EFFECTS OF SPRINT INTERVAL TRAINING ON INSULIN SENSITIVITY, GLUCOSE TOLERANCE, AND CENTRAL CIRCULATION IN SEDENTARY, OVERWEIGHT WOMEN

by

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(Under the Direction of Kirk J. Cureton)

ABSTRACT

Sprint interval training (SIT) increases muscle oxidative capacity and $\dot{V}O_{2max}$, but whether insulin sensitivity, glucose tolerance and central circulatory capacity are improved is unknown. **PURPOSE:** To examine the effects of SIT on insulin sensitivity, glucose tolerance, $\dot{V}O_{2max}$ and its determinants (Q_{max}, SV_{max}, HR_{max}, $(a\text{-}v)O_2$ $diff_{max}$) in sedentary, overweight women. **METHODS:** Twenty-eight women were randomly assigned to SIT (n = 14; age = 30 ± 7 yr, BMI = 36 ± 6 kg/cm^2; $\dot{V}O_{2max}$ 22 ± 4 ml/kg·min) or control (CON, n = 14; age = 31 ± 6 yr, BMI = 35 ± 6 kg/cm^2; $\dot{V}O_{2max}$ 20 ± 3 ml/kg·min) groups. SIT trained 3 d/wk (4-7, 30-s maximal-effort sprints on a stationary cycle ergometer with 5% body weight as resistance and 4 min active recovery between sprints), while CON remained sedentary (exercise ≤ 1 day/wk). Pre- and post-intervention, a 2-hr oral glucose tolerance test (OGTT) was performed to assess changes in fasting insulin and glucose, area under the curve for insulin (I-AUC) and glucose (G-AUC), the homeostasis model assessment for insulin resistance (logHOMA-IR) and the

insulin sensitivity index (ISI). $\dot{V}O_{2max}$ and HR_{max} were measured during a cycling graded exercise test, and a 20-min ride at 50% $\dot{V}O_{2max}$ was used to estimate maximal cardiac output ($\dot{Q}_{max}$), stroke volume (SV_{max}), and $(a\text{-}v)O_2$ $diff_{max}$ by CO_2-rebreathing. Data were analyzed using a mixed-model, repeated measures ANOVA. **RESULTS:** Changes in fasting glucose (SIT: -6% vs. CON: -1%), I-AUC (SIT: -19% vs. CON: -7%), and G-AUC (SIT: -5% vs. CON: -4%) were not different between SIT and CON ($P > 0.05$). LogHOMA-IR decreased ($P = 0.005$) more in SIT (-25%) than in CON (0%). A greater improvement in fasting insulin (SIT: -22% vs. CON: -4%) and ISI (SIT: 30% vs. CON: 0%) was clinically-meaningful but not significant ($P > 0.05$). SIT increased over CON ($P < .05$) for $\dot{V}O_{2max}$ (12% vs. -1%), $\dot{Q}_{max}$ (10% vs. -6%) and SV_{max} (11% vs. -4%). Changes in HR_{max} and $(a\text{-}v)O_2$ $diff_{max}$ were not different between groups ($P > 0.05$). **CONCLUSION:** SIT improves insulin sensitivity without affecting glucose tolerance and improves $\dot{V}O_{2max}$ by increasing SV_{max} and Q_{max} in sedentary, overweight women.

INDEX WORDS: Sprint Interval Training, Insulin Sensitivity, Glucose Tolerance, $\dot{V}O_{2max}$, Cardiac Output, Stroke Volume

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B.S., Iowa State University, 1999

M.S., California State Polytechnic University, 2003

A Dissertation Submitted to the Graduate Faculty of The University of Georgia in Partial Fulfillment of the Requirements for the Degree

DOCTOR OF PHILOSOPHY

ATHENS, GEORGIA

2009

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May 2009

DEDICATION

I dedicate this to my mom and dad, who taught me how to never give up.

ACKNOWLEDGEMENTS

I would like to acknowledge those who have helped me with this project and those that have helped me during my academic career: Dr. Kirk J. Cureton, Dr. Kevin K. McCully, Dr. Rodney Dishman, and Dr. Stephen Olejnik. I have deep appreciation to my fellow graduate and undergraduate students who assisted me: Jonathan Wingo, Arpit Singhal, Kevin Bigelman, Nate Jenkins, Caroline Schik, Leland Neilsen, Jake Resch, Rebecca Larson, Miley Duvall, Mai Nguyen, Hemal Patel, Anna Gelbrich, and Sahir Ahsan. I could not have gotten through the last 4 years without your help. And finally, to my parents, my family members, and my best friend, Dean, for your unconditional love and support.

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CHAPTER 1

INTRODUCTION

Obesity and a sedentary lifestyle impair health and increase the risk of many chronic diseases. Two of the most prevalent chronic diseases are cardiovascular disease (CVD) and type 2 diabetes, which are the first and seventh leading causes of death in the United States, respectively (23). Adults with type 2 diabetes have 2-4 times the mortality rate from CVD compared to healthy individuals (23), and although incidence of disease used to be greatest in adults over 40 yr of age, health care providers are now diagnosing type 2 diabetes in adolescents and younger adults (23). Therefore, efforts to decrease obesity and increase physical activity have been implemented in the United States to improve the nation's health and decrease the burden of the associated morbidity that results from this epidemic (5, 86).

Maximal aerobic power ($\dot{V}O_{2max}$) is frequently used as an indicator of health (11, 59), as men and women with low $\dot{V}O_{2max}$ values have up to 4 times the age-adjusted, all-cause mortality rate compared to those with high values (11). Traditionally, moderate-intensity aerobic exercise training has been used to increase $\dot{V}O_{2max}$ and skeletal muscle oxidative capacity, which are correlated with improved insulin sensitivity and glucose tolerance (6, 31, 34, 53, 54, 109). However, recent and novel studies using repeated bouts of very intense cycling of short-duration, termed sprint interval training (SIT), also have increased $\dot{V}O_{2max}$ and skeletal muscle oxidative capacity, along with glycogen content, GLUT-4 protein, and carbohydrate utilization in as little as 2-6 wk in healthy,

recreationally-active men and women (19-22, 41, 91). For example, 2 wk of SIT increased citrate synthase activity 38% (22), and 6-7 wk of SIT increased $\dot{V}O_{2max}$ ~7% (21, 67).

Coyle (27) suggested that because the exercise stimulus that promotes mitochondrial biosynthesis probably stimulates other healthy metabolic adaptations in skeletal muscle, SIT may be effective in promoting insulin action and health. A significant relationship exists between citrate synthase activity and insulin sensitivity ($r = 0.71$, $P < 0.001$) and markers of muscle oxidative capacity have been shown to be up to 200% higher in trained individuals than in type 2 diabetics (17). Therefore, if SIT improves skeletal muscle oxidative capacity, it may improve insulin sensitivity, which would be beneficial to individuals who are at risk for type 2 diabetes.

In addition to some potential health outcomes of SIT that are likely to result from muscle adaptations, other health benefits may be linked to cardiovascular adaptations that limit total body $\dot{V}O_{2max}$, such as increased maximal cardiac output ($\dot{Q}_{max}$), stroke volume (SV_{max}), and skeletal muscle oxygen extraction ($(a\text{-}v)O_2\ diff_{max}$) (24, 25, 103). Low- to moderate-intensity aerobic endurance training of long-duration increases $\dot{V}O_{2max}$, $\dot{Q}_{max}$, SV_{max}, and $(a\text{-}v)O_2\ diff_{max}$ (9, 35, 36, 93, 97, 101), but the magnitude of improvement depends on the initial level of training as well as the intensity, frequency and duration of the exercise program. The effects of SIT on the peripheral and/or central circulatory changes responsible for improvements in $\dot{V}O_{2max}$ have not been studied in humans. However, 6-8 wk of SIT in rats (healthy and after induced myocardial infarction, MI) increased $\dot{V}O_{2max}$, $\dot{Q}_{max}$, SV_{max}, and blood flow to working skeletal muscle without increasing $(a\text{-}v)O_2\ diff_{max}$ or HR_{max} (78, 80). In contrast, 8-10 wk of endurance training in

MI rats increased (a-v)O_2 $diff_{max}$ but did not significantly increase $\dot{Q}_{max}$ or SV_{max} (79). Investigators concluded that the lower training intensity may have been insufficient to produce changes in central circulation, and that higher intensities may be necessary for central adaptations in a shorter time frame (79). Based on these findings, SIT may produce positive health outcomes linked to $\dot{V}O_{2max}$ by improving $\dot{Q}_{max}$, $SV_{max,}$ and (a-v)O_2 $diff_{max}$, which would be beneficial to humans at risk for type 2 diabetes and CVD.

In summary, SIT improves muscle oxidative capacity and $\dot{V}O_{2max}$ and therefore may produce favorable health benefits in overweight/obese sedentary individuals by improving insulin sensitivity, glucose tolerance, and central circulatory capacity. Although challenging, the very short exercise bout duration of SIT may be better tolerated in some individuals with low aerobic capacities who are resistant to participation in long-duration exercise. However, it is not established whether SIT would be a suitable training modality for improving insulin sensitivity, glucose tolerance, and $\dot{V}O_{2max}$ and its determinants in individuals at risk for type 2 diabetes and CVD.

Purposes

The primary purpose of this study was to determine if SIT improves insulin sensitivity and glucose tolerance in sedentary, overweight/obese women. The secondary purpose of this study was to determine if SIT improves $\dot{V}O_{2max}$ and its determinants ($\dot{Q}_{max}$, $SV_{max,}$ and (a-v)O_2 $diff_{max}$) that limit $\dot{V}O_{2max}$ and exercise capacity.

Hypotheses

It is hypothesized that:

1. SIT improves insulin sensitivity and glucose tolerance in sedentary, overweight/obese women.

2. SIT improves $\dot{V}O_{2max}$ by increasing $\dot{Q}_{max}$, $SV_{max,}$ and $(a\text{-}v)O_2$ $diff_{max}$ in sedentary, overweight/obese women.

Significance of the Study

Examining the effects of a SIT program in a sedentary, overweight/obese population would offer new insight into the dose-dependent relationship between exercise intensity and improved insulin sensitivity and glucose tolerance. Results of studies in the literature are equivocal in determining the importance of intensity and duration for improved glucose homeostasis in normal and overweight/obese, sedentary individuals. Since a dose-response for exercise intensity and insulin sensitivity and glucose tolerance exists when total exercise volume is equivalent (31, 54), SIT might prove to be a feasible means of exercise training to improve health in those who are resistant to long-duration exercise.

Secondly, if SIT improves $\dot{V}O_{2max}$ via increases in central and peripheral circulation, sedentary individuals may be able to attenuate the development of disease using a high-intensity but short-duration exercise protocol. The feasibility of using a SIT program in the field and its effectiveness in a sedentary population or in those with decreased insulin sensitivity, glucose tolerance and low $\dot{V}O_{2max}$ is unknown because previous SIT interventions have only been performed on healthy, recreationally active, normoglycemic subjects (20, 22, 41, 106).

Finally, the majority of studies published demonstrating positive effects of exercise intensity on insulin sensitivity, glucose tolerance, and central circulatory responses during exercise have been performed on men (20, 24, 25, 44, 74, 83). Studies on women are underrepresented in the literature. Type 2 diabetic women have greater risk for CVD

compared to diabetic men (3), and diabetic women who have had a heart attack have lower survival rates and a poorer quality of life than men (111). Women are also at a greater risk of blindness from diabetes than men (111). When diagnosed before age 40 yr, women tend to live 2 yr less than men diagnosed at the same age (111). In addition, delimiting the study to only women decreases the heterogeneity of the subjects under study and increases the sensitivity of the experimental design to detect a treatment effect if one exists (66).

CHAPTER 2

REVIEW OF THE LITERATURE

Decreased insulin sensitivity and glucose tolerance are common among sedentary, overweight/obese individuals. Risk of developing type 2 diabetes and cardiovascular disease (CVD) increases by 50%, and risk of premature mortality from disease is also increased (111). Much research has been performed on the dose-dependent relationship of exercise intensity and improvements in insulin sensitivity, glucose tolerance, and $\dot{V}O_{2max}$ and its determinants; however, no study until now had examined the effectiveness of very-intense exercise of short-duration on these variables in sedentary, overweight/obese individuals.

The review of current literature pertaining to the effects of exercise training on insulin sensitivity, glucose tolerance, and central circulation is organized as follows: 1) pathophysiology of type 2 diabetes; 2) indicators of insulin action; 3) effects of exercise on insulin sensitivity and glucose tolerance; 4) frequency, intensity, time and type (FITT) and their role in improving glucose homeostasis; 5) metabolic mechanisms of improvement in glucose homeostasis; 6) determinants of $\dot{V}O_{2max}$; 7) effects of exercise training on central and peripheral circulation; and 8) a summary of the findings.

Pathology to Type 2 Diabetes

In a normal metabolic environment, insulin is secreted from pancreatic β-cells during the basal state and in response to a post-prandial rise in blood glucose concentration. Tyrosine kinase insulin receptors located on muscle and adipose cells

respond to insulin signaling via second messenger phosphorylation of protein kinases within the cytoplasm and induce a cascade of events that subsequently cause activation and translocation of insulin-dependent GLUT-4 glucose transporters to the cell membrane (98). GLUT-4 transporters take up glucose from the circulation into the cell to either be used via glycolysis and oxidative phosphorylation, or synthesized into glycogen. Uptake of glucose into muscle and adipose tissue lowers blood glucose concentration, which causes negative feedback signaling on the pancreas and decreases the rate of insulin secretion. Under normal glucose homeostasis, glucose concentrations are <100 mg/dl and <140 mg/dl for the fasting and post-prandial state (after a 2-h oral glucose tolerance test), respectively.

Obesity and a sedentary lifestyle are risk factors for insulin resistance and type 2 diabetes (52, 57). Skeletal muscle is responsible for 75-90% of glucose disposal due to insulin-dependent glucose uptake at rest and insulin-independent, contraction-mediated GLUT-4 translocation to the skeletal muscle cell surface during exercise (74). However, physical inactivity decreases GLUT-4 transporter response to insulin, reducing the skeletal muscle's ability to take up glucose. This causes a need for greater insulin secretion from the pancreas and subsequent hyperinsulinemia (52). With obesity, increased adipocyte volume decreases insulin receptor density and glucose uptake. Failure of the receptor to bind insulin and promote glucose clearance causes a circulating hyperglycemia and triggers the pancreas to release greater amounts of insulin in an attempt to decrease the elevated glucose concentration. Inside the cells, lack of glucose decreases the availability of α-glycerol phosphate, decreasing triglyceride synthesis and subsequently reducing free fatty acid clearance. Lack of glucose in the adipocyte also

stimulates hydrolysis of stored triglycerides and increases circulating free fatty acid concentration. This stimulates hepatic gluconeogenesis and secretion which elevates circulating glucose concentration. Hyperglycemia causes a reactive hyperinsulinemia, and for a period of time, glucose homeostasis is maintained (32). However, the vicious cycle of hepatic gluconeogenesis and output, elevated blood glucose, and continual secretion of large amounts of insulin results in β-cell damage and eventually diminished insulin secretion. The inability of the pancreas to secrete adequate amounts of insulin causes hyperglycemia, which is toxic to tissues, leading to glycation of proteins as well as impairment and/or destruction of the microvasculature and nerves (10). The intolerance to circulating glucose can cause cardiovascular disease, kidney disease, and neuropathy of the eyes (3). Impaired glucose tolerance and insulin resistance will lead to type 2 diabetes if lifestyle interventions including exercise and weight loss are not adopted.

Indicators of Insulin Action

Clinical diagnosis of insulin resistance and type 2 diabetes is usually made through measurement of fasting blood glucose concentration and/or glucose concentration after a 2-h oral glucose tolerance test (OGTT) (1). However, various methods for assessing degrees of glucose homeostasis and whole-body insulin action exist in the literature. They include: 1) the hyperinsulinemic-euglycemic clamp technique, 2) fasting insulin and fasting glucose measurements, 3) the product of the areas under the glucose and insulin response curves, 4) the quantitative insulin sensitivity check index, 5) the homeostasis model assessment for insulin resistance, and 6) the insulin sensitivity index. These seven indicators are used in epidemiologic, randomized-controlled, and clinical studies to estimate relative risks of developing type 2 diabetes and to track the effects of

exercise interventions over time. The quantitative insulin sensitivity check index and insulin sensitivity index are positively related to insulin sensitivity, whereas the remaining indices are negatively related. The homeostasis model assessment for insulin resistance and the quantitative insulin sensitivity check index incorporate fasting glucose and insulin concentration, whereas the area under the curve for insulin and glucose and insulin sensitivity index measure insulin action and glucose tolerance following a standardized (75g glucose solution) oral glucose tolerance test. Each of these indices has its strengths and limitations.

The variability and repeatability of a number of these methods has recently been assessed in 253 clamp studies in 153 lean and obese subjects (70) using the coefficient of variation (CV) and the descriminant ratio (DR) (63). The DR is considered more powerful as it is not dependent on the absolute value of the population mean. It includes the within- and between-subject errors and is a measure of a test's ability to distinguish individuals. The DR allows for statistical comparisons between tests and therefore gives a better estimate of the true underlying correlation between repeated tests (70). Higher values are related to better repeatability, and values given below are for pooled lean and obese subjects.

