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Duration of improved insulin sensitivity after high intensity exercise in young overweight men

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**Duration of improved insulin sensitivity after high intensity exercise in young
overweight men**

by

Kelsey Quinn

A thesis submitted to the graduate faculty
in partial fulfillment of the requirements for the degree of

MASTER OF SCIENCE

Major: Kinesiology

Program of Study Committee:

Rick L. Sharp, Major Professor

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Iowa State University

Ames, Iowa

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NOMENCLATURE

BMI	Body Mass Index
FFA	Free Fatty Acid
GLUT-4	Glucose Transporter Type 4
HIT	High Intensity Interval Training
NIDDM	Non-Insulin-Dependent Diabetes Mellitus
OGTT	Oral Glucose Tolerance Test
RPM	Revolutions Per Min
SIT	Sprint Interval Training
T2D	Type 2 Diabetes

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ABSTRACT

Insulin resistance, an impaired ability of the tissues to respond to insulin, is a prevalent health concern in the U.S., with 8.3% of the population diagnosed with diabetes. Numerous studies have found exercise programs increase insulin sensitivity, but research on the effects of high intensity interval training on insulin sensitivity is limited. Of those studies, few have observed the length of the effect of a single bout of high intensity interval training (HIT) on insulin sensitivity to determine the minimal exercise time and frequency that stimulates improved insulin sensitivity. **Purpose:** This study investigated the length of the effect of a single bout of HIT on insulin sensitivity and glucose tolerance in young overweight/obese males. **Methods:** Ten overweight/obese men aged 20.9 ± 2.0 y participated. An oral glucose tolerance test (OGTT) was performed five d prior to the exercise trial to determine basal insulin sensitivity. Participants completed eight 30-s intervals with 4 min recovery between each (HIT). Two, three and four d post-exercise, OGTTs were performed. **Results.** The IG index was significantly lower 48 h post-exercise compared to baseline (10128 ± 3910 vs 4867 ± 2080 , $P=0.013$) demonstrating improved insulin sensitivity, but was not significantly different from baseline at 72 h (+) or 96 h (+) post-exercise. Plasma glucose concentration was significantly lower at 60 min during the OGTT 72 h (7.1 ± 0.7 vs 8.2 ± 0.6 , $P=0.033$) and 96 h (6.9 ± 0.7 vs 8.2 ± 0.6 , $P=0.023$) post-exercise, but was not significantly different from baseline at 48 h post-exercise. **Conclusion.** An acute bout of 8 x 30 s high intensity interval exercise results in significantly improved plasma glucose concentrations at 60 min during an OGTT at 72 and 96 h post-exercise. A single bout of HIT improves insulin sensitivity for 48 h in sedentary, overweight/obese young men.

CHAPTER I

INTRODUCTION

Insulin resistance is defined as an impaired ability of tissues to respond to insulin (Watt & Bruce, 2009). Insulin resistance impairs muscle glucose uptake, resulting in elevated levels of circulating glucose and free fatty acids in the blood, and necessitates increased insulin secretion (Roden et al., 1996, Homko, Cheung & Boden, 2003). Insulin resistance is associated with obesity and is linked to the development of non-insulin dependent diabetes mellitus (type 2 diabetes) and cardiovascular disease (Bonora et al., 1998, Facchini, Hua, Abbasi & Reaven, 2001, Metcalfe, Babraj, Fawcner & Vollaard, 2012).

With 8% percent of the United States population diagnosed with diabetes, and 90% of those individuals diagnosed with type 2 diabetes, the need for insulin resistance reversal is compelling (ADA, 2013). Insulin sensitivity is inversely related to the level of insulin necessary for proper glucose uptake. Improving insulin sensitivity is associated with a decrease in the subsequent effects of obesity and chronic disease and is important for chronic disease prevention (Facchini et al., 2001). Determining the most effective strategies to improve insulin sensitivity through exercise is vital to improving the health and well-being of those with insulin resistance and/or diabetes worldwide.

CHAPTER II

REVIEW OF LITERATURE

Functions of Insulin and Insulin Resistance

Insulin has a significant role in several physiological functions of the human body. When insulin is released in response to elevated blood glucose levels it triggers glucose uptake by cells, returning blood glucose to normal levels. Insulin stimulates the liver to both store glucose in the form of glycogen and synthesize fatty acids. Insulin also has a significant effect of sparing fat by inhibiting lipase and facilitating increased glucose transport into adipocyte cells (Kono, 1969, Suzuki & Kono, 1980).

Insulin resistance is defined as an impaired ability of tissues to respond to insulin (Watt & Bruce, 2009). Insulin resistance impairs muscle glucose uptake, resulting in elevated levels of circulating glucose and free fatty acids in the blood that necessitates increased insulin secretion (Roden et al., 1996, Homko et al., 2003). Insulin resistance is associated with obesity and is linked to chronic disease development; specifically non-insulin dependent diabetes mellitus (type 2 diabetes), which is inclusive of chronically elevated plasma glucose, as well as cardiovascular disease among others (Bonora et al., 1998, Facchini, Hua, Abbasi & Reaven., 2001, Metcalfe et al., 2012).

