 hours). At follow-up, the OGTT will occur 24 hours following the last exercise session and precede exercise testing to reduce any acute training effect of insulin sensitivity. Serum samples for glucose and insulin were thawed after completion of the study and measured with the Beckman Coulter DxC600i Clinical Diagnostic System (Brea, CA). Samples were measured in duplicate.

Intervention and Training

All assessments were completed at baseline and 10 weeks (after completion of the weight loss intervention). After completion of the baseline assessments, participants were placed on the OPTIFAST diet. The OPTIFAST diet was a medically supervised weight loss program that consists of lifestyle education and total meal replacement products (shakes, bars, soups). The products that the participants received were provided by Vidant Wellness Center in Greenville, NC. While on the OPTIFAST diet participants were instructed to consume five products per day at approximately 160 calories per product estimating 800 kcals per day. The participants were allowed to supplement the OPTIFAST diet with leafy vegetables. The goal of the OPTIFAST program was to achieve a clinically significant weight loss of 7% or greater. During this 10-week study, participants attended lifestyle educational classes at Vidant Wellness Center. The classes were designed to teach participants goal setting, motivation, eating cues and triggers, mindful eating, relaxation techniques, cooking, and managing setbacks with weight loss. During each session, participants were weighed and asked to fill out a food intake questionnaire. The classes that were utilized in this study are shown in Figure 4.

Along with the OPTIFAST diet, participants came to East Carolina University (ECU) 2-3 times per week to complete supervised aerobic exercise training. The aerobic exercise took place on the treadmill and had the participants exercised at 50-75% VO_2max, which was determined from the modified Balke protocol conducted at baseline. At the beginning of the intervention participants were prescribed an intensity at the low end of the 50-75% VO_2max and then gradually increased to the high end of the range towards the end of the 10-week intervention. The amount of exercise that the participants performed was quantified by MET minutes, with the initial level being 300 MET minutes per week. A ramping protocol as shown in Figure 5 was

used to increase the MET minute level, which was increased by 50 MET minutes every week until 700 MET minutes per week was achieved by increasing frequency and duration of the exercise sessions. At the beginning of each week, the participants were weighed on an electronic calibrated scale to the nearest tenth of a kilogram to track progression of weight loss.

During the first session of each week, participants were reminded to drink plenty of water, report any medication changes, or changes in physical activity outside of the study protocol. During each session heart rate was continuously recorded using a Zephyr Bioharness (Medtronic Annapolis, MD). The Zephyr was dampened with water prior to the participant putting it on to ensure conductivity, and it was positioned below the inferior portion of the sternum, with the monitor on the left side of the body. After the heart rate monitor was on, the participant sat for 5 minutes, and then resting heart rate and blood pressure were recorded. After resting vitals were taken the participant completed a 5-minute warmup of light to moderate intensity on the treadmill. Following the warmup participants immediately started their exercise session for a predetermined speed, grade, and duration. During the exercise session, heart rate was kept in a specific range determined by the modified Balke protocol conducted at baseline. Speed and grade were adjusted to keep participants within their heart rate range. Every 10 minutes heart rate, rating of perceived exertion (RPE), speed, and grade was recorded. The time that the exercise started and finished was also recorded. After completion of the exercise session and a 5-minute cooldown on the treadmill participants sat down until their heart rate returned to resting value, and then post-exercise blood pressure was taken and recorded. After post-exercise vitals were recorded; the participant removed their heart rate monitor, and the exercise session was completed. Following the completion of the exercise session, the mean heart rate was calculated using OmniSense Analysis version 5.0 software (Medtronic Annapolis, MD) (warmup

and cooldown were excluded from this analysis). Heart rate, RPE, speed, and grade for every 10 minutes were entered into an Excel spreadsheet to calculate mean heart rate and RPE, total, energy expenditure, MET minutes exercised, total distance walked, and total exercise time. This data was entered into the PREVAIL study database on RedCap (Research Electronic Data Capture).

Statistical Analysis

All baseline participant characteristics were compiled. Continuous data such as weight, body composition, cardiorespiratory fitness, insulin sensitivity, and glucose were displayed as means and standard deviations (SD). All categorical data such as age, sex, race/ethnicity were displayed as percentages. Baseline correlations to the Matsuda index and its subscales were computed using the Pearson correlation. This will include correlations between Matsuda index scores and weight, body composition, cardiorespiratory fitness. The changes from pre to post outcome measures were calculated using Paired T-tests. Pearson correlations were used to assess the associations of change between the Matsuda index and mediators such as body composition, weight, and cardiorespiratory fitness.

Chapter IV: Results

Baseline characteristics of the study participants (N=29) are displayed in Table 1. The sample had a mean (SD) age of 44.8 (9.7) years, mean weight of 95.6 (12.8) kg, and a mean BMI of 34.2 (3.3) kg/m^2. The sample was 79.3% female and 20.7% male. The sample was 55.2% Caucasian, 37.9% African American, 3.4% Asian American, and 3.4% mixed Race. For overall insulin sensitivity, the sample had a baseline mean of 4.7 based on the Matsuda index. Insulin sensitivity was measured using the Matsuda index with insulin sensitive being defined by a score of 3 or better.[48] At baseline the percentage of insulin sensitive participants was 17.2% (5 out of 29), while the percentage of insulin resistant participants was 82.8% (24 out of 29). At baseline insulin sensitivity via the Matsuda index was associated with waist circumference (r=-0.47, p=0.011), baseline insulin (r=-0.72, p<0.001), HOMA-IR (r=-0.74, p<0.001), and estimated METS (r=0.38, p=0.043). However, insulin sensitivity was not associated with weight (r=-0.22, p=0.245), BMI (r=-0.08, p=0.674), fat mass (r=-0.28, p=0.874), VAT mass (r=-0.28, p=0.149), VAT volume (r=-0.28, p=0.148), VAT area (r=-0.27, p=0.151), lean mass (r=-0.23, p=0.241), total cholesterol (r=-0.23, p=0.236), LDL cholesterol (r=-0.28, p=0.236), HDL cholesterol (r=0.32, p=0.093), triglycerides (r=-0.28, p=0.142), baseline glucose (r=-0.23, p=0.233), relative VO_{2peak} (r=0.28, p=0.140), or absolute VO_{2peak} (r=0.09, p=0.628).