Hyperinsulinemic-euglycemic clamp technique. The hyperinsulinemic-euglycemic clamp technique developed by DeFronzo et al. (29) provides a quantitative assessment of whole body insulin action and glucose disposal. A continuous intravenous infusion of insulin and a variable rate infusion of glucose are administered to maintain euglycemia, so the exogenous rate of glucose infusion equals glucose uptake rate by all tissues of the body (29). Due to the ability to measure whole body glucose uptake *in vivo,* along with

the high repeatability (CV=0.10, DR=6.4), the hyperinsulinemic-euglycemic clamp technique yields the most accurate evaluation and therefore is considered the "gold-standard" for measuring whole body insulin action. However, the invasiveness (intravenous catheterization, multiple blood sampling), the labor-intensive process (an experienced operator is required to adjust glucose infusion over a 3-6 h period) and cost, limit the practicality for use in the field, in non-hospital laboratories, and in epidemiological studies (70, 82, 90).

Fasting insulin and glucose. Simple blood analyses of plasma, serum, or whole-blood insulin and glucose concentrations after a 12-h fast are commonly used clinically as an indicator of insulin resistance (70) and in cross-sectional and longitudinal research to either compare trained vs. sedentary individuals or exercise training effects, respectively (82). Fasting glucose concentrations are elevated in the impaired glucose tolerant state but not in the insulin resistant state with normal glucose tolerance (90). Fasting insulin, however, is elevated in the insulin resistant state with normal glucose tolerance, indicating that the hyperinsulinemia is maintaining normal glucose concentrations.

Strengths of fasting blood glucose and insulin measures include cost-effectiveness, administrative ease, and good repeatability if carbohydrate ingestion is standardized for at least 2 d prior to measurements and the measure is taken in the fasting state. Limitations include lower repeatability for the insulin measure (CV=0.53, DR=3.0) and increased variation across the range of repeated insulin values (heteroscedasticity) (70). Fasting measures do not give a representation of insulin action or glucose disposal in the post-prandial state.

Area under the glucose and insulin response curves. The oral glucose tolerance test (OGTT) is a procedure developed by Purves (89) and is used for evaluating whole-body glucose tolerance *in vivo*. After a 12-h fast, an individual ingests a 75 g glucose solution and rests while blood measurements are taken throughout a 2 to 3 h time period to determine glycemic and insulinemic response to the glucose load. Area under the curve is calculated using the trapezoidal method (89) to determine concentration of glucose or insulin in plasma over time. Interpretation of the area under the curve is dependent upon the method used to calculate it (incremental, positive incremental, or total area under the curve), because each may yield a different result. The total area under the curve method is typically the preferred method because it is not dependent upon an ever-changing 'baseline' level for glucose and insulin (87). The 2-h OGTT is correlated (r = 0.67) to the hyperinsulinemic-euglycemic clamp (112), indicating that it is an acceptable and less-invasive method for determining glucose and insulin responses to a glucose challenge.

Q*uantitative insulin sensitivity check index (QUICKI).* Developed by Katz et al. (55), the QUICKI method is calculated from fasting glucose and insulin concentrations and incorporates inversion and logarithmic transformations.

$$QUICKI = 1/[\log(\text{insulin, mU/ml}) + \log(\text{glucose, mg/dl})]$$

The QUICKI method is positively associated with insulin sensitivity and is weakly correlated to the hyperinsulinemic-euglycemic clamp method in lean subjects (r = 0.36), moderately in obese subjects (r = 0.73), and strongly correlated (r = 0.94) in type 2 diabetics. The repeatability (CV=0.05, DR=10.2) of the QUICKI measure is superior to the fasting insulin/glucose and the area under the curve methods (70). Since it uses a log

transformation in its calculation, it stabilizes the heteroscedasticity found in the fasting insulin concentration that is used in its calculation.

Homeostasis model assessment for insulin resistance (HOMA-IR). The HOMA-IR is calculated from fasting insulin and glucose measures and is used in epidemiologic and exercise training studies to assess risk of type 2 diabetes and to track effects of training interventions, respectively (14). The non-transformed calculation developed by Matthews et al. (72) is:

$$\text{HOMA-IR} = [\text{insulin, mU/ml}) \times \text{glucose, mmol/dl})]/22.5.$$

The measure exhibits heteroscedasticity inherent to the insulin measurement used in its calculation (70), and untransformed, the HOMA-IR displays a hyperbolic relationship to the hyperinsulinemic-euglycemic clamp. However, normalizing the variability of the insulin measure through log transformation (logHOMA-IR) eliminates the heteroscedasticity. Similar to QUICKI, logHOMA-IR correlates weakly to the hyperinsulinemic-euglycemic clamp method in lean subjects ($r = 0.38$), moderately in obese subjects ($r = 0.72$), and strongly ($r = 0.93$) in type 2 diabetics (70). The logarithmic transformation makes the CV of the logHOMA-IR in pooled lean and obese subjects (CV=0.55) difficult to interpret; however, when comparing it to other methods using the DR (13.4), the logHOMA-IR is considered a superior method to those described above (70).

Insulin sensitivity index. The Matsuda and Fronzo (71) calculation of the insulin sensitivity index (ISI) takes into account basal and post-prandial glucose homeostasis. The calculation is:

$$\text{ISI} = 10{,}000/\sqrt{(I_f \times G_f \times \text{insulin } I_{mean} \times G_{mean})}$$

where I_f is the fasting insulin, G_f is fasting glucose, I_{mean} and G_{mean} are the mean of the insulin and glucose concentrations for the 2-h test, respectively. Recently, Schianca et al. (99) suggested that the insulin sensitivity index (71) is a more efficient and accurate measure in patients with metabolic syndrome than either the HOMA-IR or QUICKI. The ISI, unlike the other methods, incorporates post-load glucose and insulin concentrations into its calculation, and unlike the HOMA-IR and the QUICKI which provide a measure of hepatic insulin sensitivity, the ISI provides an additional estimate of peripheral insulin sensitivity (99). In a cross-sectional study comparing sprint-trained, endurance-trained runners, and a sedentary control group, Niakaris et al. (82) found that the three measures are not interchangeable (82). Therefore, using multiple measures to assess insulin sensitivity appears prudent.

Effects of Acute and Chronic Exercise on Insulin Sensitivity and Glucose Tolerance

Acute exercise. Acute exercise increases glucose disposal and improves insulin sensitivity by two independent processes; 1) through an insulin-independent, contraction-mediated GLUT-4 translocation during exercise, and 2) through increased sensitivity of muscular glucose transport to insulin after exercise (18, 44, 95). A dose-dependent relationship between the intensity of a single bout of exercise and insulin sensitivity exists (18, 44, 95). Acute exercise at 85% HR_{max} improved insulin sensitivity 70-119% in healthy men (18), whereas a lower-intensity bout (~45% $\dot{V}O_{2max}$) increased glucose effectiveness 56% but not insulin sensitivity (95). Similarly, 20 min of cycling at 70% $\dot{V}O_{2max}$ increased glucose disappearance and insulin sensitivity 152% and 225%, respectively, but not significantly at 50% $\dot{V}O_{2max}$ (44).

A distinctive way to examine the transient effects of acute exercise is to observe the effects of detraining on insulin sensitivity. When well-trained subjects undergo 10-14 d of inactivity, plasma insulin response to a glucose load is 67-100% higher than before inactivity, and circulating glucose concentration either does not change or can increase (45, 58). This inactivity-induced hyperinsulinemia with either no change in, or an increase in, glucose concentration indicates a substantial decrease in insulin sensitivity with short-term inactivity (58).

Chronic exercise training. Chronic moderate-to-vigorous physical activity protects against the development of type 2 diabetes (46, 61) by increasing insulin sensitivity and improving glucose tolerance (56). Leisure-time physical activity (kcal/wk) has been shown to decrease the risk of type 2 diabetes 6% for every 500 kcal expended (up to 3500 kcal) independent of obesity, hypertension, and a parental history of diabetes (46). Prevention of type 2 diabetes has been successful in individuals who increased their moderate-to-vigorous, or strenuous and structured leisure-time physical activity (61). In a meta-analysis that compared the effects of 12 aerobic and 2 resistance training interventions on patients with type 2 diabetes, Boule et al. (15) observed that glycosylated hemoglobin (HbA_{1c}), a measure of average blood glucose concentration over a 1-month duration, was lower in the exercise groups compared with the control groups. The effect (Cohen's d) of 4 wk of resistance circuit training or 12 wk of moderate-intensity aerobic cycling on glucose disposal rates (tested with the hyperinsulinemic-euglycemic clamp) or insulin response to a 2-h OGTT in adolescent and adult females ranges between d = 0.57-1.08 (51, 81).

Chronically trained individuals have markedly lower circulating insulin and glucose concentrations compared to untrained individuals (31, 100), primarily due to a greater percentage of muscle mass, mitochondrial density, oxidative enzymatic activity, and GLUT-4 protein concentration and translocation (50, 52). Glucose disposal rate has been shown to increase 11% (during a high-insulin infusion hyperinsulinemic-euglycemic clamp), skeletal muscle glycogen 24%, and GLUT-4 concentration 60% after 12 wk of cycling between 50% and 75% heart rate reserve in older glucose-intolerant men and women (50). Glucose disposal rate in sedentary type 2 diabetics increased 48% after 4-6 wk of resistance training (51), and muscle glycogen content increased 66% after 5 mo of resistance training (68).

Acute vs. chronic. Increased insulin sensitivity and response to a glucose load may partially be due to a residual effect of acute exercise, and not entirely to an adaptation to chronic exercise training. A single exercise session can increase insulin sensitivity and glucose tolerance in healthy participants (12) and improve insulin sensitivity in non-diabetic obese individuals (75) immediately following exercise. Even 24 h after exercise, glucose tolerance can be improved up to 35% (12). When acute and chronic exercise are examined in a single study, improvements after both are observed. After a single exercise session and 6 wk of progressive training on a stair-climbing machine, Perseghin et al. (85) observed a 69% (acute) and 102% (chronic) improvement in non-oxidative glucose disposal in insulin-resistant offspring of type 2 diabetics. Detraining studies show that plasma insulin response to an OGTT and circulating glucose concentration are increased after 10-14 d of inactivity in trained individuals (45, 58). However, insulin and glucose responses to an OGTT decreased to pre-detraining levels immediately after return to

exercise (45), indicating a substantial decrease in insulin sensitivity with short-term inactivity (58). In contrast, individuals who engage in chronic exercise training have higher muscle oxidative activity, GLUT-4 protein content, and markedly lower circulating insulin and glucose concentrations compared to untrained individuals, suggesting that chronic exercise training does contribute to improved insulin sensitivity (100).

In summary, improved insulin sensitivity and glucose tolerance likely result from a combination of both acute and chronic exercise. Both show benefits in normoglycemic and insulin resistant individuals by reducing the onset of type 2 diabetes (52). Physical activity also improves insulin sensitivity and glucose tolerance in type 2 diabetics helping to decrease risk of associated diseases (15).

Frequency, Intensity, Time, and Type (FITT) and Their Role in Improving Glucose Homeostasis

The exercise prescription required for greatest improvement in insulin sensitivity and glucose tolerance is not known (48). Current recommendations given by the American Diabetes Association for type 2 diabetics are to exercise at intensities between 50 and 70% of $\dot{V}O_{2max}$ (4), whereas the American College of Sports Medicine recommends exercise intensities between 50–85% $\dot{V}O_{2max}$ as a guideline for the general population (2). It is difficult to determine whether the frequency, intensity, duration, or mode of exercise is the most influential on improvements in metabolic function and insulin sensitivity, because the components are interactive. The Surgeon General's recommendation of moderate to vigorous physical activity 30 min per day most days of the week is considered the appropriate combination of stimuli for general health

promotion. However, this public health message does not take into account the insulin resistant individual nor does it give specific recommendations as to the degree of importance each FITT component may have on improving metabolic function.

Frequency. Frequency of exercise refers to the number of times per week one engages in physical exercise or exercise training. Frequency of physical activity and decreased incidence of type 2 diabetes is dose-dependent (60) and is positively related to insulin sensitivity in men and women independent of culture (73). The Pima Indians, who have the greatest incidence of type 2 diabetes in the United States, have lower age-adjusted prevalence of type 2 diabetes when categorized in the middle and top tiers for frequency of leisure-time physical activity than those in the lowest frequency of physical activity (60). Men from the Physician's Health Study who were initially free of type 2 diabetes and engaged in physical activity at least 1 time/wk had a 33% decreased risk (age- and BMI-adjusted) of diabetes incidence 5yr later than inactive men (69). Also, the relative risk of diabetes incidence decreased with increasing frequency of physical activity (0.77, 0.62 and 0.58 for 1/wk, 2-4/wk, and $\geq$5/wk, respectively), and the association was strongest among overweight men. In summary, the more frequent the exercise, the greater the metabolic benefits and protective effects against developing type 2 diabetes.

Intensity. The intensity of an exercise bout is usually expressed as percentage of maximal oxygen uptake ($\%\dot{V}O_{2max}$), percentage of maximal heart rate (HR_{max}) or as metabolic equivalents (METS). Higher-intensity training is dose-dependent for effects on insulin sensitivity and glucose tolerance (49, 69), which suggests that higher intensities elicit a greater protective effect against development of type 2 diabetes. Relative risk of

developing type 2 diabetes decreased linearly (relative risk=1.0, 0.95, 0.0.80, 0.81, 0.74) with increasing intensity (<0.5, 0.6-2.0, 2.1-3.8, 3.9-9.9, ≥10 METS, respectively) in an 8-y follow-up on female nurses free of diabetes at baseline (49). In randomized controlled trials, higher-intensity exercise has been shown to improve insulin sensitivity and glucose tolerance more than moderate-intensity exercise when holding total energy expenditure constant (31, 54). Glucose utilization has been shown to improve linearly (8%, 16% and 21%) with increasing exercise intensity (50%, 65% and 80% VO_2peak, respectively), after a 9 mo training intervention in women with a wide range of insulin sensitivities (31). Insulin action and subsequent glucose uptake in obese men improved after exercising at 70% $\dot{V}O_{2max}$, but not at 50% $\dot{V}O_{2max}$ when total energy expenditure was held constant (54).

In summary, when holding volume and duration of exercise constant, higher-intensity training appears to be more effective and/or more time-efficient than either moderate- or low-intensity training at improving insulin sensitivity and glucose tolerance.

Time/Duration. Duration of exercise is defined as the amount of time it takes to complete a single exercise bout. Studies evaluating effects of different intensities and total volume of training suggest that longer exercise durations elicit greater improvements in insulin sensitivity when holding intensity of exercise constant (48). A longitudinal study revealed that for each MET-hour (the product of number of hours spent on an activity by the MET value of the activity) spent in physical activity, a linear reduction in risk of developing type 2 diabetes was observed (49). A training study revealed that 6 mo of jogging for ~170 min at 65-80% VO_2peak (20 miles/wk) improved insulin sensitivity (85%) in overweight/obese individuals greater than ~115 min of

jogging (12 miles/wk) at the same intensity (45%) (48). The authors in this study suggested that the duration of the exercise bout, regardless of weekly training volume (12 vs. 20 miles/wk), was the primary determinant for improvement in insulin sensitivity. However, more energy was expended jogging 20 miles/wk (2000 kcal/wk) than was expended for the 12 miles/wk (1200 kcal/wk), confounding the interpretation of the results.

When duration and intensity of exercise were adjusted (142.5 min at 50% $\dot{V}O_{2max}$ vs. 89.6 min at 75% $\dot{V}O_{2max}$) to keep total energy expenditure constant (3,116 kJ), acute changes in insulin sensitivity were shown to be no different between intensities in type 2 diabetic women (16). It should be noted that walking at 50% $\dot{V}O_{2max}$ took 53 min longer to attain the same acute effect in insulin action than walking at 75% $\dot{V}O_{2max}$. A 24-wk cycle training study revealed that improvements in insulin sensitivity were no different between 44 min at 60% $\dot{V}O_{2max}$ and 33 min at 80% $\dot{V}O_{2max}$ when volume was held constant (84). Therefore, when energy expenditure is equivalent, higher-intensity exercise is more time-efficient for producing the same metabolic benefits in less time.

*Exercise Type. R*esistance training, aerobic steady-state endurance training, and interval training all improve insulin sensitivity and glucose tolerance. Both normoglycemic and type 2 diabetics benefit from isometric or dynamic resistance exercise training through improvement in insulin action (51, 68). Glucose disposal rate is increased >48% in type 2 diabetics after 6 wk of resistance training (51), and muscle glycogen content is increased 32% in normoglycemic men after 5 mo of heavy resistance training (68). Fasting plasma insulin levels and insulin AUC were decreased, and glucose disposal rates during a hyperinsulinemic-euglycemic clamp increased after 16 wk of

strength training in older men (74). Therefore, resistance exercise training improves insulin sensitivity and glucose tolerance in normoglycemic and type 2 diabetic individuals.

Aerobic steady-state endurance training typically involves running, cycling, swimming, etc., for ≥30 min at sub-$\dot{V}O_{2max}$ intensities. Endurance training improves insulin sensitivity and prevents onset of type 2 diabetes (15, 26, 31, 38, 39, 52, 61, 73, 84) through improving whole body glucose metabolism (30, 56) and glucose tolerance (50, 94). Risk of developing type 2 diabetes in men and women with impaired glucose tolerance decreased by ~64% after 12 mo of strenuous, structured physical activity (61), and fasting insulin and logHOMA-IR decreased by ~2.46 uU/L and -0.55, respectively after 24 wk of exercising at 60-80% $\dot{V}O_{2max}$ (84). Even 7 d of exercise training at 75% VO2max increases whole body insulin action 2-fold and GLUT-4 protein 3-fold in men and women regardless of age (26).