With 8.3% percent of the United States population diagnosed with diabetes, and 90% of those individuals diagnosed with type 2 diabetes, the need for insulin resistance reversal is compelling (ADA, 2013). Insulin sensitivity has an inverse relationship with the level of insulin necessary for proper glucose uptake; thus, high insulin sensitivity requires a low amount of insulin. Increasing insulin sensitivity is correlated with a

decrease in the subsequent effects of obesity and chronic disease and is important for chronic disease prevention (Facchini et al., 2001).

Mechanisms of Insulin Resistance

Insulin Resistance and Free Fatty Acid Mobilization and Oxidation

Studies on the effects of free fatty acid mobilization on insulin resistance have observed an inhibition of glucose transport/uptake with elevated plasma free fatty acids (Roden et al., 1996, Homko et al., 2003). Inhibition of glucose uptake is followed by reduced glucose oxidation and skeletal muscle glycogen synthesis, leading to insulin resistance (Boden, Chen, Ruiz, White & Rossetti, 1994, Roden et al., 1996, Homko et al., 2003). A two to three-fold increase in plasma FFA and a simultaneous insulin resistance was observed immediately post-exercise in comparison to one d after exercise, suggesting the elevated plasma FFA was related to the immediate post-exercise impaired glucose uptake (King et al., 1995).

Separate studies tested the effects of incrementally-increased FFA, observing a dose-dependent inhibition of insulin-stimulated glucose uptake and increased insulin-suppressed hepatic glucose production with increasing FFA (Boden et al., 1994), versus inhibition of glucose transport and reduction in glucose oxidation (Roden et al., 1996). These results suggest insulin resistance could be decreased through the lowering of plasma FFA, though the mechanisms by which FFA would be most drastically reduced remain tentative.

Results from several studies suggest reduced FFA mobilization is the primary mediator of increased insulin sensitivity (Santamauro et al., 1999, Schenk, Harber, Shrivasta, Burant & Horowitz, 2009). This was shown through reduced insulin resistance/increased insulin sensitivity in both drug-induced lowering of FFA in lean and obese subjects (Santamauro et al., 1999) and weight-loss-induced lowering of FFA (Schenk et al., 2009). Further research observed no improvements in insulin sensitivity post-liposuction, which includes weight loss absent of reduced fatty acid mobilization, supporting previous findings and concluding reduced FFA mobilization, as opposed to increased fat oxidation, facilitates an increase in insulin sensitivity (Klein et al., 2004). In contrast to studies supporting FFA reduction as a mediator of insulin sensitivity, Schenk, Cook, Kaufman & Horowitz (2005) observed no decreases in post-exercise increased insulin sensitivity after an overnight lipid infusion, suggesting the mechanisms of post-exercise improvements in insulin sensitivity are not affected by increased plasma FFA levels.

Insulin Resistance, Obesity and FFA

Both early and recent research suggests that obesity is strongly associated with, and possibly causes, insulin resistance (Freidenberg, Reichart, Olefsky & Henry, 1988, Schenk et al. 2009). FFAs are thought to be a main facilitator in the development of insulin resistance with obesity (Santamauro et al., 1999, Schenk et al. 2009). Research has shown that drug-induced lowering of FFA resulted in improved insulin resistance through increased insulin sensitivity in both normal and diabetic obese subjects

(Santamauro et al., 1999). A more recent study observed returning fatty acid levels to pre-weight-loss levels via overnight lipid infusion completely reversed the improvement in insulin sensitivity from weight loss and exercise, despite increased fat oxidation (Schenk et al. 2009). Further research is needed to conclude the possible causal effect of obesity on insulin resistance.

Insulin Resistance and GLUT4 Uptake

Glucose transport is mediated by a carrier protein across the plasma membrane. The main carrier protein for glucose transport in human and rat skeletal muscle is GLUT-4 (Klip & Paquet, 1990). Research has found skeletal muscle GLUT-4 expression to be normal in humans in an insulin-resistant state, indicating that decreased glucose uptake is a result of altered recruitment of glucose transporters to the plasma membrane (Lund, Holman, Schmitz & Pedersen, 1995). Restoring GLUT4 availability in the plasma membrane to non-insulin resistant levels has the possibility of counteracting decrease glucose uptake in insulin resistance.

Exercise Effects on GLUT4 and Insulin Resistance

Through independent stimulus by either insulin or exercise, or a combination of both, glucose transport is increased by increasing maximal velocity of transport (v_{\max}) (Narahara, Ozand & Cori, 1960, Holloszy & Narahara, 1965, Nesher, Karl & Kipnis, 1985, Hansen et al., 1995). V_{\max} may be increased by; 1) an increase in the rate of

glucose transport by each GLUT4 protein, referred to as transporter turnover number or intrinsic activity (Douen, Ramlal, Cartee & Klip, 1990, Brozinick, Etgen, Yaspelkis & Ivy, 1994, Kristiansen, Hargreaves & Richter 1996), 2) an increase in the number of GLUT4 proteins available in the plasma membrane, referred to as GLUT4 translocation (Suzuki & Kono, 1980, Goodyear, Hirshman, Smith & Horton, 1991, Gao, Ren, Gulve & Holloszy, 1994, Ploug, van Deurs, Ai, Cushman & Ralston, 1998), or a combination of increased intrinsic activity and GLUT4 protein availability (King et al., 1995).