Table 2 presents the mean change values in the outcome variables from the weight loss and aerobic exercise program. We observed a significant improvement in insulin sensitivity (3.1 points, p<0.001). After the intervention, 93.1% (27 out of 29) of the participants were insulin sensitive, while 6.9% (2 out of 29) of the participants were insulin resistant. We also observed a significant reduction in body weight with a mean change of -9.1 (3.5) kg, with a percent weight loss of -9.4% (3.2). Additionally, there was a significant reduction in waist circumference, BMI,

fat mass, visceral fat mass, visceral fat volume, visceral fat area, and lean mass (p's<0.05). As shown in Table 2, we observed a significant reduction in total cholesterol, LDL cholesterol, triglycerides, fasting glucose, and insulin ($p<0.05$). However, we observed a slight reduction in HDL cholesterol ($p>0.05$). We also observed a significant reduction in 2-hour glucose and insulin which contributed to the significant reduction in the kinetics for 2-hour glucose and insulin. For cardiorespiratory fitness, we observed a significant increase in relative VO_{2peak} and estimated METS (p's<0.05); however, there was no significant change in absolute VO_{2peak} ($p>0.05$). As shown in Figure 6 insulin sensitivity significantly improved from 4.7 to 7.8 after the completion of the intervention ($p<0.001$); Figure 7 shows a significant reduction in 2-hour glucose from 114.8 to 101.8 ($p=0.032$), and a significant reduction in 2-hour insulin from 72.29 mg/dL to 34.56 mg/dL ($p<0.001$).

Table 3 displays the significant correlations observed between change values in insulin sensitivity, in weight, body composition, cardiometabolic levels, and cardiorespiratory fitness. Figures 9-11 show the scatter plots for the correlations between the Matsuda index and its predictors. Change in insulin sensitivity due to the intervention was associated with percent weight loss and the change in weight ($p<0.05$). Additionally, insulin sensitivity was correlated with changes in waist circumference, BMI, and VAT levels (p's<0.05). Change in insulin sensitivity was not associated with the change in fat mass, lean mass, cholesterol variables, or cardiorespiratory fitness levels. ($p>0.05$).

Chapter V: Discussion

The primary finding of this study was that the combined weight loss intervention of the OPTIFAST diet and aerobic exercise significantly improved insulin sensitivity in overweight and obese adults. Secondly, the improvement of insulin sensitivity as measured by the Matsuda index was associated with changes in weight, BMI, waist circumference, and VAT. To our knowledge, this is the first intervention that has investigated the impact of the OPTIFAST diet and aerobic exercise on insulin sensitivity. This study has clinical implications for using the OPTIFAST diet in obesity management settings for overweight and obese adults who have a heightened risk for T2D.

While the OPTIFAST diet is a medically supervised weight loss program, there are no published studies, to our knowledge, that have evaluated the response of insulin sensitivity following participation in the program. Ard et al. performed the largest study on the OPTIFAST diet to date that significantly improved weight by 12.4% and body composition variables, but they did not report any glycemic or insulin sensitivity variables in their findings. Additionally, while physical activity was unsupervised, potential predictors involving exercising were not evaluated.[12] In the present study, we observed that a combined intervention of the OPTIFAST diet and aerobic exercise resulted in an improvement in weight loss with an average weight loss of 9.4% and robust changes in insulin sensitivity. The intervention produced approximately a 2-fold change in insulin sensitivity, which is similar to Meyer et al.; who also found that after a low-calorie diet and aerobic exercise insulin sensitivity was improved approximately 2-fold after losing 10.2% body weight.[54] At baseline, only 17.2% of the participants were insulin sensitive, which improved to 93.1% at the end of the intervention. This finding is similar to Clamp et al. and Schenk et al. who found that after a diet and exercise program insulin sensitivity was

improved after clinically significant weight loss of ≥7%.[36,55] This finding was similar to Pederson et al. who found that the number of insulin-sensitive patients was increased by approximately 55% after a weight loss and aerobic exercise intervention that achieved 9.9% weight loss.[41] Thus, the results of our intervention with the OPTIFAST diet are parallel with published studies in other settings.

Additionally, other clinically relevant measures of insulin action changed during the study. According to the ADA, 2-hour glucose from an OGTT can be used as a marker for T2D, with T2D having 2-hour glucose greater than 200 mg/dL and prediabetes having 2-hour glucose of 140-199 mg/dL. On average our participants decreased their 2-hour glucose by 13.0 mg/dL; making them less at risk for prediabetes or T2D. Matsuda and DeFronzo found that AUC for both 2-hour glucose and insulin were lower in insulin-sensitive patients compared to patients with insulin resistance.[48] This is similar to our finding that AUC was decreased when participants became more insulin sensitive following the intervention. Pedersen et al. also found that after a weight loss and aerobic exercise intervention glucose and insulin AUC was decreased by 103 and 30.9 respectively.[41]

Another important contribution from our research is the evaluation of relationships of these improvements in insulin sensitivity in an overweight and obese population in response to the intervention of the OPTIFAST diet with aerobic exercise. We observed that changes in weight, waist circumference, BMI, and VAT were highly correlated with insulin sensitivity improvements, which suggests that these factors may represent intervention targets for reducing diabetes risk. These findings are similar to Kang et al., who conducted a longitudinal study on the body composition of 565 patients using DEXA and other anthropometric parameters. They found that patients with insulin resistance according to HOMA-IR had a VAT area of 149.8 cm^2

compared to the patients that were insulin sensitive who had a VAT area of 104.9 cm^2. They concluded that body composition variables that are associated with decreased amounts of VAT (e.g., waist circumference and BMI) are responsible for the improvement of insulin sensitivity.[44] A study by Ryan investigated the impact of aerobic exercise and weight loss on insulin sensitivity during a 6-month intervention while reducing caloric intake by approximately 300 kcals per day. The results showed that after 7% weight loss and aerobic exercise insulin sensitivity was significantly improved by approximately 25%. Ryan found that weight, waist circumference, BMI, and VAT were associated with the improvement in insulin sensitivity.[56] We also observed that cardiorespiratory fitness was not associated with the improvement of insulin sensitivity. This finding was similar to Brennan et al. who measured insulin sensitivity utilizing the hyperinsulinemic-euglycemic clamp while measuring aerobic fitness; they found that cardiorespiratory fitness was not a mediator for improvement in insulin sensitivity.[47] This finding is supported by the ADA and multiple other studies that have also concluded that cardiorespiratory fitness is not an independent predictor of insulin sensitivity.[47,8]