Whether resistance training or aerobic steady-state endurance training is superior is difficult to determine due to lack of equating for total energy expenditure in comparison studies. Resistance training and aerobic training have been shown to reduce glucose and insulin AUC in men with a wide range of insulin sensitivities/type 2 diabetes, however there were no significant differences between the two training modalities (105). Total energy expenditure for either modality was not calculated and equating exercise volume based on energy expenditure was not considered.

Interval training. Interval training involves repeated bouts of exercise lasting between 5 s and 4 min, interspersed with active or inactive rest periods of variable duration (62). Sprint interval training (SIT) entails exercising at explosive intensities

(175-300% $\dot{V}O_{2max}$) that can only be sustained for 30-60 s. No studies to date have examined the effects of SIT on insulin sensitivity and glucose tolerance in humans; however SIT improves insulin sensitivity and glucose tolerance in rats through increasing GLUT-4 protein content and maximal glucose transport activity in skeletal muscle (107).

There is concern that all-out maximal intensity may be too intense to sustain for individuals beginning a training program, especially if they are not clinically healthy (106). However, preliminary data indicated that a SIT protocol identical to Burgomaster et al. (22) was tolerable in sedentary to low-active, college-aged men and women. Therefore, SIT training may be an effective approach to increasing insulin sensitivity and glucose tolerance. If the dose-dependent relationship holds, it may be a more effective and time efficient method than exercise at moderate to high intensities. To postulate why SIT in particular may be more effective in increasing insulin sensitivity and reducing glucose intolerance with less exercise time and volume than low-, moderate-, or even high-intensity steady state exercise, it is helpful to understand the underlying mechanisms. In the following section, metabolic adaptations that have been observed with high- and supramaximal-intensity exercise are discussed. These mechanisms provide a rationale for using SIT to improve insulin sensitivity and glucose tolerance in sedentary, pre-diabetic women.

Metabolic Mechanisms of Improvement in Glucose Homeostasis with SIT

In humans, the insulin resistance of skeletal muscle in obese individuals is associated with reduced activity of muscle oxidative enzymes and a disproportionate increase in activity of glycolytic enzymes (104). Activities of phosphofructokinase, glyceraldehye phosphate dehydrogenase, and hexokinase are highest in type 2 diabetics,

followed by obese and lean non-diabetics, whereas the maximum activity of citrate synthase and cytochrome-*c* oxidase is lowest in type 2 diabetics (104). The relation between the ratio of muscle glycolytic:oxidative enzyme activities and insulin sensitivity in individuals with type 2 diabetes suggests that a deregulation between mitochondrial oxidative capacity and capacity for glycolysis is an important component of insulin resistance (104). Improving oxidative enzymatic activity within the muscle has been shown to improve insulin sensitivity and glucose tolerance (48, 84). Therefore, training with SIT may be an efficient way to improve metabolic control via increased mitochondrial density, enzymatic activity, and increased GLUT-4 protein synthesis and translocation.

The duration of the sprint determines whether oxidative enzyme and/or glycolytic enzyme activity is increased (33, 64, 65). A minimum bout of 15 s is needed to activate the oxidative pathways in type I and type II skeletal muscle fibers; for example, 5-s bouts increase the glycolytic enzyme phosphofructokinase, but do not increase citrate synthase (64). Conversely, 30-s bouts increase citrate synthase and succinate dehydrogenase as well as phosphofructokinase activity after training (67). The rest periods (or "intervals"), also are important to the adaptation seen in sprint interval training, as recovery periods of 4 min between exercise bouts have been shown to be favorable for complete resynthesis of the creatine phosphate pool in facilitating subsequent high-intensity exercise (40). Also, multiple bouts are needed to reduce phosphocreatine and glycolysis utilization and increase the capacity for oxidative phosphorylation via increases in mitochondrial density, oxidative enzyme activities, and improve metabolic control (40, 108).

SIT is effective for increasing mitochondrial biogenesis and muscle oxidative enzyme activity due to recruitment and adaptation of all muscle fiber types (33). Type II fibers are equally as adaptive as Type I in their ability to increase oxidative enzyme activity. Dudley et al. (33) observed that rats who were trained at very high intensities for short durations actually had higher cytochrome-c oxidative activities after training in the white vastus lateralis than in the red soleus. This result illustrates the ability for adaptation in the least oxidative fibers with intense exercise training and the greater adaptation in skeletal muscle oxidative capacity in all muscle fiber types than with lower-intensity training. The greater adaptation is likely due to greater motor unit recruitment and increased force and/or frequency of contractions.

Another mechanism of increased insulin sensitivity using SIT includes contraction-induced depletion in muscle glycogen. Glycogen is an important key regulator of muscle glucose uptake (92), because glycogen depletion in the muscle increases available storage space and activity of glycogen synthase, which promotes glucose uptake and decreases circulating glucose. Increased circulating insulin, in turn, decreases insulin secretion and increases insulin sensitivity. Depletion of muscle glycogen content in type I and type II fibers up to 38% occurs after a single 30-s supramaximal bout of cycling (37). Supramaximal exercise of 30-s duration increases contraction-induced glucose flux (increase in hepatic gluconeogenesis and output along with increased muscle glucose uptake) and improves insulin sensitivity (110).

Mechanisms underlying improved insulin sensitivity with SIT may not be isolated to improved muscle mitochondrial capacity. Metabolic adaptations to 7 d of training that precede changes in the oxidative enzymes SDH, HAD and CS, include conserved PCr

concentrations, depressed PFK and phosphorylase activity, and lower post-training LA/pyruvate and ATP/ADP ratios (42). These findings suggest that short-term training reduces glycogen utilization that is unaccompanied by alterations in substrate preference as indicated by the RER. Indeed, increased transport across the muscle membrane via GLUT4 transporters may facilitate glycogen synthesis that occurs concomitantly with glycogenolysis (13). In summary, short-term adaptations that preclude mitochondrial adaptations include a shift toward a greater dependence on blood glucose acting as a substrate for glycolysis and/or as a substrate for glycogenesis, a comparable glycolytic flux rate, and an enhanced lactate clearance after training (43).

In summary, improving glucose homeostasis by increasing muscle oxidative capacity, GLUT-4 transporter protein and translocation activity and uptake, and a shift toward a greater dependence on blood glucose acting as a substrate for glyconeogenesis, may all be beneficial adaptations that can be elicited by SIT. It is still in question as to whether SIT would provide a stimulus for these effects.

Circulatory Factors as Determinants of $\dot{V}O_{2max}$

Maximal oxygen uptake ($\dot{V}O_{2max}$) is defined as the highest rate that oxygen can be taken up and utilized by the body during severe exercise. $\dot{V}O_{2max}$ is determined by the ability of the body to deliver oxygen to the working muscles (central factors) and by the muscle's ability to extract and utilize the delivered oxygen (peripheral factors). Hill et al. (47) originally identified the central factors as the primary determinants of $\dot{V}O_{2max}$, because the lungs, heart and blood limit the rate at which oxygen is delivered to the active skeletal muscle. The pulmonary system limits $\dot{V}O_{2max}$ only in extreme circumstances, such as in elite endurance athletes who have superior cardiac outputs or

muscle oxidative capacities (88), or in patients who have chronic obstructive pulmonary disease or low lung compliance (8). Therefore, for the untrained and trained individual, the primary limiting factor for $\dot{V}O_{2max}$ is maximal cardiac output ($\dot{Q}_{max}$), which is the product of maximal stroke volume (SV_{max}) and heart rate (HR_{max}) (9). SV_{max} peaks at approximately 40-50% $\dot{V}O_{2max}$ in untrained individuals (7), so $\dot{Q}_{max}$ is reached when HR_{max} is reached. As $\dot{V}O_{2max}$ is approached, SV plateaus as HR and muscle oxygen extraction ((a-v)O_2 diff) continue to rise, causing $\dot{Q}$ and oxygen uptake to plateau (77).

Effects of Exercise Training on Circulatory Factors

Aerobic exercise training. $\dot{V}O_{2max}$ increased up to 33% in sedentary men who underwent 55 d of aerobic exercise training after 20 d of bed rest (97). The increase in $\dot{V}O_{2max}$ observed after whole body aerobic endurance training is partly due to an increase in $\dot{Q}_{max}$ (+4.4-16.4%) via increased SV_{max} (+8.5-16.7%) and partly to an increase in (a-v)O_2 $diff_{max}$ (+3.6-16.4%) (96). Alternatively, others using 2-leg aerobic cycle training have shown no adaptations in maximal (a-v)O_2 $diff_{max}$ after 9 wk, although $\dot{V}O_{2max}$ still increased 34% (28). The increased SV_{max} results from a training-induced enlargement of left ventricular chamber size (76), an increase in blood volume and greater venous return (both allow for greater ventricular filling during diastole) (102), and cardiac muscle hypertrophy with increased calcium activation of ventricular cardiocytes to enhance contractility during systole (76). The increase in (a-v)O_2 $diff_{max}$ observed is due to adaptations in peripheral factors such increased capillary number:muscle fiber ratio (102), increased muscle oxidative capacity (103), and a greater fraction of the cardiac output passing through active skeletal muscles (102).

The adaptations in central circulatory factors and peripheral factors after exercise training depends on the muscle groups (small or large) activated during training as well as during testing. Muscle and central adaptations are specific to the training stimulus, such as type of training, intensity, and duration. When exercise training involves a lower than critical amount of muscle mass, an increase in $(a\text{-}v)O_2$ diff may occur without a concomitant increase in $\dot{Q}$ (25). On the other hand, when exercise training is performed involving a larger portion of muscle mass, HR during submaximal exercise is reduced equally during leg cycling and arm-crank post-testing (25). When training and testing alternate muscle groups, arm work is limited by the intrinsic power of the active muscles in the arm, 1-legged ergometry is limited equally by central circulatory and muscular factors, and that 2-legged ergometry is almost entirely dependent on the central circulatory transport of oxygen (103). Therefore, central circulatory adaptations that contribute to an individual's ability to increase $\dot{V}O_{2max}$ after aerobic exercise training is conditional to activating a certain critical fraction of muscle mass, the state of training of the muscles utilized during testing, and the type of exercise performed (24).

Sprint interval training. SIT can increase $\dot{V}O_{2max}$, but length of the training program appears to be an important factor. Burgomaster et al. (22) found that 6 d of SIT was insufficient for producing increases in $\dot{V}O_{2max}$; however, MacDougall et al. (67) found that 7 wk of SIT increased $\dot{V}O_{2max}$ 7%. Both studies found improvements in skeletal muscle oxidative capacity, but changes in $\dot{Q}_{max}$, SV_{max} and $(a\text{-}v)O_2$ $diff_{max}$ were not measured, therefore no data are available to determine whether peripheral or central factors were responsible for the increase in $\dot{V}O_{2max}$.

Although no previous studies in humans have examined the effects of SIT on central and peripheral adaptations, SIT in MI rats have been shown to increase $\dot{V}O_{2max}$, $\dot{Q}_{max}$ and SV_{max} by 11%, 18% and 15%, respectively, with no increase in $(a\text{-}v)O_2\ diff_{max}$ or HR_{max} (78). In contrast, endurance training in MI rats increased $(a\text{-}v)O_2\ diff_{max}$ 12% but failed to significantly increase $\dot{Q}_{max}$ or SV_{max} (79). The authors for these studies concluded that the lower training intensity may not have been sufficient to produce changes in central circulation (79) and that higher intensities may be needed to see central adaptations in a short time frame.

Summary

Insulin resistance is a common disease among sedentary, overweight women, and the risk of type 2 diabetes, CVD, and premature mortality is increased with insulin resistance. A dose-response relationship of exercise intensity and insulin sensitivity and glucose tolerance exists with acute and chronic exercise. When holding duration constant, higher-intensity exercise training of shorter duration seems to be a superior exercise prescription compared to moderate-intensity and/or longer duration. This may be due to the greater increases in mitochondrial density, oxidative enzyme activity, and GLUT-4 transporter protein synthesis and translocation elicited after highly-intense exercise. SIT improves muscle oxidative enzyme activity *in vitro*, muscle glycogen content, and $\dot{V}O_{2max}$ in humans. Therefore, it is possible that SIT may improve glucose homeostasis.

SIT increases $\dot{V}O_{2max}$ ~7% in humans after 7 wk. Possible mechanisms of improved $\dot{V}O_{2max}$ include increased $\dot{Q}_{max}$, SV_{max} and $(a\text{-}v)O_2\ diff_{max}$. However, until now, the effects of SIT on the determinants of $\dot{V}O_{2max}$ have not been studied in humans. Increases in $\dot{Q}_{max}$ and SV_{max} without an increase in $(a\text{-}v)O_2\ diff_{max}$ have been found in rats

after SIT. Improvements in cardiac function as a result of SIT may be beneficial to individuals at risk for type 2 diabetes and CVD.

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CHAPTER 3

EFFECTS OF SPRINT INTERVAL TRAINING ON INSULIN SENSITIVITY AND GLUCOSE TOLERANCE IN SEDENTARY, OVERWEIGHT WOMEN[1]

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Abstract

Sprint interval training (SIT) increases muscle oxidative capacity, but whether insulin sensitivity and glucose tolerance are improved is unknown. **PURPOSE:** To examine the effects of SIT on insulin sensitivity and glucose tolerance in healthy but sedentary, overweight women. **METHODS:** Women were randomly assigned to SIT (n = 13, age = 30 ± 7 yr, BMI = 35 ± 6 kg/cm^2; DXA %fat = 48 ± 6; $\dot{V}O_{2max}$ 22 ± 4 ml/kg·min) and trained 3 d/wk for 4 wk, with 1-2 d rest between sessions, or to CON (n = 14; age = 31 ± 6 yr, BMI = 35 ± 6 kg/cm^2; DXA %fat = 47 ± 5; $\dot{V}O_{2max}$ 20 ± 3 ml/kg·min) and maintained baseline physical activity (exercise ≤ 1 day/wk). Training consisted of 4-7, 30-s maximal-effort sprints on a stationary cycle with 5% body weight as resistance and 4 min active recovery between sprints. Before and 2 d after the intervention period, 12-hr fasting glucose and insulin responses to a 2-hr oral glucose tolerance test (OGTT) were measured, and insulin sensitivity was assessed using the homeostasis model assessment for insulin resistance (logHOMA-IR) and the insulin sensitivity index (ISI). **RESULTS:** Changes in fasting glucose (SIT: -6%, -0.289 mmol/L; CON: -1%, -0.049 mmol/L), and glucose area under the curve (SIT: -5%, -33.36 mmol/L/min; CON: -4%, -26.00 mmol/L/min) were not statistically significantly different in SIT and CON ($P > 0.05$). LogHOMA-IR decreased significantly more in SIT (-25%, -0.135) compared to CON (0%, -0.002, $P = 0.005$), and there was a clinically-meaningful greater change in fasting insulin (SIT: -22%, -4.11 μU/ml; CON: -4%, -0.84 μU/ml), insulin area under the curve (SIT: -19%, -2143.1 μU/ml/min; CON: -7%, -835.9 μU/ml/min), and ISI (SIT: 30%, +0.845; CON: 0%, +0.005) but the difference was not

statistically significant ($P > 0.05$). **CONCLUSION:** SIT improves insulin sensitivity without affecting glucose tolerance in sedentary, overweight women.

Keywords: sprint interval training, insulin sensitivity, glucose tolerance, muscle oxidative capacity

Introduction

Obesity and a sedentary lifestyle can contribute to reduced insulin sensitivity and glucose tolerance, which may progress to type 2 diabetes if lifestyle changes are not adopted (37, 42). Increased adipocyte volume decreases insulin receptor density, whereas physical inactivity decreases muscle oxidative capacity and GLUT-4 transporter response to insulin, reducing skeletal muscle glucose uptake (37). Insulin sensitivity is commonly assessed using the homeostasis model assessment for insulin resistance (HOMA-IR) and insulin sensitivity index (ISI), which are simple indices validated to estimate relative risks of developing type 2 diabetes and to track effects of exercise interventions over time (2, 46, 47). Glucose homeostasis and intolerance are typically measured using a fasting glucose concentration and an oral glucose tolerance test (OGTT) (2, 3). Individuals who are obese and sedentary have increased fasting insulin and HOMA-IR values (31), decreased ISI (46), increased fasting glucose concentration and decreased glucose tolerance (1).

Aerobic exercise training of moderate-to-high intensities increases skeletal muscle oxidative capacity and $\dot{V}O_{2max}$, which are correlated to improved insulin sensitivity and glucose tolerance (3, 21, 22, 39-41, 60). Repeated bouts of very-intense cycling of short-duration, termed sprint interval training (SIT), also increase skeletal muscle oxidative capacity, $\dot{V}O_{2max}$, GLUT-4 protein, and carbohydrate utilization in healthy, sedentary and recreationally-active, normal-weight individuals (12-15, 26, 56). Coyle (17) suggested that because the exercise stimulus that promotes mitochondrial biosynthesis probably stimulates other healthy metabolic adaptations in skeletal muscle, SIT may be effective in promoting insulin action and health.

A significant relationship exists between muscle oxidative capacity and insulin sensitivity. These measures are much higher in trained individuals than in type 2 diabetics (9). Because SIT increases skeletal muscle oxidative capacity (15) and GLUT-4 protein (12), and because insulin sensitivity increases in proportion to exercise intensity when total exercise volume is equivalent (21, 40), SIT may also increase insulin sensitivity and glucose tolerance. Despite involving very-high intensity, the very-short exercise duration of SIT may be better tolerated in some individuals with low aerobic capacities who are resistant to participation in long-duration exercise. However, it has not been established if SIT would be a suitable training modality for improving insulin sensitivity and glucose tolerance in individuals at risk for type 2 diabetes.