This present study possesses several strengths. First, the sample was diverse, with 37.9% African Americans. This percentage of African Americans is approximately the representation of Greenville, NC. Secondly, all exercise sessions were monitored by study staff with heart rate monitored continuously and RPE recorded every 10 minutes. Exercise amount was tracked and monitored, strictly each week. Additionally, the OPTIFAST diet is a medically supervised diet that was monitored by registered dietitians in a local weight loss center; this enhances the external validity of the study. Clinically significant weight loss was achieved (9.4%), which makes this study generalizable to the overweight/obese BMI class.

This study also possesses several limitations. First, the sample was comprised of 79.3% women which caused an underrepresentation of men. According to the BMI scale, the sample only consisted of 3 individuals in the overweight classification (BMI 25-29.9 kg/m^2), while the remaining 26 participants were in the obesity class I and class 2 range (BMI 30-40 kg/m^2). Therefore, our findings may not be generalizable to individuals of a higher BMI class. Another limitation that this study possessed was age. We could not make conclusions about individuals above the age of 65 since that was one of the exclusion criteria. Additionally, the OPTIAST diet may have caused a decrease in lean mass due to rapid weight loss. The main limitation of this study was that data was gathered from a weight maintenance study, which involved getting participants to clinically significant weight loss in the first phase of the study. Since the data for the present study came from the weight loss phase of the weight maintenance study, there is no control group to serve as a comparison to our results.

In conclusion, a combined intervention of the OPTIFAST diet and aerobic exercise may lead to improvements in insulin sensitivity, and that weight in addition to BMI, waist circumference, and VAT may serve as predictors for improvement in insulin sensitivity. This study was novel, filling the gap of how insulin sensitivity would be influenced by the OPTIFAST diet and aerobic exercise. The clinical implications of this study are that this information could be used to lead to other clinical research studies to use the OPTIFAST diet when assessing weight loss and aerobic exercise interventions on insulin sensitivity. Future studies should investigate the impact of the OPTIFAST diet and aerobic exercise on insulin sensitivity during weight maintenance, the influence of strength training, or age differences on predictors of insulin sensitivity.

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Tables and Figures

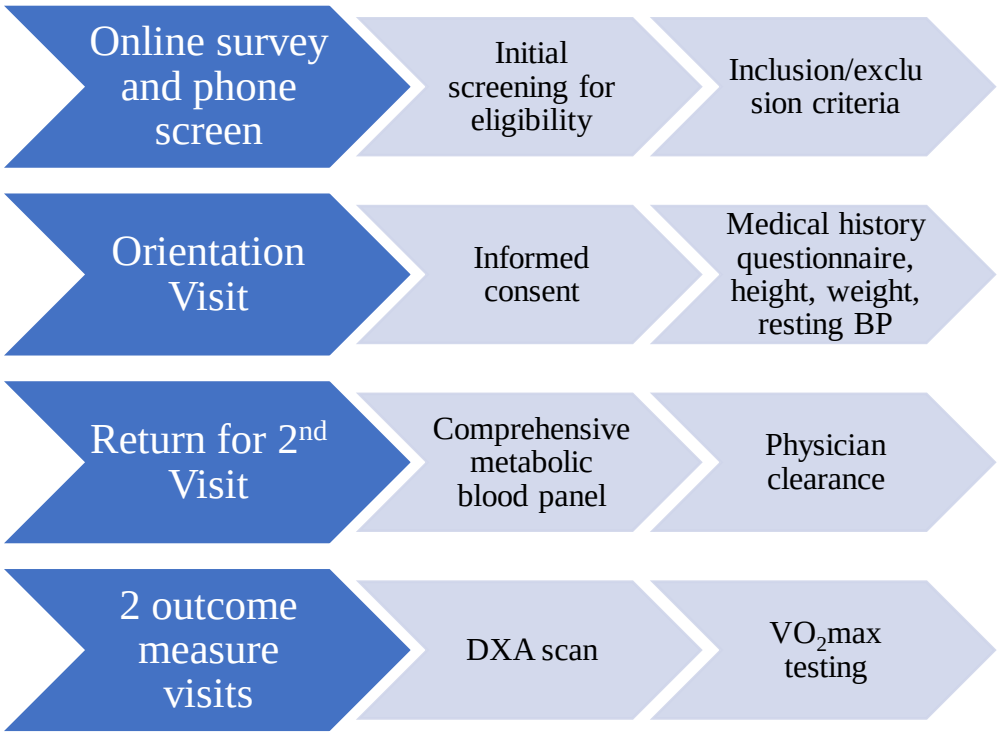


Figure 1: Flow chart displaying participant screening and orientation visits

$$\mathrm{ISI(comp)} = \frac{10000}{\sqrt{g_0 \times i_0 \times \frac{(g_0 \cdot 15 + g_{30} \cdot 30 + g_{60} \cdot 30 + g_{90} \cdot 30 + g_{120} \cdot 15)}{120} \times \frac{(i_0 \cdot 15 + i_{30} \cdot 30 + i_{60} \cdot 30 + i_{90} \cdot 30 + i_{120} \cdot 15)}{120}}}$$

Figure 2: Mathematical calculation of the Matsuda index. 1000 represents a constant. $g_{0,30,60,90,120}$ represent glucose at the different timepoints during the OGTT. $I_{0,30,60,90,120}$ represent insulin at the different timepoints during the OGTT.