The objective of our study was to examine the effects of SIT on insulin sensitivity and glucose tolerance in sedentary, overweight/obese women. It was hypothesized that SIT would improve insulin sensitivity and glucose tolerance.

Methods

Participants. Twenty-eight women were recruited from the University and surrounding community. To reduce the heterogeneity of the outcome variables and to increase statistical power, only women were included. In previous research that evaluated glucose disposal rates (tested with the hyperinsulinemic-euglycemic clamp) or insulin response to a 2-h OGGT in adolescent and adult females, effect sizes ranged from d = 0.57-1.08 after 4-12 weeks of a resistance circuit or moderate-intensity aerobic cycle training (36, 51). Using a mixed-model repeated measures ANOVA, a sample size of 14 per group was sufficient to detect a moderate Group x Time interaction effect (Cohen's d = 0.57) for ISI, with an experiment-wise α level of 0.05 and a power of 0.8, assuming a

correlation between repeated trials of 0.9 for the 2-hr OGTT (54). Inclusion criteria included women who were sedentary (exercise ≤ 1 d/wk) and had a body mass index (BMI) > 25 kg/m^2. Exclusion criteria included women who had been clinically diagnosed with type 1 or type 2 diabetes, had a history of smoking (≤ 6mo), hypertension, polycyctic ovarian syndrome, or were on antidepressant, antianxiety, or hypertension medication. The experimental protocol was approved by the University's Institutional Review Board, and all participants provided written informed consent.

Research design. A randomized, pretest-posttest control group design was used for the study. Participants were randomly assigned to sprint interval training (SIT, n=14) or control (CON, n=14) groups. Outcome variables were measured on both groups before and after the intervention period. The post-intervention tests were administered 2 d after completing the intervention period to decrease confounding effects of the training with persistent responses to acute exercise. The 2-h oral glucose tolerance test was measured after a 12-h fast on day 1, and a graded exercise test (GXT) was performed on day 2 to assess $\dot{V}O_{2max}$.

Familiarization. Participants came to the laboratory 1 wk before pre-testing to become familiarized with the training protocol and testing procedures. Participants read the informed consent and completed physical activity and medical history forms to evaluate whether any medical problems existed that would prevent them from participating in the study. During this time, investigators answered questions, reviewed the forms, and obtained written informed consent. Anthropometric data were collected and participants performed a cycling GXT. Following recovery, participants performed

two practice sprints on a mechanically-braked cycle ergometer (Monark, Sweden) to simulate a partial training session.

2-h oral glucose tolerance test. Participants were instructed to abstain from caffeine and alcohol 24 h before testing. They consumed a diet of ≥ 150 g carbohydrate/day and recorded their daily food consumption for 2 d before testing. The food diaries were collected, photocopied and returned to the participants after pretesting. Two days prior to posttesting, participants were instructed to replicate their pretest diet to decrease any confounding effects of food intake.

Participants came to the laboratory early in the morning after a 12-h fast. Body mass was measured on an electronic scale (A & D Company, Ltd., Tokyo, Japan) and body composition was assessed using dual-energy x-ray absorptiometry (iDXA, GE Healthcare-Lunar, Madison, WI). Then, a sterile, flexible catheter (Angiocath™, Becton Dickinson, Franklin Lakes, NJ) was inserted into a forearm vein and kept patent with 0.5 mL of 10 USP units/mL heparin lock flush. Participants sat upright for 20 min in order for plasma volume to stabilize before a blood sample was drawn.

After the fasting blood sample was obtained, participants ingested a 75 g glucose solution (Fisherbrand, Swuanee, GA) and remained seated during a 2-h oral glucose tolerance test (OGTT). Blood samples were collected at 30, 60, 90, and 120 min. Blood was drawn into EDTA and sodium heparin vacutainer tubes (Becton Dickson, Franklin Lakes, New Jersey) and was immediately centrifuged for 10 min at 2000 rpm. Plasma was aliquoted and stored in -80ºF until later analysis. Glucose was analyzed using a colorimetric assay (Stanbio™, Boerne, Texas), and insulin concentration was determined by radioimmunoassay (Linco®, Billerica, Massachusettes). Insulin and glucose were

measured in duplicate, and any duplicates that had a coefficient of variation greater than 10% were reanalyzed. The average coefficients of variation for the glucose and insulin assays were 1.4% and 3.7%, respectively.

Insulin sensitivity indicies and glucose tolerance. The plasma glucose and insulin concentrations obtained during the OGTT were used to measure insulin sensitivity and glucose tolerance. The log-transformed homeostasis model assessment for insulin resistance (logHOMA) and the Matsuda and DeFronzo calculation for insulin sensitivity index (ISI) were chosen as surrogate measures of insulin sensitivity (46, 47). The calculation for logHOMA-IR is:

$$\text{logHOMA-IR} = \log [(\text{fasting insulin} \times \text{fasting glucose})/22.5]).$$

The calculation for ISI is:

$$\text{ISI} = 10{,}000/\sqrt{(I_f \times G_f \times \text{insulin } I_{mean} \times G_{mean})}$$

where I_f is the fasting insulin, G_f is fasting glucose, I_{mean} and G_{mean} are the mean of the insulin and glucose concentrations for the 2-hour test, respectively. Glucose and insulin concentrations obtained during the 30-min time increments of the 2-h OGTT were calculated to obtain the area under the curve for glucose (G-AUC) and insulin (I-AUC) using the trapezoidal method (55).

$\dot{V}O_{2max}$. A continuous, progressive, load-incremented cycle ergometer (Lode, Groningen, Netherlands) GXT was used to measure $\dot{V}O_{2max}$. We chose a work rate increment magnitude large enough to induce a test duration of 8-17 min in order to optimize maximal effort and to obtain a true $\dot{V}O_{2max}$ in non-trained individuals (11). Therefore, the graded exercise test was adapted and modified for young, obese women (18, 27, 44). Participants began cycling at a power output of 40 W, which was increased

20 W every 2 min until they could no longer continue. $\dot{V}O_2$, ventilation, and heart rate (HR) were recorded continuously and averaged over 1-min intervals. Rating of perceived exertion (RPE) using the Borg 15-point scale (8) was obtained at the end of each 2-min stage and at exhaustion. A fingerstick blood sample was obtained 3 min after the GXT to determine end-test lactate concentration (Lactate Pro, Quesnel, BC, Canada).

To ensure that a plateau in $\dot{V}O_2$ was attained, participants completed an additional bout of cycling following 20 min of rest. Participants cycled to exhaustion at a power output equivalent to the last workload performed during the graded test (if < 1 min was completed during the last stage of the graded test) or at a power output 20 W higher than the last workload performed during the graded test (if ≥ 1 min was completed during the last stage of the graded test).

Attainment of $\dot{V}O_{2max}$ was based on evidence of a plateau in $\dot{V}O_2$ with increasing power output customized for this population. Lafortuna et al (44) found that the mean (± S.D.) increase in $\dot{V}O_2$ (L/min) for obese women (age 23.2 ± 1.6 years, BMI 40.4 ± 1.2 kg/m^2) undergoing a 20-W incremental graded exercise test was 0.264 ± 0.027 L/min. Therefore, the $\dot{V}O_2$ increase accepted as the maximum allowed to provide evidence of a plateau was > 2 standard deviations less than the expected $\dot{V}O_2$ increase associated with the increase in work (i.e. < 0.210 L/min). Using this criterion, all participants met the plateau criterion on both tests.

Interventions. Participants in SIT followed a protocol modified from Burgomaster et al. (15). Each training session consisted of repeated, 30-s cycling sprints (4 to 7 bouts/session) followed by 4 min of active recovery between bouts on a Monark ergometer. Participants warmed up with no resistance for 4 min. At the end of 4 min,

participants began pedaling at maximal cadence ~5 s before a fixed resistance of 0.05 kg/kg BW (59) was applied. Then, participants continued pedaling against the resistance at power outputs estimated to elicit ~250% $\dot{V}O_{2max}$ (extrapolated from GXT) for 30 s. After the sprint, they continued cycling for a 4-min active recovery with no resistance. These intervals were repeated until the prescribed number was performed. After the last sprint, participants actively cooled down while pedaling against no resistance until their HR recovered to ≤ 130 bpm. On the first training day, participants performed a total of 4 sprints with 4 min of active recovery between bouts. On subsequent training sessions, the number increased by one sprint bout every week, finishing with cycling 7 sprints/session in the last week. Participants trained 3 d/wk (1-2 d rest between sessions) for 4 wk and were instructed to maintain their pre-study physical activity outside of the training intervention.

Work performed by SIT during the 4-wk training regimen was recorded to quantify the training volume. An optical sensor (Sports Medicine Industries, Inc., St. Cloud, Minnesota) was secured to the ergometer frame and 16 reflective markers were placed on the flywheel to record flywheel revolutions. The sensor was interfaced with a computer-based SMI Power software program (version 1.02) that recorded revolutions per minute and calculated power output per second (W/s). The W/s for the 30-s sprint was summed and converted to Joules (J) to obtain work performed for the exercise session, and the work for each session over the 4 wk was calculated to obtain weekly and total work of the intervention. Finally, work done on the 4^{th} sprint of each session was used as an indicator of the intensity of the training across the training period.

Participants in CON were instructed to maintain their baseline physical activity during the intervention period and to neither increase nor decrease their activity level. After completion of their posttests, participants in CON were offered the opportunity to participate in SIT training for 4 wk. Participants in both groups were instructed to maintain their usual diet (quantity of intake and type of foods) throughout the intervention period.

Statistical Analysis. Data were analyzed using SPSS v. 15.0, (SPSS, Inc., Chicago, IL). Differences between groups at the pretest for all physical characteristics and outcome variables were determined using *t*-tests for independent samples. Differences in work performed by SIT across the 4 wk of training were analyzed using a one-way ANOVA with repeated measures. Post hoc tests were performed (Bonferroni-adjusted) to test for differences between weeks. To test the significance of the effects of the intervention before and after training, a two-way (Group x Time), mixed model ANOVA was used. If an interaction exsisted, tests for simple effects were performed to examine the effect of the treatment on each group separately. All tests were considered significant if $P < 0.05$.

Results

Participant characteristics and work performed. One participant from the SIT group was dropped from the study after being clinically diagnosed for polycystic ovarian syndrome post-intervention, therefore all data analysis for SIT was based on 13 participants. No differences existed between groups at baseline for age, BMI, body mass, percentage body fat, or $\dot{V}O_{2max}$ ($P > 0.05$, Table 1). The individual analyses for the Group x Time interaction in the 2-way ANOVA for changes in weight, BMI, or percentage body

fat as a result of the intervention in either group were not significant ($P > 0.05$), indicating that any changes observed in SIT were not different from changes in CON. Work performed in SIT during the 30-s all-out efforts increased linearly by an average of 35 ± 2 kJ (mean ± SEM) per week and was significantly different among the 4 wk ($P < 0.001$, Figure 1). Post-hoc pairwise comparisons (Bonferroni-adjusted) indicated that work performed increased significantly from week 1-2 ($P = 0.002$), week 2-3 ($P = 0.007$), and week 3-4 ($P = 0.001$). Work performed on the 4th sprint of each session was not statistically significantly different among sessions ($P = 0.220$), indicating that no variability in effort existed among sessions and that the participants were giving equal efforts to the sprints.

Fasting insulin and glucose. Fasting insulin and glucose were not different between SIT and CON at the pretest ($P = 0.393$ and 0.950, respectively). For fasting insulin, the Group x Time interaction in the 2-way ANOVA was not statistically significant ($P = 0.145$, Figure 2a); however, the 22% decrease in fasting insulin observed after the intervention in SIT compared to the 4% decrease in CON may be clinically important (Cohen's d = 0.38). For fasting glucose, the Group x Time interaction in the 2-way ANOVA was not statistically significant ($P = 0.213$, Cohen's d = 0.51, Figure 2b), indicating that the 6% decrease observed in SIT was not different from 1% decrease in CON.

logHOMA-IR. LogHOMA-IR was not different between SIT and CON at the pretest ($P = 0.537$). The Group x Time interaction in the 2-way ANOVA was statistically significant ($P = 0.005$, Cohen's d = 0.80, Figure 3). Tests for simple effects showed that

logHOMA-IR decreased significantly by 25% after the intervention for SIT (-0.135, $P < 0.001$), while CON showed no change (0%, $P = 0.944$).

Insulin Sensitivity Index. ISI was not different between SIT and CON at the pretest ($P = 0.610$). The Group x Time interaction in the 2-way ANOVA was not significant ($P = 0.142$, Cohen's d = 0.55, Figure 4); however, the 30% increase observed in SIT compared to 0% in CON may be clinically important.

Insulin-AUC and Glucose-AUC. Neither I-AUC nor G-AUC were different between SIT and CON at the pretest ($P = 0.704$ and 0.961, respectively). The Group x Time interaction in the 2-way ANOVA was not statistically significant for I-AUC ($P = 0.381$, Figure 5), but the 19% decrease after SIT compared to the 7% decrease in CON may be clinically important (Cohen's d = 0.27). The Group x Time interaction was not significant for G-AUC ($P = 0.852$, Cohen's d = 0.06, Figure 6), indicating that the change in SIT was not different from CON.

$\dot{V}O_{2max}$. $\dot{V}O_{2max}$ (L/min) was not different between SIT and CON at the pretest ($P = 0.372$). The Group x Time interaction in the 2-way ANOVA was statistically significant ($P < 0.001$, Cohen's d = 0.76), indicating the change by SIT was statistically significantly different than CON. $\dot{V}O_{2max}$ increased 0.24 L/min (12%, $P < 0.001$) in SIT whereas CON did not change (0%, $P = 0.571$; Figure 6). Because there were no significant changes in body mass with training ($P = 0.602$), $\dot{V}O_{2max}$ expressed relative to body mass also increased significantly by 2.6 ml/kg·min for SIT ($P < 0.001$) but not for CON ($P = 0.617$).

Discussion

The purpose of our study was to determine whether SIT improves insulin sensitivity and glucose tolerance in sedentary, overweight/obese women. The primary finding was that SIT improves insulin sensitivity without affecting glucose tolerance. Our study is the first to demonstrate that very-high-intensity, low-volume training using SIT cycling can be used to improve health and decrease the risk of type 2 diabetes.

Participants in our study were women who were overweight/obese (BMI > 25) and were not physically active, which are risk factors for type 2 diabetes. McAuley et al. (48) determined a fasting insulin of 12.1 ± 0.1 uU/L (mean ± SD) as a diagnostic cutoff point for insulin resistance in the general population. According to their criteria, 12 participants in SIT and 9 participants in CON were classified as insulin resistant before the intervention. Hoffstedt et al. (31) classified intermediate insulin sensitivity and low insulin sensitivity as logHOMA-IR = 0.36 ± 0.01 and 0.66 ± 0.02, respectively. We took the median of these values (logHOMA-IR = 0.51) as the cutoff point for low insulin sensitivity, and according to this criteria, 8 participants in SIT and 7 participants in CON were classified as having low insulin sensitivity before the intervention. Neither of the groups had fasting glucose or AUC-G values that were indicative of impaired glucose homeostasis or glucose intolerance (6). Consequently, many of our subjects were classified as insulin resistant without being glucose intolerant, indicative of stage 1 of pre-diabetes (37).

SIT elicited a 25% decrease in logHOMA-IR, and 6 SIT participants improved from the low- to the intermediate category of insulin sensitivity (31). There were no changes for CON. For fasting insulin, one participant in SIT became non-insulin

resistant, whereas two participants from CON actually became insulin resistant. Although not statistically significant ($P > 0.05$), the 22% decrease in fasting insulin, 30% increase in ISI, and 19% decrease in I-AUC after training are large enough improvements to be clinically important. Drug therapy (Troglitazone, Metformin) is widely used clinically for type 2 diabetes treatment and prevention (19, 25, 32, 53) and has been shown to improve logHOMA-IR by 17% after 3 wk (53) and reduce fasting insulin concentration and I-AUC by 26% and 30%, respectively, after 1 y of use (32). Because the 22% decrease in fasting insulin and 19% reduction in I-AUC achieved in just 4 wk of SIT compares favorably with drugs prescribed to treat insulin resistance and type 2 diabetes long-term, the SIT-induced improvements in fasting insulin, I-AUC and ISI are considered clinically important.

When comparing SIT to traditional aerobic exercise training, investigations have found that 7-10 d of prolonged duration (40 – 120 min), moderate-intensity aerobic training at 60-70% $\dot{V}O_{2max}$ decreases fasting insulin 21% in pre-diabetic individuals (4), decreases I-AUC 12-17% (3, 28), and increases ISI 27% in healthy centrally-obese adults (60). Some suggest that longer exercise durations and greater total exercise volume (energy expenditure) elicit greater improvements in insulin sensitivity (33). However, when total energy expenditure is held constant, a dose-response exists for intensity and improved insulin sensitivity (21, 40, 52). Epidemiologic studies show that relative risk of developing type 2 diabetes decreases linearly with increasing intensity of training (34). Therefore, higher intensity elicits a greater protective effect against insulin resistance and subsequent development of type 2 diabetes.