Variable	Test/Assessment	Baseline	Follow-Up
Weight (kg)	Calibrated physical beam scale	X	X
Body Composition	DXA	X	X
Cardiometabolic Levels (lipids, insulin, glucose)	Blood draw sent to LabCorp	X	X
Aerobic fitness	Modified Balke treadmill test with metabolic cart	X	X
Insulin Sensitivity	OGTT (Matsuda Index)	X	X

Figure 3: List of outcome visits for baseline and follow up measures

DIDACTIC CONTENT FOR OPTIFAST CLASS SCHEDULE	
WEEK 1	Product Info/Program Logistics/Goal Setting – RD & Behaviorist
WEEK 2	Motivation to Change - Behaviorist
WEEK 3	Importance of Self-Monitoring - RD
WEEK 4	Exercise Update – Exercise Specialist
WEEK 5	Identifying Eating Cues, Triggers, and Eating Style? - RD
WEEK 6	Where are the calories? / Food Label Reading - RD
WEEK 7	Mindful Eating/Emotional Eating - Behaviorists
WEEK 8	Relaxation Techniques – Mind Body Staff
WEEK 9	Eating Out/Special Occasions/Cooking Quick and Lite - RD
WEEK 10	Effects of Stress on Body Weight - Behaviorist

Figure 4: Didactic content for the OPTIFAST lifestyle education classes

	Exercise amount
Week 1	300 MET min.
Week 2	350 MET min.
Week 3	400 MET min
Week 4	450 MET min.
Week 5	500 MET min.
Week 6	550 MET min.
Week 7	600 MET min.
Week 8	650 MET min.
Week 9-10	700 MET min.

Figure 5: Aerobic exercise progression from week 1 to week 10

Variable	
Age (Years)	44.8 (9.7)
Sex, (%)	
Female	79.3 (23.0)
Male	20.7 (6.0)
Race, (%)	
Caucasian	55.2 (16.0)
African American	37.9 (11.0)
Asian American	3.4 (1.0)
Mixed Race	3.4 (1.0)
Weight Loss %	-9.4 (3.2)
Weight, (kg)	95.6 (12.8)
Waist Circumference, (cm)	97.6 (9.7)
BMI, (kg/m^2)	34.2 (3.3)
Fat Mass, (kg)	39.3 (6.0)
Visceral Fat Mass, (kg)	0.66 (0.198)
Visceral Fat Volume, (cm^3)	709.0 (214.09)
Visceral Fat Area, (cm^2)	136.0 (41.05)
Lean Mass, (kg)	54.8 (11.48)
Resting Systolic Blood Pressure, (mmHg)	117.9 (19.1)
Resting Diastolic Blood Pressure, (mmHg)	75.3 (11.7)
Total Cholesterol, (mg/dL)	188.6 (32.5)
Low Density Lipoprotein, (mg/dL)	115.4 (29.6)
High Density Lipoprotein, (mg/dL)	51.9 (12.1)
Triglycerides, (mg/dL)	105.9 (56.3)
Glucose, (mg/dL)	90.1 (7.6)
Insulin, (uIU/mL)	8.8 (4.5)
Insulin Resistant (%)	82.8
Matsuda Index	4.7 (2.5)
HOMA-IR	2.0 (1.1)
Relative VO_{2peak}, (mL/kg/min)	21.8 (4.2)
Absolute VO_{2peak}, (L/min)	2.08 (0.53)
Estimated METs	8.4 (1.1)

Table 1. Baseline participant characteristics. Continuous variables are displayed as mean (SD) and categorical variables are summarized as % (n). BMI: Body Mass Index, VO_{2peak}: Maximal Oxygen Consumption.

Variable	Mean Change	95% CI Lower	95% CI Upper	p-value
Weight, (kg)	-9.1	-10.4	-7.7	<0.001
Waist Circumference, (cm)	-8.5	-10.4	-6.6	<0.001
BMI, (kg/m^2)	-3.2	-3.7	-2.8	<0.001
Fat Mass, (kg)	-5.5	-6.4	-1.4	<0.001
Visceral Fat Mass, (kg)	-0.11	-0.15	-0.08	<0.001
Visceral Fat Volume, (cm^3)	-120.9	-158.6	-83.1	<0.001
Visceral Fat Area, (cm^2)	-23.2	-30.4	-15.9	<0.001
Lean Mass, (kg)	-3.5	-4.4	-2.6	<0.001
Resting Systolic Blood Pressure, (mmHg)	-6.6	-13.4	0.12	0.054
Resting Diastolic Blood Pressure, (mmHg)	-6.7	-11.1	-2.2	0.005
Total Cholesterol, (mg/dL)	-18.4	-25.2	-11.6	<0.001
Low Density Lipoprotein, (mg/dL)	-11.4	-16.7	-6.0	<0.001
High Density Lipoprotein, (mg/dL)	-1.7	-4.1	0.82	0.181
Triglycerides, (mg/dL)	-26.7	-42.8	-10.5	0.002
Glucose, (mg/dL)	-4.5	-6.8	-2.1	<0.001
Insulin, (uIU/mL)	-3.7	-4.9	-2.4	<0.001
Matsuda Index	3.1	1.9	4.3	<0.001
HOMA-IR	-0.9	-1.2	-0.64	<0.001
Relative VO_{2peak}, (mL/kg/min)	2.5	1.9	3.0	<0.001
Absolute VO_{2peak}, (L/min)	0.02	-0.04	0.07	0.546
Estimated METs	0.09	0.53	1.3	<0.001

Table 2: Change scores from baseline to 10-week follow up. Presented as mean change with 95% confidence intervals. BMI: Body Mass Index, VO_{2peak}: Maximal Oxygen Consumption

		Δ Matsuda Index
Weight Loss, (%)	r	**-0.59**
	p	**<0.001**
Δ Weight, (kg)	r	**-0.46**
	p	**0.012**
Δ Waist Circumference, (cm)	r	**-0.54**
	p	**0.003**
Δ BMI, (kg/m^2)	r	**-0.49**
	p	**0.007**
Δ Fat Mass, (kg)	r	-0.36
	p	0.058
Δ VAT Mass, (kg)	r	**-0.38**
	p	**0.041**
Δ VAT Volume, (cm^3)	r	**-0.38**
	p	**0.040**
Δ VAT Area, (cm^2)	r	**-0.39**
	p	**0.039**
Δ Lean Mass, (kg)	r	-0.35
	p	0.063
Δ Total Cholesterol, (mg/dL)	r	0.04
	p	0.818
Δ LDL Cholesterol, (mg/dL)	r	-0.16
	p	0.413
Δ HDL Cholesterol, (mg/dL)	r	0.12
	p	0.526
Δ Triglycerides, (mg/dL)	r	0.27
	p	0.155
Δ Baseline Glucose, (mg/dL)	r	-0.10
	p	0.593
Δ Baseline Insulin, (uIU/mL)	r	-0.02
	p	0.902
Δ HOMA-IR	r	-0.038
	p	0.844
Δ Relative VO_{2peak}, (mL/kg/min)	r	0.08
	p	0.666
Δ Absolute VO_{2peak}, (L/min)	r	-0.26
	p	0.175
Δ Estimated METS	r	-0.16
	p	0.417

Table 3: Pearson correlations between change in insulin sensitivity via the Matsuda index and change in weight, body composition, cardiometabolic, and cardiorespiratory fitness.

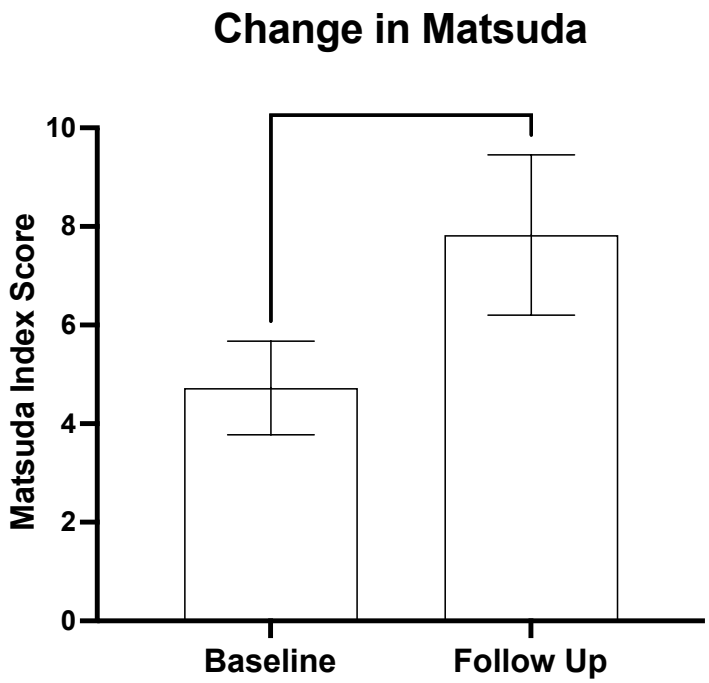


Figure 6: Change in Matsuda index with 95% CI from baseline to follow up

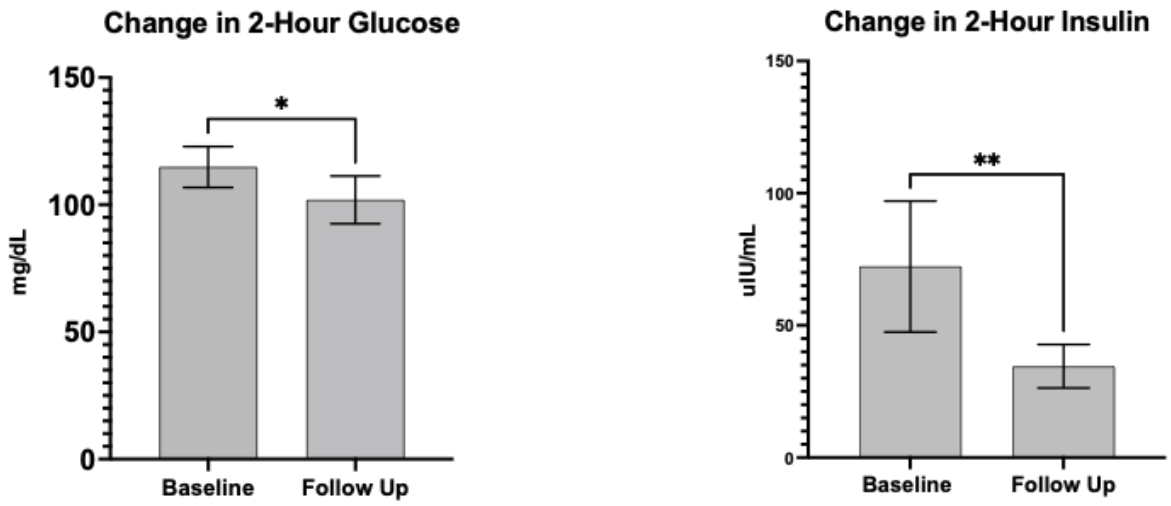


Figure 7: Change in 2-Hour glucose and insulin with 95% CI from baseline to follow up