The training used in our study involved a much higher intensity and lower volume than in previous studies showing improved insulin sensitivity with aerobic exercise training. Based on the power outputs used in training and extrapolation of the oxygen uptake required by overweight/obese women during submaximal intensities (44), we estimated participants trained at an intensity of 243% to 284% of $\dot{V}O_{2max}$ during the sprint intervals. However, total volume of work performed during sprinting (mean ± SEM) was 772 ± 37 kJ and total duration of sprinting was 33 min. In contrast, if the women in our study would have exercised at 65% $\dot{V}O_{2max}$ for 30 min, 3 times/wk for 4 wk, they would have expended ~1469 kJ and would have cycled a total of 6 h. Therefore, our study extends previous research by showing that SIT may be an effective and efficient training modality to improve insulin sensitivity in sedentary, overweight/obese, insulin-resistant women.

SIT may have improved insulin sensitivity through improvements associated with increased $\dot{V}O_{2max}$ after training. $\dot{V}O_{2max}$ is related to basal blood flow (r = 0.63), glucose disposal during an insulin infusion (r = 0.65) and muscle GLUT-4 concentration (r = 0.61) (22). A close correlation (r = 0.88) exists between blood flow and glycogen synthase fractional activity (22). Mitochondrial enzyme activity is related to insulin sensitivity (r = 0.71, $P < 0.001$) and is higher in trained individuals than in type 2 diabetics (9). Also, GLUT-4 concentration nearly doubles in healthy humans in as little as 7-10 d of cycle ergometer exercise training (28), and maximal glucose transport activity through GLUT-4 up-regulation is related to insulin sensitivity (16, 38). SIT has already been shown to increase skeletal muscle oxidative capacity (15, 45) skeletal

muscle GLUT-4 protein content and translocation activity (12), and blood flow to and subsequent glucose disposal by skeletal muscle (5).

Fasting blood glucose was not changed by SIT. Results of other studies using endurance and interval, short-term (7 d to 6 wk) and longer-term (> 6 wk) training agree (28, 39) and conflict (3, 20, 60) with our results. Decreased glucose tolerance in overweight/obese individuals is a consequence of insulin resistance, which was present in our population. Because insulin resistance precedes glucose intolerance and type 2 diabetes (23), it is possible to have positive changes in insulin sensitivity without a change in glucose tolerance after acute (24) and chronic exercise training (28, 39). Magnitude of change in glucose tolerance after chronic exercise training likely depend on the population under study (normal weight vs. obese, healthy vs. insulin resistant or impaired glucose tolerant), baseline glucose tolerance or insulin sensitivity, and training protocol (intensity, duration, and protocol length). Whereas healthy, normoglycemic, normal weight individuals do not show significant changes in fasting glucose or G-AUC after exercise training (28, 39), obese individuals or those with impaired glucose tolerance or type 2 diabetes demonstrate a significant improvement in glucose tolerance (3, 4, 57, 60). Therefore, although different training protocols produce varying results on glucose tolerance, the protective effect of exercise may be greatest in persons at the highest risk for the disease (30).

In an attempt to assess adaptations to training and to decrease the transient effects of acute exercise, we scheduled our posttests 2 d after the last exercise session. Increased insulin sensitivity and response to a glucose load may partially be due to a residual effect of acute exercise, and not entirely an adaptation to chronic exercise training. A single

exercise session can increase insulin sensitivity (49) and glucose tolerance (7) in healthy participants and improve insulin sensitivity in non-diabetic obese individuals (50) immediately following exercise. Even 24 h after exercise, glucose tolerance can be improved up to 35% (7). With acute exercise, glucose uptake is enhanced though an insulin-independent, contraction-mediated GLUT-4 transport to the sarcolemma during exercise and through increased sensitivity of muscular glucose transport to insulin after exercise (10). After exercise training, aerobic insulin sensitivity (37) and glucose tolerance (35, 57) are improved through increased skeletal muscle oxidative capacity, GLUT-4 concentration and blood flow (22, 35, 37). Studies on detraining of trained individuals show that plasma insulin response to an OGTT and circulating glucose concentration are increased after 10-14 d of inactivity in trained individuals (29, 43). However, insulin and glucose responses to an OGTT decreased to pre-detraining levels immediately after return to exercise (29), indicating a substantial decrease in insulin sensitivity with short-term inactivity (43). In contrast, individuals who engage in chronic exercise training have higher muscle oxidative activity and GLUT-4 protein and markedly lower circulating insulin and glucose concentrations compared to untrained individuals, suggesting that chronic exercise training also contributes to improved insulin sensitivity (58). It is likely that the increased insulin sensitivity observed in our study was a combination of acute and chronic effects of exercise.

One limitation of our study is low statistical power. The number of volunteers tested (SIT, n = 13 and CON, n = 14) provided sufficient power ($1 - \beta = 1.10$) to detect a large treatment effect ($d = 0.80$) in logHOMA-IR, but insufficient power to detect a moderate treatment effect for ISI ($d = 0.55$, $1 - \beta = 0.74$), and small treatment effects for

I-AUC ($d = 0.27$, $1 - \beta = 0.08$), and fasting insulin ($d = 0.38$, $1 - \beta = 0.40$). A second limitation may have been that the variability within the participants' measures may have been too wide to achieve significance. Testing more participants would have established with more certainty whether SIT was different than CON for fasting insulin and ISI.

In summary, this is the first study examining the effects of SIT on insulin sensitivity and glucose tolerance in sedentary, overweight/obese women. The low volume and duration of sprint exercise resulted in improved insulin sensitivity without affecting glucose tolerance. These findings provide support for the use of SIT as a time-efficient and effective exercise modality that could be used in the lifestyle management of individuals who are overweight/obese and/or are at risk for type 2 diabetes. Further studies are needed to examine if SIT would be effective in other population subgroups and how it can be best implemented in real-life settings.

Acknowledgements

The authors thank Miley Duvall, Mai Nguyen, Hemal Patel, Anna Gelbrich, Diana Kim and Sahir Ahsan for their technical assistance with the study.

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Table 3.1. *Participant physical characteristics (means ± SD)*

	SIT	CON
Age (y)	30.54 ± 6.9	31.43 ± 5.5
Mass (kg)	94.9 ± 14.0	96.61 ± 22.7
Height (cm)	164.9 ± 6.3	166.35 ± 7.7
Body mass index	34.8 ± 5.7	34.57 ± 5.9
Fat Mass (%)	47.9 ± 5.9	46.85 ± 5.2
$\dot{V}O_{2max}$ (L/min)	2.06 ± 4.2	1.94 ± 0.30
$\dot{V}O_{2max}$ (mL/kg FFM·min)	43.8 ± 5.6	40.6 ± 4.7

Values are means ± SD, n = 13 for SIT and n = 14 for CON.

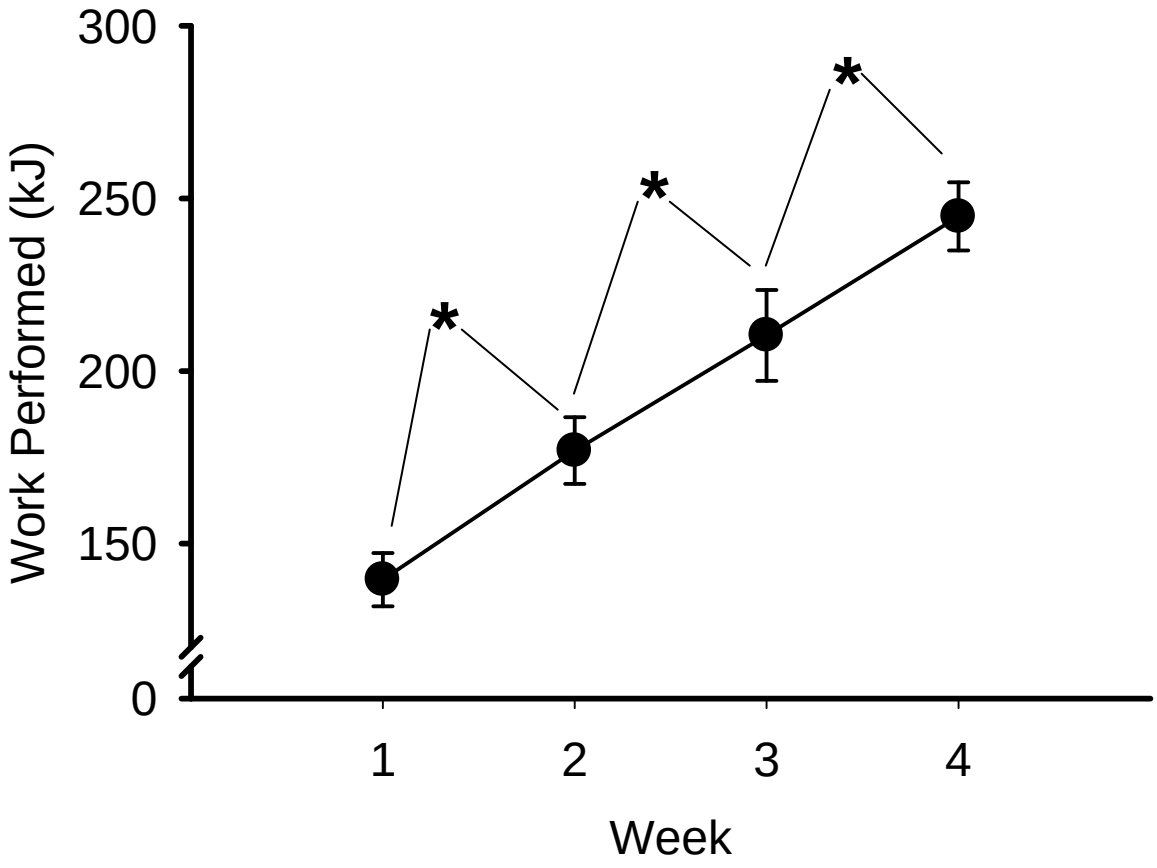

Figure 3.1. Work performed over the 4 weeks (n = 13). Values are means ± SEM.

*Significant increase between weeks ($P < 0.05$).

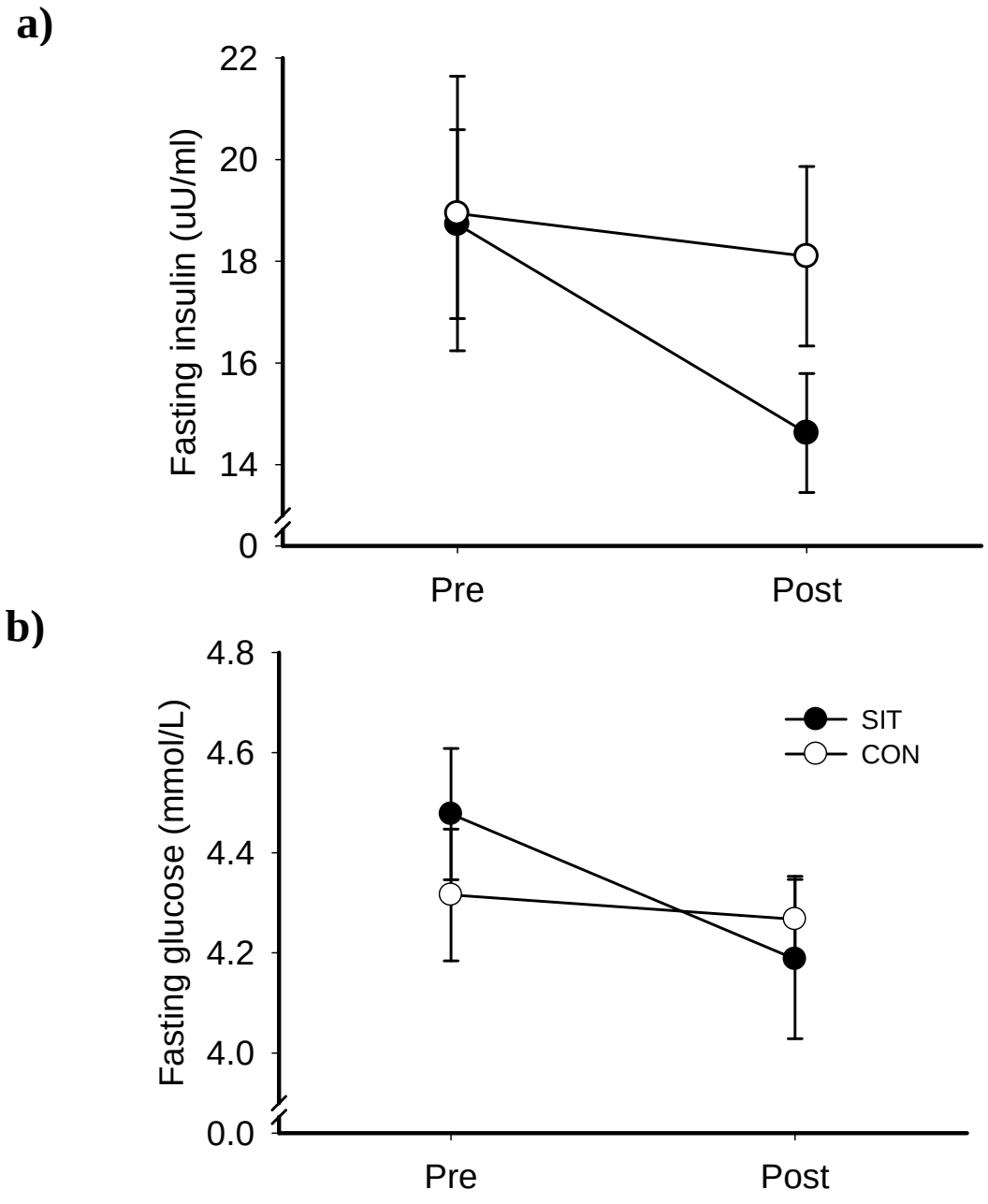

Figure 3.2. Changes in a) fasting insulin and b) fasting glucose before and after the intervention. Values are means ± SEM.

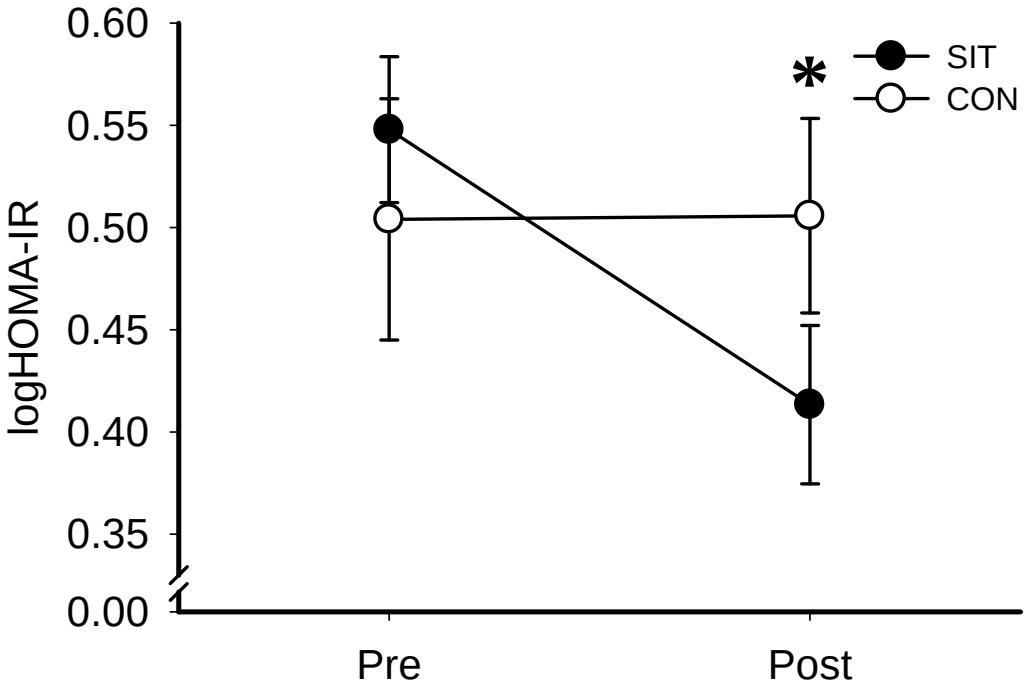

Figure 3.3. Changes in logHOMA-IR before and after the intervention. Values are means ± SEM. *Significant Group x Treatment interaction (P = 0.005).