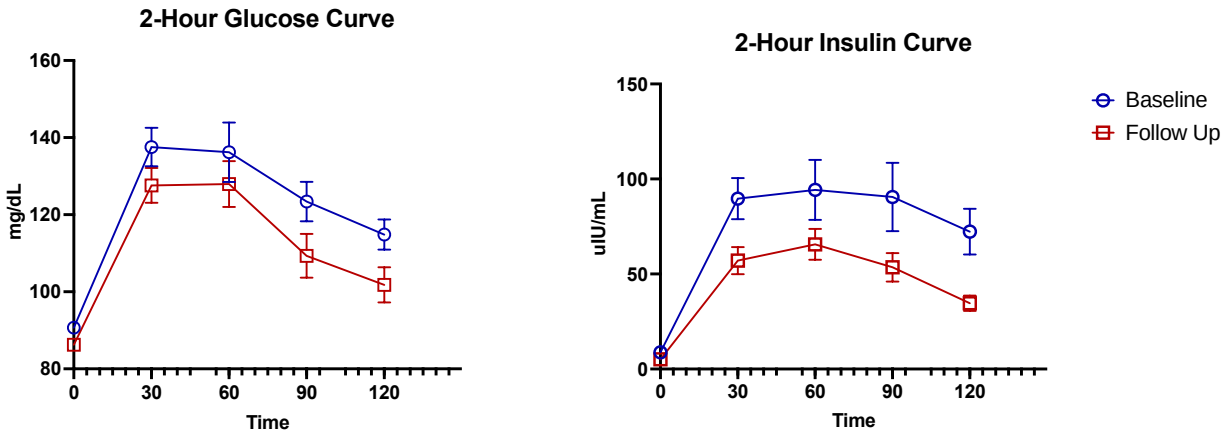


Figure 8: 2-Hour glucose and insulin kinetics with SEM from baseline to follow up representing change over time.

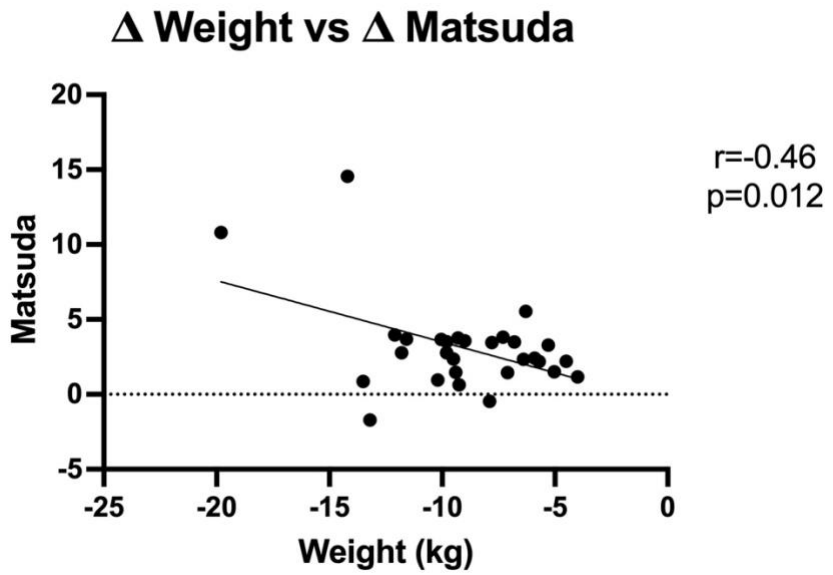


Figure 9: Scatter plots displaying the correlation between change in weight and insulin sensitivity

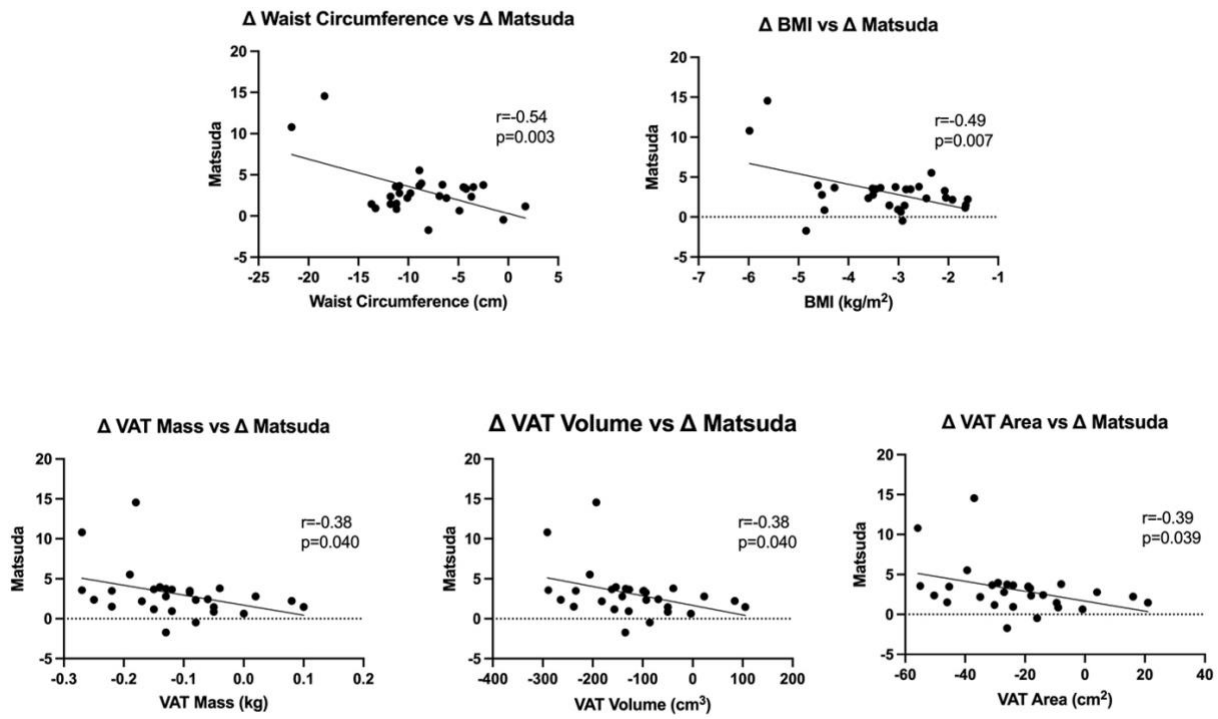


Figure 10: Scatter plots displaying correlations between body composition changes and insulin sensitivity

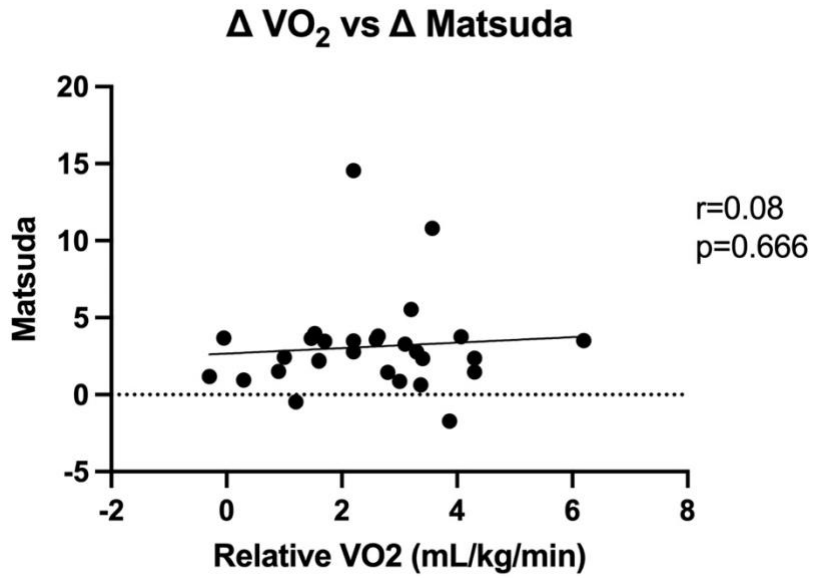


Figure 11: Scatter plot displaying the correlation between change in relative VO_2 peak and insulin sensitivity

Appendix: IRB Approval Letter

EAST CAROLINA UNIVERSITY
University & Medical Center Institutional Review Board
4N-64 Brody Medical Sciences Building· Mail Stop 682
600 Moye Boulevard · Greenville, NC 27834
Office **252-744-2914** · Fax **252-744-2284** ·
rede.ecu.edu/umcirb/

Notification of Continuing Review Approval: Expedited

From: Biomedical IRB
To: Damon Swift
CC:

Anna Huff
Date: 10/26/2020
Re: CR00008847
UMCIRB 18-001904
PREVAIL-P

The continuing review of your expedited study was approved. Approval of the study and any consent form(s) is for the period of 10/19/2020 to 10/18/2021. This research study is eligible for review under expedited category # 8c. The Chairperson (or designee) deemed this study no more than minimal risk.

As the Principal Investigator you are explicitly responsible for the conduct of all aspects of this study and must adhere to all reporting requirements for the study. Your responsibilities include but are not limited to:

1. Ensuring changes to the approved research (including the UMCIRB approved consent document) are only initiated with UMCIRB review and approval except when necessary to eliminate an apparent immediate hazard to the participant. All changes (e.g. a change in procedure, number of participants, personnel, study locations, new recruitment materials, study instruments, etc.) must be prospectively reviewed and approved by the UMCIRB before they are implemented;

2. Ensuring that only valid versions of the UMCIRB approved, date-stamped informed consent document(s) are used for obtaining informed consent (consent documents with the IRB approval date stamp are found under the Documents tab in the ePIRATE study workspace);

3. Promptly reporting to the UMCIRB all unanticipated problems involving risks to participants and others;

4. Applying for continuing review and receive approval of continuation of the study prior to the study's current expiration date. Application for continuing review should be submitted no less than 30 days prior to the expiration date. Lapses in approval (i.e. study expiration) should be avoided to protect the safety and welfare of enrolled participants and liability to the University; and

5. Submission of a final report when the study meets the UMCIRB criteria for closure. Study approval should not be allowed to expire simply because the study is completed, rather the UMCIRB should be formally notified of study completion via the final report process.

The approval includes the following items:

Document	Description
Compensatory Health Beliefs Scale.doc(0.01)	Surveys and Questionnaires
compensatory health beliefs scale.pdf(0.01)	Surveys and Questionnaires
Dr. Swift's letter of intent for IRB review.pdf(0.01)	Additional Items
Food Cravings Questionnaire-State(0.02)	Surveys and Questionnaires
Food frequency Questionnaire(0.01)	Surveys and Questionnaires
Food-Craving Inventory(0.03)	Surveys and Questionnaires
Light Scanner Protocol(0.01)	Study Protocol or Grant Application
PDF of study website(0.01)	Recruitment Documents/Scripts
PREVAIL-EMAIL recruitment (0.01)	Recruitment Documents/Scripts
PREVAIL-P Consent Study 1-Clean(0.04)	Consent Forms
PREVAIL-P-Consent-Study-2-Clean(0.01)	Consent Forms
Retrospective VAS(1).docx(0.01)	Surveys and Questionnaires
SF-36(0.01)	Surveys and Questionnaires
Study 1- Recruitment(0.03)	Recruitment Documents/Scripts
Study 2 Flyer (0.03)	Recruitment Documents/Scripts
Study protocol (0.04)	Study Protocol or Grant Application
Three Factor Eating Questionnaire(0.02)	Surveys and Questionnaires
Web-screener(0.01)	Recruitment Documents/Scripts
Weight Efficacy Life-Style Questionnaire (0.02)	Surveys and Questionnaires
Weight Stigma questionnaire(0.02)	Surveys and Questionnaires

For research studies where a waiver or alteration of HIPAA Authorization has been approved, the IRB states that each of the waiver criteria in 45 CFR 164.512(i)(1)(i)(A) and (2)(i) through (v) have been met. Additionally, the elements of PHI to be collected as described in items 1 and 2 of the Application for Waiver of Authorization have been determined to be the minimal necessary for the specified research.

The Chairperson (or designee) does not have a potential for conflict of interest on this study.

East Carolina University

Hello, Damon Swift

Compare

- 1 - Study Personnel & Funding
  - 1 Study Identification
  - 1.1 Study Staff Roles and Responsibilities
  - 1.2 IRB Researcher Training Records
  - 1.3 Funding Sources
  - *1.31 Industry Sponsor Information*
  - 1.32 Federal Government Sponsored Studies
  - *1.33 Non-Profit Sponsored Studies*
  - *1.34 State or Local Government*
  - *1.35 Other University or College*
  - *1.36 Internally Funded (ECU)*
  - 1.4 Conflict of Interest
  - 1.43 Sponsored Programs & Conflict of Interest
  - 1.5 Study Locations
  - *1.51 Multi-Site Coordination Center*
  - *1.53 External IRB*
- 2 - Study Objectives & Design
  - 2.0 Required Reviews

You Are Here: PREVAIL-P

Reading: UMCIRB 18-001904

Go to forms menu | Print | Help

Study Identification Information

This is the first step in your Human Research Application. You will automatically be guided to the appropriate page views needed to complete your submission. If a question is not applicable to your study, you may state this as your response. Please read the help text located on the right side of the page throughout this application.