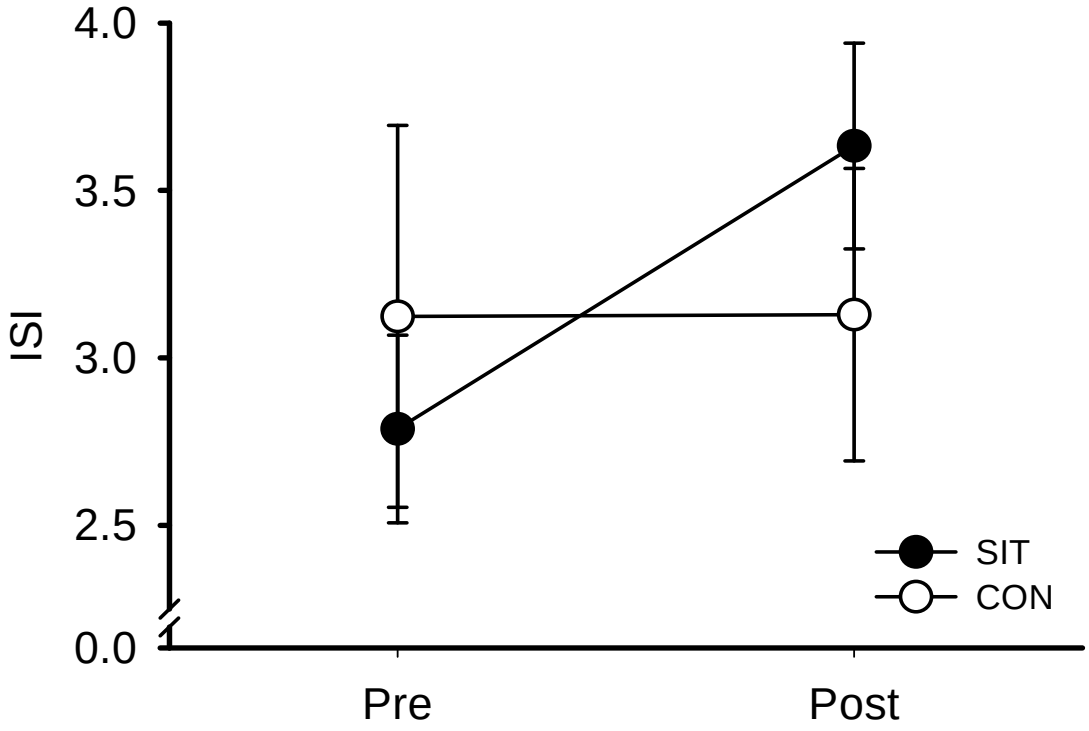

Figure 3.4. Changes in the insulin sensitivity index (ISI) before and after the intervention. Values are means ± SEM.

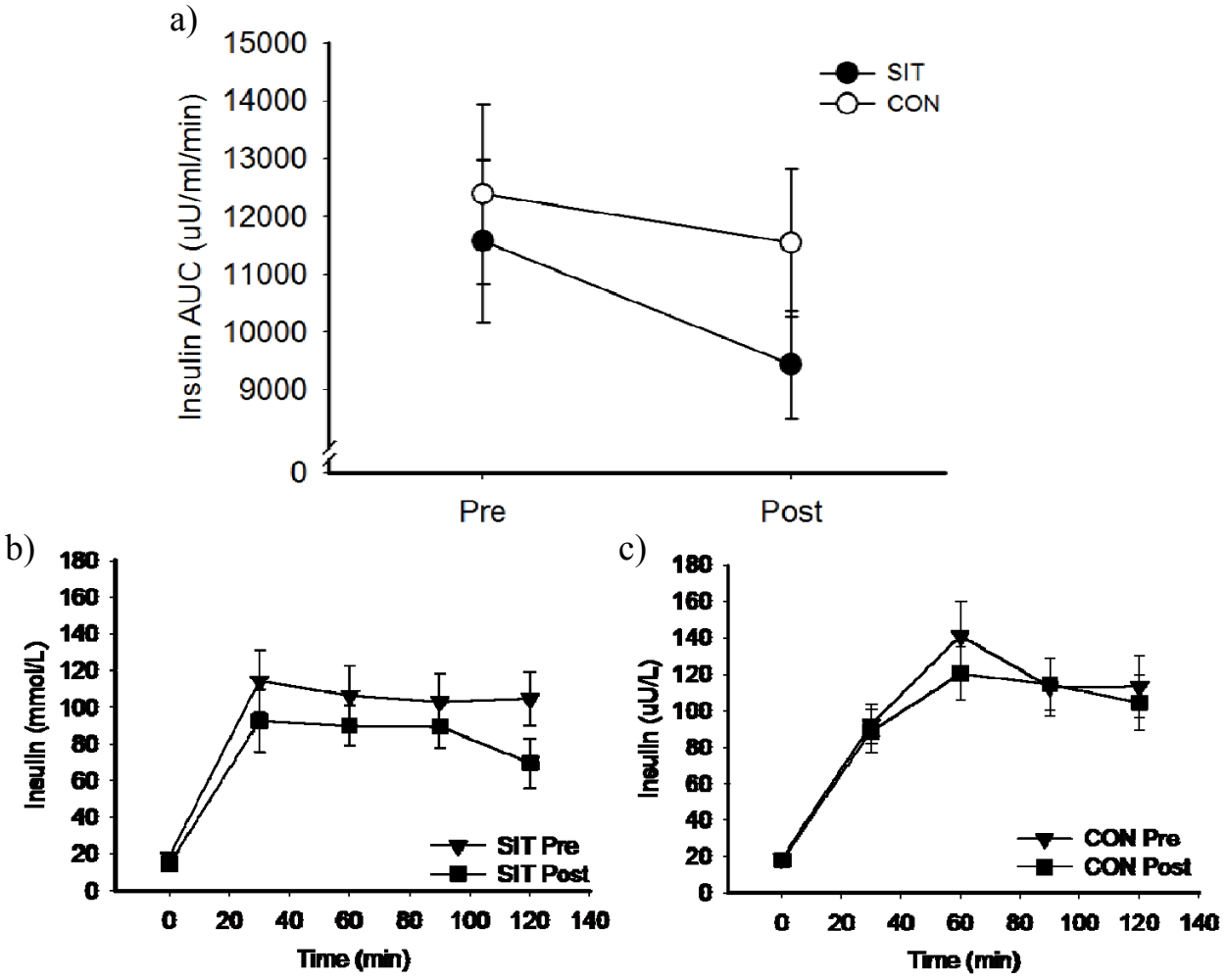

Figure 3.5. Changes in insulin area under the curve (I-AUC) from 2-h oral glucose tolerance test before and after the intervention; b) raw data for SIT; c) raw data for CON. Values are means ± SEM.

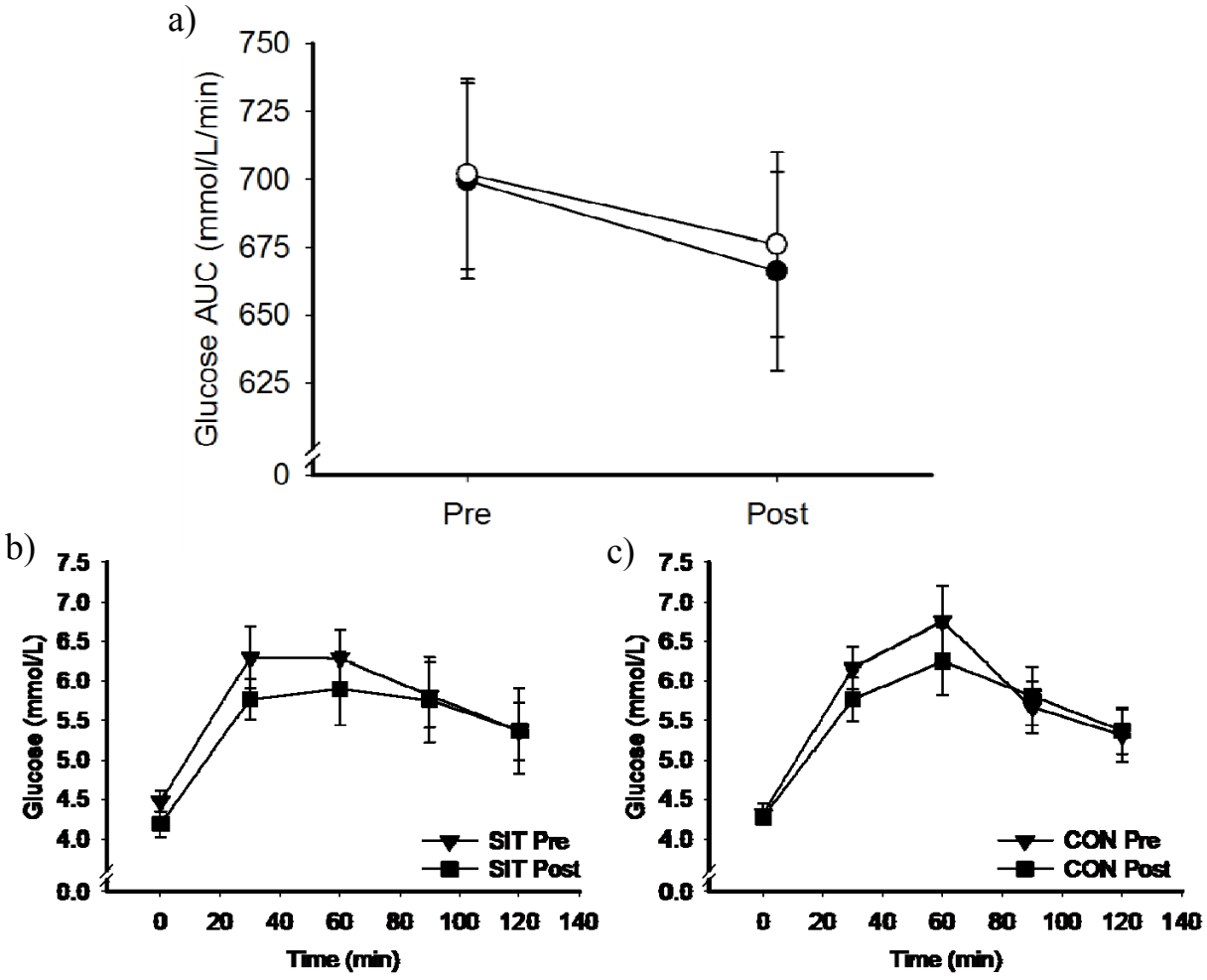

Figure 3.6. Changes in glucose area under the curve (G-AUC) from 2-h oral glucose tolerance test before and after the intervention; b) raw data for SIT; c) raw data for CON. Values are means ± SEM.

CHAPTER 4

SPRINT INTERVAL TRAINING INCREASES $\dot{V}O_{2max}$ AND CENTRAL CIRCULATORY CAPACITY IN SEDENTARY, OVERWEIGHT WOMEN

[1] Trilk, J.L., Singhal, A., Bigelman, K. A., and Cureton, K. J. To be submitted to *Journal of Applied Physiology*

Abstract

Sprint interval training (SIT) increases muscle oxidative capacity and may increase maximal oxygen uptake ($\dot{V}O_{2max}$), but whether central circulatory capacity is increased is unknown. **PURPOSE:** To examine the effects of SIT on $\dot{V}O_{2max}$ and its determinants ($\dot{Q}_{max}$, SV_{max}, HR_{max}, and $(a\text{-}v)O_2$ $diff_{max}$) in sedentary, overweight women. **METHODS:** Twenty-eight women with BMI > 25 were randomly assigned to SIT (n = 14; age = 30 ± 7 yr, BMI = 36 ± 6 kg/cm^2; DXA %fat = 48 ± 6; $\dot{V}O_{2max}$ 22 ± 4 ml/kg·min) or control (CON, n = 14; age = 31 ± 6 yr, BMI = 35 ± 6 kg/cm^2; DXA %fat = 47 ± 5; $\dot{V}O_{2max}$ 20 ± 3 ml/kg·min) groups. SIT trained 3 d/wk for 4 wk, with 1-2 d rest between sessions, while CON continued baseline physical activity (exercise ≤ 1 d/wk). Training consisted of 4-7, 30-s sprints on a stationary cycle with 5% body weight as resistance and 4 min active recovery between sprints. Before and after the intervention, $\dot{V}O_{2max}$ and HR_{max} were measured during a cycling graded exercise test, while a 20-min ride at 50% $\dot{V}O_{2max}$ was used to estimate cardiac output ($\dot{Q}$) and stroke volume (SV) by CO_2-rebreathing. Maximal responses were estimated using measured $\dot{V}O_{2max}$ and HR_{max}, and assuming SV was maximal at 50% $\dot{V}O_{2max}$, $\dot{Q}_{max}$ and $(a\text{-}v)O_2$ $diff_{max}$ were calculated. **RESULTS:** Increases in SIT were significantly greater than in CON ($P < 0.05$) for $\dot{V}O_{2max}$ (0.245 L/min, 12% vs. -0.011 L/min, -1%), $\dot{Q}_{max}$ (1.5 L/min, 10% vs. -0.9 L/min, -6%) and SV_{max} (10 ml/b, 11% vs. -3.2 ml/b, -4%). Changes by SIT and CON in HR_{max} (-2 bpm, -1% vs. -2 bpm, -1%) and $(a\text{-}v)O_2$ $diff_{max}$ (0.4 ml/100 ml, 3% vs. , 0.6 ml/100 ml, 5%) were not significantly different ($P > 0.05$). **CONCLUSION:** Four weeks of SIT improves $\dot{V}O_{2max}$ by increasing SV_{max} and $\dot{Q}_{max}$.

Keywords: sprint interval training, cardiac output, muscle oxidative capacity

Introduction

Maximal aerobic power ($\dot{V}O_{2max}$) is frequently used as an indicator of health (3, 26) and is inversely related to all-cause mortality, primarily due to lowered risk of cardiovascular disease (3). Individuals with low $\dot{V}O_{2max}$ have four times the age-adjusted, all-cause mortality rate of those with high values (3). Low $\dot{V}O_{2max}$, physical inactivity, and being overweight/obese are all risk factors for developing cardiovascular disease, hypertension, and diabetes, and individuals with these diseases have increased morbidity and mortality. Therefore, improving $\dot{V}O_{2max}$ and maintaining moderate-to-high levels of physical activity in sedentary, overweight individuals is essential to preserving health.

Repeated bouts of very-intense cycling of short-duration, termed sprint interval training (SIT) (9), increases skeletal muscle oxidative capacity and may increase $\dot{V}O_{2max}$ in healthy men and women (6-9, 19, 28, 36), but whether peripheral and/or central circulatory changes are responsible for improvements in $\dot{V}O_{2max}$ after SIT is unknown. Prolonged moderate-intensity training improves $\dot{V}O_{2max}$ by increasing maximal stroke volume (SV_{max}), cardiac output ($\dot{Q}_{max}$) and arteriovenous oxygen content difference ($(a\text{-}v)O_2\ diff_{max}$) (2, 17, 18, 37, 38, 40), but the magnitude of improvement depends on the individual's initial level of training as well as the intensity, frequency and duration of the exercise training. SIT in rats (healthy and after induced myocardial infarction, MI) increases $\dot{V}O_{2max}$, $\dot{Q}_{max}$, SV_{max}, and blood flow to working skeletal muscle, but does not increase $(a\text{-}v)O_2$ diff or maximal heart rate (HR_{max}) (31, 33). In contrast, endurance training in MI rats increases $(a\text{-}v)O_2\ diff_{max}$ and tends to increase $\dot{Q}_{max}$ (32). Based on these findings, SIT may be helpful for producing positive health outcomes linked to $\dot{V}O_{2max}$ in humans, especially those at risk for health-related morbidity and mortality.

Although SIT has been shown to improve $\dot{V}O_{2max}$ in healthy, normal-weight college-aged individuals, it has not been established whether SIT would be a suitable modality for improving $\dot{V}O_{2max}$ in individuals who are sedentary and overweight/obese.

The objective of our study was to examine the effects of SIT on $\dot{V}O_{2max}$ and its determinants ($\dot{Q}_{max}$, HR_{max} and SV_{max}, and $(a\text{-}v)O_2$ $diff_{max}$) in sedentary, overweight/obese individuals. It was hypothesized that SIT would increase $\dot{V}O_{2max}$, $\dot{Q}_{max}$, SV_{max} and $(a\text{-}v)O_2$ $diff_{max}$.

Methods

Participants. Twenty-eight women participated in the study. To reduce the heterogeneity of the outcome variables and to increase statistical power, only women were included. Using a mixed model repeated measures ANOVA, a sample size of 14 per group is sufficient to detect a moderate (Cohen's d = 0.57) Group x Time interaction effect for $\dot{V}O_{2max}$ (8) with an experiment-wise α level of 0.05 and a power of 0.8, assuming a correlation between repeated trials of 0.9 (34). Inclusion criteria included women who were sedentary (exercise ≤ 1 day per wk) and had a BMI of > 25 kg/m^2. Exclusion criteria included women who had been clinically diagnosed with type 1 or type 2 diabetes, had a history of smoking (≤ 6 mo), hypertension, or who were on antidepressant, antianxiety, or hypertension medication. The experimental protocol was approved by the University's Institutional Review Board, and all participants provided written informed consent.

Research design. A randomized, pretest-posttest control group design was used for the study. Participants were randomly assigned to either a sprint interval training group

(SIT, n = 14) or control (CON, n = 14) group. Outcome variables were measured on both groups before and after the intervention period.

Familiarization. One week prior to pre-testing, the participants came to the laboratory to practice testing procedures. Anthropometric data were collected, and then participants cycled for 10 min (Lode, Groningen, Netherlands) at a power output estimated to elicit 50% $\dot{V}O_{2max}$ to practice the CO_2-rebreathing method used to measure cardiac output. To obtain $\dot{V}O_{2max}$, participants performed a graded cycling exercise test (GXT), beginning at 40 W and increasing 20 W every 2 min until exhaustion. Following recovery, participants performed two practice sprints on a mechanically-braked cycle ergometer (Monark, Sweden) to simulate a partial training session.

Experimental trials. All testing was performed in thermoneutral conditions (~25ºC, ~40% RH). Body weight was measured on an electronic scale (A & D Company, Ltd., Tokyo, Japan) and body composition was measured by dual-energy x-ray absorptiometry (iDXA, GE Healthcare-Lunar, Madison, WI). Then, a sterile, flexible catheter (Angiocath™, Becton Dickinson, Franklin Lakes, NJ) was inserted into a forearm vein and kept patent with 0.5 mL of 10 USP units/mL heparin lock flush. Participants sat upright for 20 min in order for plasma volume to stabilize, and expired air was analyzed by open-circuit spirometry for 2 min to measure $\dot{V}O_2$ and $\dot{V}CO_2$ using a Parvo Medics TrueOne 2400 Metabolic Measurement System (Parvo Medics, Inc., Sandy, UT). Resting HR was recorded (Polar Electro, Inc, Woodbury, NY, model 145900) and two trials of CO_2-rebreathing were performed. A resting 2-mL blood sample was drawn into a Vacutainer blood collection tube containing EDTA (Becton Dickinson, Franklin Lakes, NJ) and analyzed for hemoglobin ([Hb]) in duplicate (HemoCue, Inc., Lake Forest, CA),

and hematocrit (Hct) in triplicate using the microhematocrit method. Resting plasma volume (PV) was estimated from fat-free mass using the equation of Sawka et al. (39). The pre- to post-treatment change in PV was estimated from changes in resting [Hb] and Hct (16).

Central circulatory measures. After the resting measures, participants performed a 20-min cycle ride on an electronically-braked ergometer (Lode Excalibur Sport, Lode B.V., Groningen, NL) at a power output estimated to elicit 50% $\dot{V}O_{2max}$ so that central circulatory measures could be obtained. From min 15-17, $\dot{V}O_2$, $\dot{V}CO_2$ and HR were measured, and from min 17-20, the CO_2-rebreathing procedure for measuring $\dot{Q}$ was performed. Two rebreathing trials, separated by approximately 1 min, were performed and averaged, and $\dot{Q}$ was calculated using the indirect Fick CO_2-rebreathing method as described by Heigenhauser and Jones (22). The reliability of values for $\dot{Q}$ from the two trials was high (ICC for $\dot{Q}$ = 0.93) and similar to that reported previously from this laboratory (45). SV was determined by dividing $\dot{Q}$ by HR.

Since SV_{max} occurs at approximately 40% $\dot{V}O_{2max}$ in untrained individuals (1), SV_{max} was assumed to equal SV measured at 50% $\dot{V}O_{2max}$. $\dot{Q}_{max}$ was estimated by multiplying SV_{max} (20-min cycling test) by HR_{max} (obtained during $\dot{V}O_{2max}$ test). Maximal (a-v)O_2 diff was calculated using the Fick equation (22).

$\dot{V}O_{2max}$. $\dot{V}O_{2max}$ was measured using a continuous, progressive, load-incremented cycle ergometer protocol. We chose a work rate increment large enough to induce a test duration of 8-17 min and to optimize maximal effort by the participants and attainment of a true $\dot{V}O_{2max}$ in non-trained individuals (5). The graded exercise test (GXT) was adapted and modified from Davies et al. (14), Godfrey et al. (20), and Lafortuna et al. (27) for

young, obese women. Participants began at 40 W and the power output increased 20 W every 2 min until participants could no longer continue. Metabolic measurements were obtained continuously and averaged over 1-min intervals. HR and rating of perceived exertion (RPE) using the Borg 15-point scale (4) were obtained at the end of each 2-min stage and at exhaustion. A fingerstick blood sample was obtained 3 min after the GXT to determine end-test lactate concentration (Lactate Pro, BC, Canada).

To ensure that a plateau in $\dot{V}O_2$ was attained, participants completed an additional bout of cycling following 20 min of rest. Participants cycled to exhaustion at a power output equivalent to the last workload performed during the graded test (if < 1 min was completed during the last stage of the graded test) or at a power output 20 W higher than the last workload performed during the graded test (if ≥ 1 min was completed during the last stage of the GXT).

Attainment of $\dot{V}O_{2max}$ was based on evidence of a plateau in $\dot{V}O_2$ with increasing power output customized for this population. Lafortuna et al (27) found that the mean (± S.D.) increase in $\dot{V}O_2$ (L/min) for obese women (age 23.2 ± 1.6 years, BMI 40.4 ± 1.2 kg/m^2) undergoing a 20-W incremental graded exercise test was 0.264 ± 0.0267 L/min. Therefore, the $\dot{V}O_2$ increase accepted as the maximum allowed to provide evidence of a plateau was > 2 standard deviations less than the expected $\dot{V}O_2$ increase associated with the increase in work (i.e. < 0.210 L/min). Using this approach, all participants met the plateau criterion on both tests.

Diet. Participants were instructed to maintain their usual diet (quantity of intake and type of foods) throughout the intervention period. Participants recorded their dietary intake detailing their daily food consumption for 2 d prior to pretesting and did not

consume caffeine or alcohol for 24 h before the test day. The food diaries were collected, photocopied and returned to the participants after pretesting. Two days prior to posttesting, participants were instructed to replicate their pretest diet to decrease any confounding effects of food intake on their performance.

Interventions. Participants in SIT followed a training protocol modified from Burgomaster et al. (9). Each training session consisted of repeated, 30-s cycling sprints (4 to 7 bouts/session) followed by 4 min of active recovery between bouts on a Monark ergometer. Participants warmed up for 4 min with no resistance, and then began pedaling at maximal cadence ~5 s before a fixed resistance of 0.05 kg/kg BW (43) was applied. Participants continued pedaling at power outputs estimated to elicit ~250% $\dot{V}O_{2max}$ (extrapolated from GXT) against the resistance for 30 s. After the sprint, the resistance was removed and they continued cycling for 4 min of active recovery. These intervals were repeated until the prescribed number was performed. After the last sprint, participants actively cooled down while pedaling against no resistance until their HR recovered to ≤ 130 bpm. On the first training day, participants performed 4 sprints with 4 min of active recovery between bouts. The subsequent training sessions increased by one sprint bout every week, finishing with cycling 7 sprints/session in the last week. Participants trained 3 d/wk (1-2 d rest between sessions) for 4 wk and were instructed to maintain their pre-study physical activity outside of the training intervention.

Work performed by SIT during the 4-wk training regimen was recorded to quantify the training volume. An optical sensor (Sports Medicine Industries, Inc., St. Cloud, Minnesota) was secured to the ergometer frame and 16 reflective markers were placed on the flywheel to record flywheel revolutions. The sensor was interfaced with a

computer-based SMI Power software program (version 1.02) that recorded revolutions per minute and calculated power output per second (W/s). The W/s for the 30-s sprint was summed and converted to Joules (J) to obtain work performed for the exercise session, and the work for each session over the 4 wk was calculated to obtain weekly and total work of the intervention. Finally, work done on the 4th sprint of each session was used as an indicator of the intensity of the training across the training period.

Participants in CON were instructed to maintain their baseline physical activity during the intervention period and to neither increase nor decrease their activity level. After completion of their posttests, participants were offered the opportunity to participate in SIT training for 4 wk.

Statistical analysis. Data were analyzed using SPSS v. 15.0, (SPSS, Inc., Chicago, IL). Differences between groups at baseline for all physical characteristics and outcome variables were analyzed using a *t*-test for independent samples. Differences in work performed by SIT across 4 wk of training were analyzed using a one-way, repeated measures ANOVA. Post hoc tests were performed (Bonferroni) to test for differences between weeks. To test the significance of the effects of the intervention before and after training, a two-way (Group x Time), mixed model ANOVA was used. If an interaction exsisted, tests for simple effects were performed to examine the effect of the treatment on each group separately. Differences were considered significant if $P < 0.05$.

Results

Participant characteristics and work performed. No differences existed between groups at the pretest for age, BMI, percentage body fat, or $\dot{V}O_{2max}$ ($P > 0.05$, Table 1). The individual analyses for the Group x Time interaction in the 2-way ANOVA for

changes in weight, BMI, or % body fat as a result of the intervention in either group were not significant ($P > 0.05$), indicating that any changes observed in SIT were not different from changes in CON. The weekly average total work performed during the 30-s all-out efforts for SIT increased linearly by an average of 35 ± 2 kJ (mean ± SEM) per week and was statistically different among the 4 wk ($P < 0.001$, Figure 1). Post-hoc pairwise comparisons (Bonferroni-adjusted) indicated that work performed increased significantly from week 1-2 ($P = 0.001$), week 2-3 ($P = 0.011$), and week 3-4 ($P = 0.001$). Work performed on the 4th sprint of each session was not statistically significantly different among sessions ($P > 0.05$), indicating that no variability in effort existed among sessions and that the participants were giving equal efforts to the sprints.

$\dot{V}O_{2max}$. $\dot{V}O_{2max}$ (L/min) was not different between SIT and CON at the pretest ($P = 0.372$). The Group x Time interaction in the 2-way ANOVA was significant ($P < 0.001$, Figure 2), indicating the change by SIT was significantly different than CON. $\dot{V}O_{2max}$ increased 0.25 L/min (12%, $P < 0.001$) in SIT while CON did not change (-1%, $P = 0.571$). Because there were no significant changes in body mass over the training program ($P = 0.602$), $\dot{V}O_{2max}$ relative to body mass (ml/kg·min) also increased significantly for SIT ($P < 0.001$) but not for CON ($P = 0.617$, Table 2). Indicators of maximal effort on the GXT were similar in the two groups before and after training (Table 2).

$\dot{Q}_{max}$. $\dot{Q}_{max}$ was not different between groups at the pretest ($P = 0.923$). The Group x Time interaction in the 2-way ANOVA for $\dot{Q}_{max}$ was significant ($P < 0.001$, Figure 3a). Tests examining simple effects showed that $\dot{Q}_{max}$ increased in SIT (1.51 L/min, 10%, $P = 0.001$) and declined in CON (0.93 L/min, -6%, $P = 0.017$).

SV_{max}. SV_{max} was not different between groups at the pretest (P = 0.753). The Group x Time interaction for SV_{max} was significant (P < 0.001, Figure 3b). Tests examining simple effects showed that SV_{max} increased (9.7 ml/beat, 11%, P = 0.002) in SIT, whereas CON tended to decrease (3.2 ml/beat, -4%, P = 0.074).

HR_{max}. HR_{max} was not different between groups at the pretest (P = 0.924). The Group x Time interaction for HR_{max} was not statistically significant (P = 0.976, Figure 3c). Mean changes by SIT and CON were –2 and –2 bpm, respectively.

$(a\text{-}v)O_2$ $diff_{max}$. $(a\text{-}v)O_2$ $diff_{max}$ was not different between groups at the pretest (P = 0.850). The Group x Time interaction for $(a\text{-}v)O_2$ $diff_{max}$ (P = 0.623, Figure 3d) was not statistically significant. Mean changes by SIT and CON were –0.4 and –0.6 ml/100ml, respectively.

Estimated resting plasma volume. Estimated PV at rest was not different between groups at the pretest (P = 0.377). The Group x Time interaction for PV was not statistically significant (P = 0.105, Figure 4), although SIT increased 4% (86 ml) compared to no increase for CON.

20-min submaximal cycling test. Relative exercise intensity (%$\dot{V}O_{2max}$) during the 20-min ride was not different between groups at the pretest (P = 0.483) and averaged 58% and 59% for SIT and CON, respectively. Post-intervention, a significant Group x Time interaction was found (P = 0.003). Tests for simple effects showed that participants' relative intensity during the 20-min cycle test decreased to 51% (P < 0.001) after training in SIT, but did not significantly change in CON (58%, P = 0.780).

Discussion

The purpose of our study was to examine whether SIT improves $\dot{V}O_{2max}$ and its determinants (estimated $\dot{Q}_{max}$, HR_{max} and SV_{max}, and $(a\text{-}v)O_2$ $diff_{max}$) in sedentary, overweight/obese women. Our primary finding was that SIT increased $\dot{V}O_{2max}$ through increases in $\dot{Q}_{max}$ and SV_{max} without increasing $(a\text{-}v)O_2$ $diff_{max}$. No studies to our knowledge have examined the effects of SIT on the determinants of $\dot{V}O_{2max}$ in humans. Therefore, ours is the first to show that SIT is an effective and efficient method for increasing SV_{max} and $\dot{V}O_{2max}$ and may be used to improve health and decrease risk for all-cause mortality in this population.

SIT elicited a 12% increase in $\dot{V}O_{2max}$. It is generally accepted that improvements in $\dot{V}O_{2max}$ are related to total amount of work (volume) completed, as determined by the intensity, duration and frequency of training (35). However, Gormely et al. (21) found that adaptation of $\dot{V}O_{2max}$ to training was directly related to intensity and independent of volume up to an intensity of 95% $\dot{V}O_{2max}$. The training used in our study involved a higher intensity and lower volume than in previous studies showing improved $\dot{V}O_{2max}$ with aerobic exercise training. Based on the power outputs elicited during training and extrapolation of the oxygen uptake required by overweight/obese women during submaximal intensities (27), we estimated participants trained at 243% to 284% of $\dot{V}O_{2max}$ during the sprint intervals. However, total volume of work performed during sprinting was 772 ± 37 kJ (mean ± SEM), and total duration was 33 min. In contrast, if the women in our study would have exercised at 65% $\dot{V}O_{2max}$ for 30 min, 3 times/wk for 4 wk, the minimum recommended quantity and quality of exercise for developing and maintaining cardiorespiratory fitness (35), they would have expended ~1469 kJ and

cycled a total of 6 h. Our study and other studies (8, 28) have shown that substantial increases in $\dot{V}O_{2max}$ can be obtained when the intensity of training is very high (>100% $\dot{V}O_{2max}$) and the volume is relatively low. This finding reinforces the conclusion that intensity is the most important element of the physical activity stimulus (23) for increasing $\dot{V}O_{2max}$. Very high intensity can apparently negate the need for high volume, a clear advantage for those who need to improve their aerobic power but are unaccustomed to long-duration exercise of moderate to high intensities.

The greater improvement in $\dot{V}O_{2max}$ observed in our 4 wk study (12%) compared to other studies of SIT (7%) lasting 6-7 wk (8, 28) may have been due to the population under study. MacDougall et al. (28) trained healthy, young, normal weight, physically-active men, whereas Burgomaster et al. (8) trained healthy young, normal weight individuals not engaged in a regular exercise training program. In contrast, our participants were sedentary, overweight/obese women. Therefore, the adaptations observed in $\dot{V}O_{2max}$ may have been greater in this population than in healthy, normal-weight, sedentary and recreationally-active, college-aged men and women.

$\dot{Q}_{max}$ and SV_{max} increased 10% and 11% in the SIT group, respectively, whereas HR_{max} and (a-v)O2 $diff_{max}$ did not change. Although no previous studies in humans have examined the effects of SIT on central circulatory capacity, SIT in MI rats increased $\dot{V}O_{2max}$, $\dot{Q}_{max}$ and SV_{max} by 11%, 18% and 15%, respectively, with no increase in (a-v)O_2 $diff_{max}$ or HR_{max} (31). Our results are consistent with the improvements found in rats after SIT. In contrast, endurance training in MI rats increased (a-v)O_2 $diff_{max}$ 12%, but failed to significantly increase $\dot{Q}_{max}$ or SV_{max} (32). The authors of these studies concluded that the lower training intensity may not have been sufficient to produce changes in central

circulation (32) and that higher intensities may be needed to see central adaptations in a short time frame. This may be one reason why central but not peripheral adaptations occurred after SIT in our study.

Contrary to our hypothesis, (a-v)O_2 $diff_{max}$ did not increase after SIT. Previous studies using SIT have consistently found increased skeletal muscle oxidative capacity, which can contribute to increased (a-v)O_2 $diff_{max}$ (24, 25, 29). The relative importance of the contributions of $\dot{Q}_{max}$ and (a-v)O_2 $diff_{max}$ to the increase in $\dot{V}O_{2max}$ has varied in different studies, with (a-v)O_2 $diff_{max}$ accounting for 0 to 50% of the change in $\dot{V}O_{2max}$ (13, 18, 24, 25, 29, 38). The interaction of volume, intensity, duration and mode of training likely plays a role in differences observed. Also, individuals who are very unfit have been shown to initially adapt to training with a central change followed by a peripheral adaptation during a longer training program (13). The increases in $\dot{V}O_{2max}$, $\dot{Q}_{max}$ and SV_{max} with no difference in (a-v)O_2 $diff_{max}$ in our study are consistent with the range of changes observed with SIT in rats (31) and short-duration aerobic training programs in unfit humans (13).

The mechanisms underlying the improvements observed in $\dot{Q}_{max}$ and SV_{max} may have included a training-induced enlargement of left ventricular chamber size (30, 38), a slight increase in blood volume (41), and cardiac muscle hypertrophy with increased calcium activation of ventricular cardiocytes to enhance contractility during systole (30). When increases in (a-v)O_2 $diff_{max}$ are observed, peripheral adaptations such as increased skeletal muscle oxidative capacity (42), increased capillarization, and a greater fraction of the cardiac output delivering more O_2 to a larger mass of working muscle are assumed to be responsible (41).

The 4% increase in resting PV after SIT, although not significantly different from CON (0%, $P = 0.105$), indicated that increased blood volume contributed little to the increase in SV_{max} and $\dot{Q}_{max}$. Convertino et al. (11) observed an increase in PV of 12% after 8 d of cycling at 65% $\dot{V}O_{2max}$. The exercise stimulus for inducing hypervolemia has thermal and nonthermal components and includes a net expansion of total body water and solutes due to increased water intake and decreased urine volume output (10). It is possible that our training duration (3.5 min total exercise per session), although intense, was too short to produce an increase in core body temperature and subsequently an effective thermal stimulus to increase PV. The intensity of the training stimulus may have caused a rapid hypervolemia immediately after exercise due to protein and fluid shifts from the extravascular to intravascular space (10), but changes in PV were not measured immediately after exercise, and it is unlikely that the shifts became chronic. Therefore, it is difficult to say what may have caused a nonsignificant trend in increased total PV after SIT in our study.