1.0 * **Study Name (Short):**
PREVAIL-P

The short study name is limited to 255 characters.

2.0 **Study Name (Long):**
Prescribed Exercise to Reduce Recidivism After Weight Loss

Most other text boxes do not have any limits on number of characters.

3.0 * **Summary of Research in Lay Terms:**
The Prescribed Exercise to Reduce Recidivism After Weight Loss pilot (PREVAIL-P) study will evaluate the effect of aerobic exercise training amount on weight maintenance following after a significant weight loss. Study participants will lose about 7-10% of their body weight and be assigned to exercise at physical activity guidelines or weight maintenance guidelines.

The lay summary should be no more than 400 words and should include the following:
Background/Purpose of Study
Description of Subjects/Participants
Research Methods/Procedures

4.0 * **Principal Investigator:**
Damon Swift

Use the "select" or "add" button to choose from a list of individuals for each applicable role.

5.0 **Faculty Investigator** (Serving as the responsible individual in the oversight of the research study when the PI is a student, resident, fellow or visiting faculty.)

Faculty Investigator IRB Certification Renewal Deadline:

6.0 **Study Coordinator or Contact Individual:**
Anna Huff

7.0 **Contact Individual(s) (if different from Study Coordinator or Principal Investigator):**

Last Name	First Name	Organization	Profile	IRB Certification Renewal Deadline

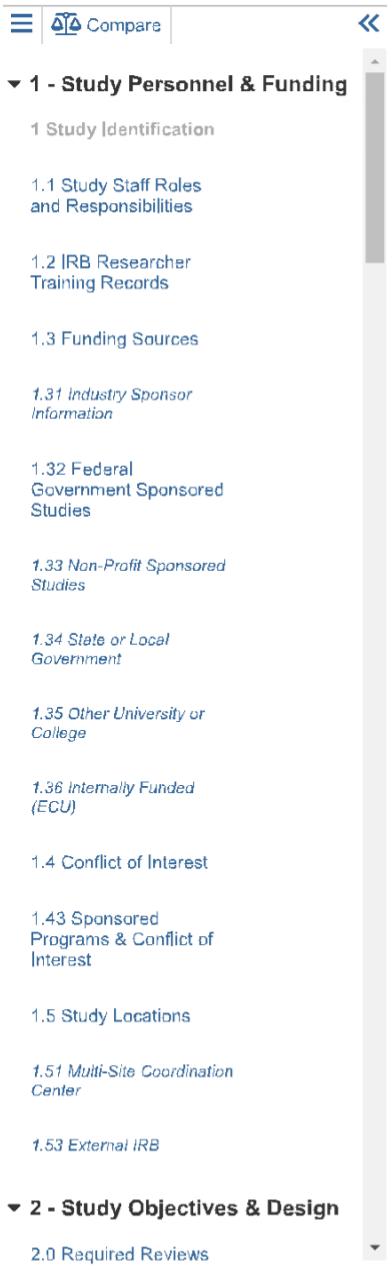
There are no items to display

*People added here **will** be able to **edit** the study.*

Clicking the "Add" button allows you to choose individuals that are already registered within ePIRATE. This function will not add individuals that have not registered in ePIRATE yet.

8.0 **Sub-Investigators:**

Last Name	First Name	Organization	Profile	IRB Certification Renewal Deadline
Anderson	Brianna	Kinesiology, Department of	Brianna Anderson's Profile	3/31/2022



Last Name	First Name	Organization	Profile	IRB Certification Renewal Deadline
Barefoot	Savanna	Kinesiology, Department of	Savanna Barefoot's Profile	9/2023
Bartlett	Allison	Kinesiology, Department of	Allison Bartlett's Profile	7/18/2022
Beyl	Robbie	Other Organization/Institution	Robbie Beyl's Profile	9/20/2021
Boone	Paige	Kinesiology, Department of	Paige Boone's Profile	9/5/2022
Brophy	Patricia	East Carolina Diabetes and Obesity Institute (ECDOI)	Patricia Brophy's Profile	3/20/2022
Brown	Taylor	Kinesiology, Department of	Taylor Brown's Profile	9/21/2021
Carels	Robert	Psychology, Department of	Robert Carels's Profile	7/18/2023
Charlton	Sarah	Kinesiology, Department of	Sarah Charlton's Profile	8/21/2022
Clark	Angela	East Carolina Diabetes and Obesity Institute (ECDOI)	Angela Clark's Profile	7/12/2021
Davis	Emily	Kinesiology, Department of	Emily Davis's Profile	1/12/2022
Dubis	Gabriel	East Carolina Diabetes and Obesity Institute (ECDOI)	Gabriel Dubis's Profile	8/27/2023
Feffer	Andrew	Kinesiology, Department of	Andrew Feffer's Profile	1/17/2022
Garner	Zoe	Kinesiology, Department of	Zoe Garner's Profile	1/13/2023
Gosney	Ryan	Kinesiology, Department of	Ryan Gosney's Profile	1/11/2023
Grammer	Emily	Kinesiology, Department of	Emily Grammer's Profile	7/2/2023
Hearne	Joshua	Kinesiology, Department of	Joshua Hearne's Profile	7/20/2022
Hiller	Kayleigh	Kinesiology, Department of	Kayleigh Hiller's Profile	7/23/2022
Holland	Kyle	Kinesiology, Department of	Kyle Holland's Profile	1/5/2023
Holsinger	Jourdyn	Kinesiology, Department of	Jourdyn Holsinger's Profile	7/15/2021
Houmard	Joseph	Kinesiology, Department of	Joseph Houmard's Profile	5/1/2023
Howell	Harrison	Kinesiology, Department of	Harrison Howell's Profile	8/12/2022