In summary, although SIT has been used to improve performance in athletes and recreationally-active individuals (12, 15, 44), this is the first study to our knowledge to examine the effects of SIT on $\dot{V}O_{2max}$ and its determinants in sedentary, overweight women. The high-intensity but low volume and duration of sprint exercise resulted in significant improvements in $\dot{V}O_{2max}$ and central circulatory capacity. The fact that the sedentary, overweight/obese, women in our study completed the training program without mishap indicates that SIT could be an effective training modality for preserving health and decreasing risk of all-cause mortality in this population subgroup. Further studies are needed to determine other potential health benefits of SIT in sedentary,

overweight/obese women, as well as to study the effects of this novel training protocol on health outcomes in other groups.

Acknowledgements

The authors thank Miley Duvall, Mai Nguyen, Hemal Patel, Anna Gelbrich, Diana Kim and Sahir Ahsan for their technical assistance with the study.

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Table 4.1. *Participant physical characteristics (means ± SD)*

	SIT	CON
Age (y)	30.14 ± 6.8	31.43 ± 5.5
Weight (kg)	96.77 ± 15.2	96.61 ± 22.7
Height (cm)	164.51 ± 6.2	166.35 ± 7.7
Body mass index	35.74 ± 6.3	34.57 ± 5.9
Fat Mass (%)	48.01 ± 5.7	46.85 ± 5.2

Table 4.2. *VO_{2max} and associated measures obtained during the GXT (means ± SD)*

Variable	SIT		CON	
	Pre	*Post*	*Pre*	*Post*
VO_{2max} (ml/kg· min)	21.6 ± 4.2	24.5 ± 3.9*	20.5 ± 3.2	20.4 ± 3.1
VO_{2max} (ml/kg FFM· min)	43.1 ± 6.0	47.7 ± 6.0*	40.6 ± 4.7	40.0 ± 3.9
O_{2pulse}max (ml/b)	11.1 ± 1.8	12.7 ± 2.0	10.7 ± 1.6	10.7 ± 1.5
Heart $Rate_{max}$ (bpm)	184 ± 10	182 ± 12	182 ± 9	180 ± 10
RER_{max}	1.16 ± 0.04	1.16 ± 0.04	1.17 ± 0.05	1.16 ± 0.06
$Lactate_{max}$ (mmol/L)	9.8 ± 1.8	10.3 ± 1.5	9.2 ± 1.4	8.5 ± 1.3*
RPE_{max}	19.4 ± 0.7	19.0 ± 0.5	19.4 ± 0.08	19.2 ± 0.7

*Significant change from pre- to post-treatment ($P < 0.05$).

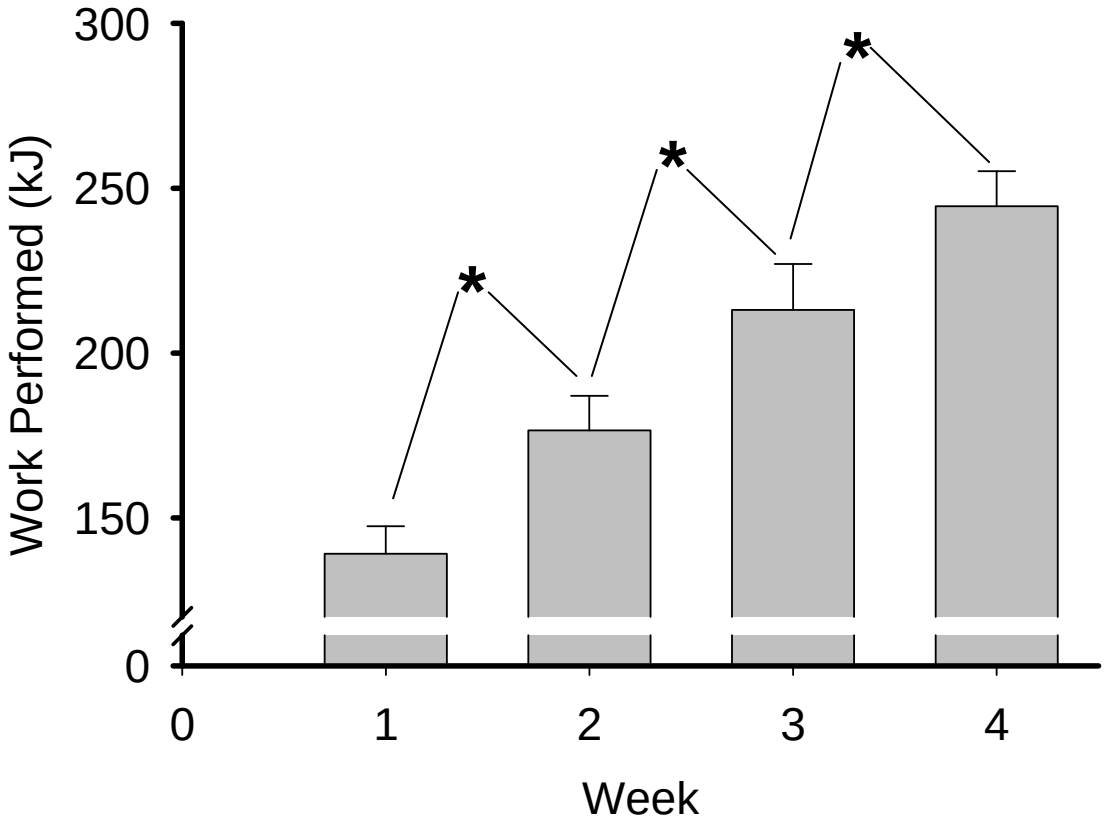

Figure 1. Work performed over the 4 weeks (n = 14) for SIT. Values are means ± SEM.

*Significant increase between weeks ($P < 0.05$).

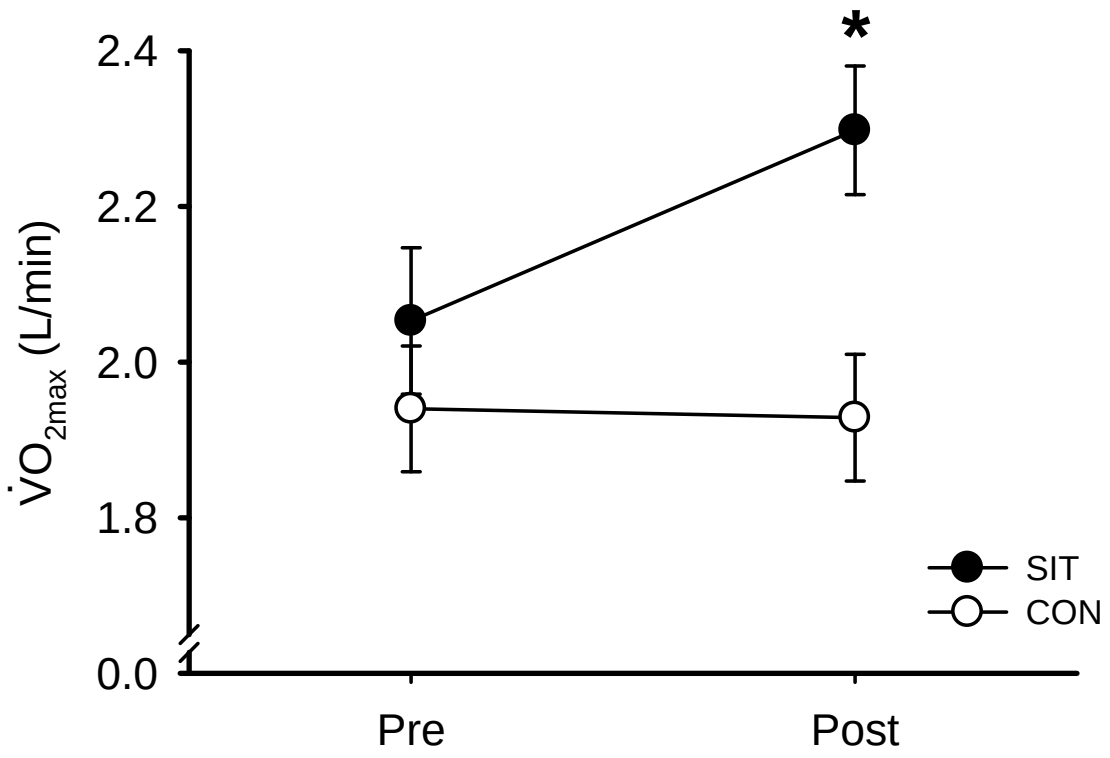

Figure 4.2. Changes in $\dot{V}O_{2max}$ before and after the intervention. Values are means ± SEM. *Significant Group x Treatment interaction ($P < 0.001$).

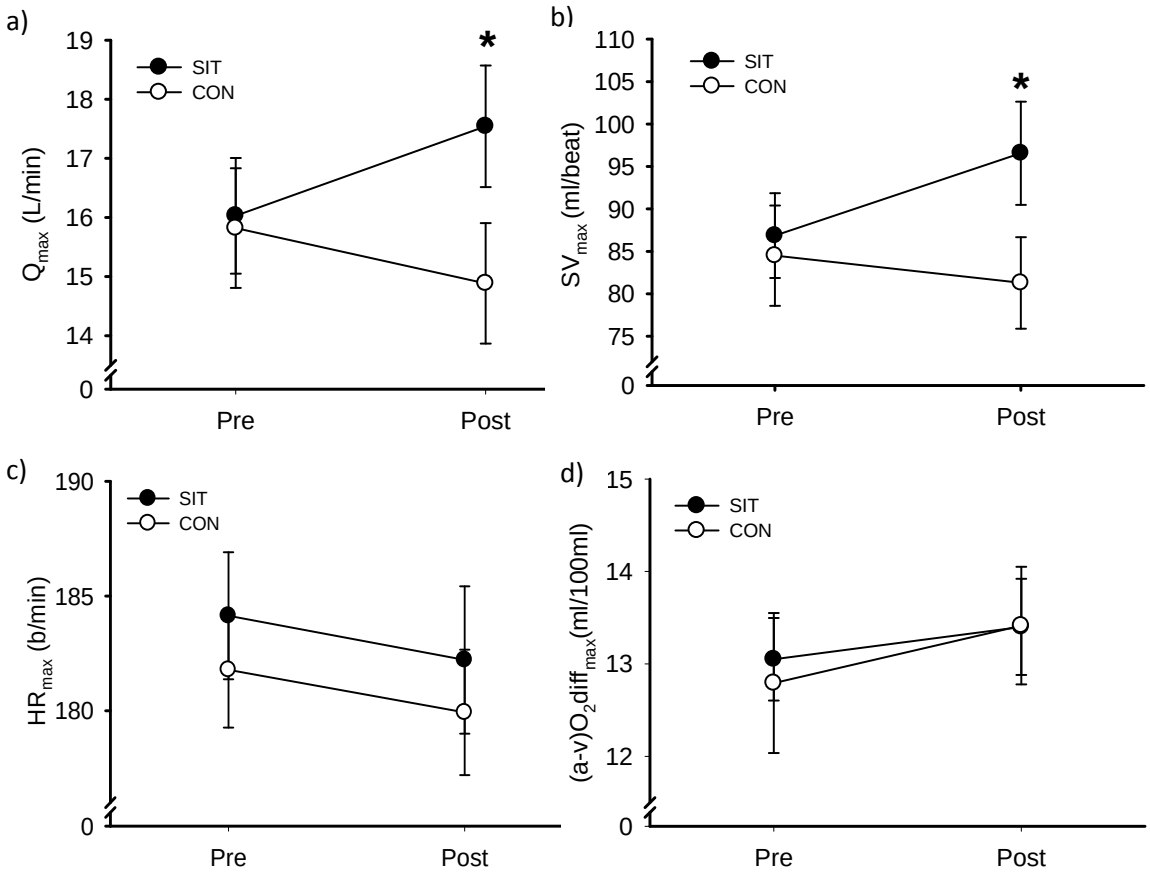

Figure 4.3. Changes in maximal circulatory measures before and after the intervention. a) cardiac output; b) stroke volume; c) heart rate; and d) oxygen extraction. Values are means ± SEM. *Significant Group x Treatment interaction ($P < 0.05$).

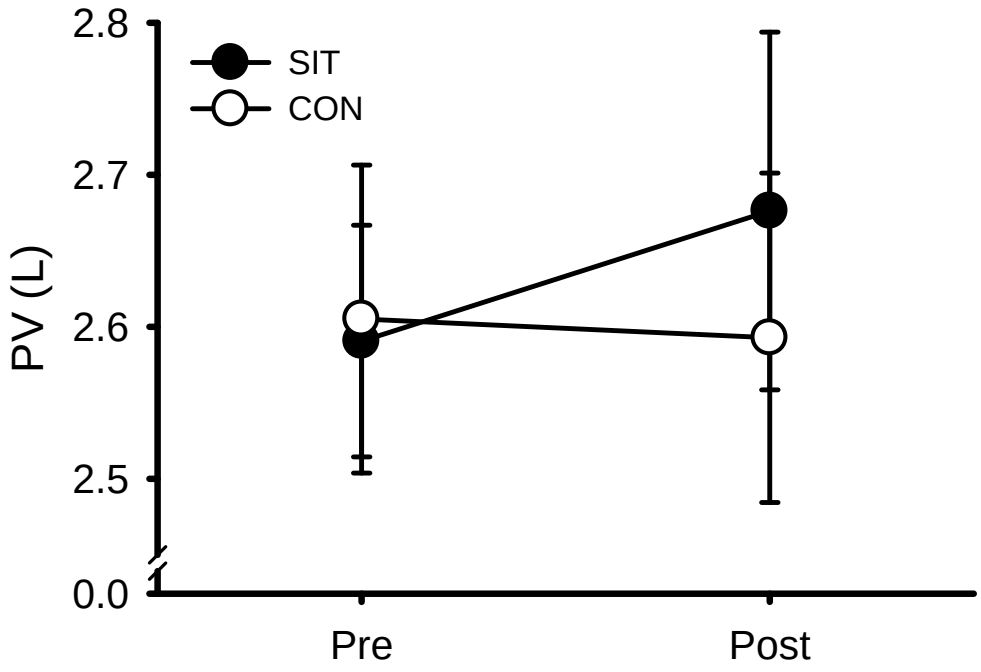

Figure 4.4. Changes in resting plasma volume before and after the intervention. Values are means ± SEM.

CHAPTER 5

SUMMARY AND CONCLUSIONS

Sprint interval training (SIT) is a common modality used by athletes to enhance performance. However, its use as a method for improving heath in sedentary, overweight/obese individuals at risk for disease has not been considered until now. Increases in $\dot{V}O_{2max}$ and skeletal muscle oxidative capacity observed after SIT in healthy, recreationally-active or sedentary individuals prompted inquiry as to whether these increases could translate to a population of sedentary, overweight/obese women and incorporate SIT as an effective and efficient training modality to improve insulin sensitivity, glucose tolerance and central circulatory capacity.

The primary purpose of this study was to determine if SIT improves markers of insulin sensitivity and glucose tolerance in sedentary, overweight/obese women. The secondary purpose of this study was to determine if SIT improves $\dot{V}O_{2max}$ and its determinants ($\dot{Q}_{max}$, $SV_{max,}$ and $(a\text{-}v)O_2\,diff_{max}$) that limit $\dot{V}O_{2max}$ and exercise capacity. A randomized, pretest-posttest control group design was used to determine the effects of SIT on 28 sedentary, overweight/obese women.

In study #1, the effects of SIT on markers of insulin sensitivity (fasting insulin concentration, logHOMA-IR, ISI, I-AUC), fasting glucose, and glucose tolerance (G-AUC) were examined before and 2 d after an intervention period that lasted 4 wk. For the SIT group, insulin sensitivity increased statistically in logHOMA-IR (P = 0.000), and the improvements in fasting insulin, ISI, and I-AUC, although not statistically significantly

different from CON, are clinically relevant. No effect of training was observed for fasting glucose and G-AUC, as changes in SIT were not statistically significantly different from CON.

In study #2, the effects of SIT on $\dot{V}O_{2max}$ and its determinants ($\dot{Q}_{max}$, $SV_{max,}$ and (a-v)O_2 $diff_{max}$) that limit $\dot{V}O_{2max}$ were examined. Increases in SIT were significantly greater than in CON ($P < 0.05$) for $\dot{V}O_{2max}$, $\dot{Q}_{max}$ and SV_{max}, however changes in HR_{max} and (a-v)O_2 $diff_{max}$ were not significantly different ($P > 0.05$) between groups.

The results of this research support the hypotheses that SIT improves health by increasing insulin sensitivity, $\dot{V}O_{2max}$, and central circulation in sedentary, overweight/obese women. The hypotheses that SIT improves glucose tolerance and (a-v)O_2 $diff_{max}$ were not supported.

Further studies are warranted to determine other potential health benefits of SIT in sedentary, overweight/obese individuals, as well as to study the effects of this novel training protocol in other population subgroups. Also, examining the feasibility of using SIT in real-life settings is needed. Our findings provide support for the use of SIT as a sound, time efficient, and valuable adjunct modality in the lifestyle management of overweight/obese individuals at risk for type 2 diabetes; however, whether individuals would adhere to the protocol is still in question. The women used in our study were able to complete the training program effectively and safely, with no attrition due to the training protocol itself. This provides encouraging information that SIT may potentially be used in real-life settings for preserving health and decreasing risk of all-cause mortality caused by disease.