Early research on glucose transport found skeletal muscle contractions can recruit GLUT4 in the absence of insulin, inferring that exercise alone can increase glucose uptake through increased GLUT4 availability in the plasma membrane (Brozinick et al., 1994). Several studies observed an additive effect of the combination of insulin+contraction of skeletal muscle, with rate of glucose transport significantly higher than with insulin or contraction alone (Nesher et al., 1985, Wallberg-Henriksson, Constable, Young & Holloszy, 1988).

Research on an additive effect led to the hypothesis that insulin and skeletal muscle contraction stimuli acquire GLUT4 transporters from two separate pools, allowing the additive effect of insulin and contraction to be greater than each stimulus independently (Nesher et al., 1985, Wallberg-Henriksson et al., 1988, Douen et al., 1990, Brozinick et al., 1994, Plough et al., 1998). Although studies have observed certain transporters are only recruited by muscular contractions in rats (Ploug et al., 1998), suggesting separate pools of GLUT4 transporters, further research is necessary to understand the mechanisms involved in GLUT4 availability for insulin and skeletal muscle contraction stimuli at the plasma membrane in humans.

A single bout of exercise has been found to increase GLUT4 translocation to the plasma membrane, causing increased glucose uptake post-exercise (Lund et al., 1995, Kristiansen et al., 1996, Kennedy et al., 1999). This increase in GLUT4 translocation is stimulated by contractions of skeletal muscle without the presence of insulin (Brozinick et al., 1994). The results from these studies suggest impaired glucose uptake from insulin resistance can be countered by increased GLUT4 translocation and intrinsic activity resulting from a single bout of exercise. Thus, through increased GLUT4 translocation and intrinsic activity, even a single bout of exercise can act as a buffer for the impaired glucose uptake caused by insulin resistance.

Research has found insulin-activated kinase Akt in skeletal muscle regulates AS160 activation, which mediates insulin-stimulated GLUT4 translocation (Sano et al., 2003). A recent study observed a 6- to 7-fold increase in Akt and a two-fold increase in AS160 36-48 h after a 6-month weight loss+aerobic exercise intervention (Ryan et al., 2014). Whether the increase is a result of the last bout of exercise prior to testing or the long-term impact of aerobic exercise has not been determined, but the effect of an increase in insulin sensitivity on Akt and AS160 is significant.

Insulin Resistance and Disease

There is evidence insulin resistance has a role in several metabolic disorders, including type 2 diabetes, hypertriglyceridemia, hypercholesterolemia, and hypertension among others (Bonora et al., 1998, Facchini et al., 2001, Metcalfe et al., 2012). Research has observed subjects with the highest rates of insulin resistance reported age-related

disease development in one-third of the subjects, in comparison to no disease development in subjects with the lowest levels of insulin resistance (Facchini et al., 2001). Euglycemic offspring of individuals with NIDDM (non-insulin-dependent diabetes mellitus) show significant insulin resistance as early as 10 years before the development of type 2 diabetes (Martin & Warram, 1992). The severe impact of insulin resistance on several diseases and metabolic disorders vindicates the need for continued research on mechanisms of decreasing insulin resistance.

Implications of Exercise on Insulin Resistance and Type 2 Diabetes

Insulin resistance has been identified as a main component of type 2 diabetes (T2D) (Bonora et al., 1998, Facchini et al., 2001, Metcalfe et al., 2012). As mentioned previously, studies have observed that despite decreased insulin-stimulated glucose uptake, individuals with T2D have normal sensitivity in skeletal muscle to exercise (Kennedy et al., 1999). Research has found individuals with T2D have a decreased GLUT4 recruitment to the plasma membrane in response to insulin stimulation (Garvey et al., 1998). Thus, the normal response to exercise has been attributed to the normal expression of GLUT4 in skeletal muscle during exercise (Goodyear et al., 1991) and indicates glucose uptake can be increased through exercise despite deficient insulin-mediated glucose uptake.

Research has found short-term moderate and HIT results in significantly increased GLUT4 content in skeletal muscle (Little et al. 2011) and drastically increased insulin sensitivity in T2D (Bordenave et al., 2008, Winnick et al., 2008), indicating short-term

effects of exercise on glucose uptake are significant. A recent study observed a drastic increase in insulin sensitivity in overweight/obese insulin-resistant men after a six-month weight loss+aerobic exercise intervention (Ryan et al., 2014), with researchers attributing improvements to the exercise portion, rather than the weight loss, alone. The exercise-mediated improvements in insulin sensitivity in subjects with T2D suggest exercise could be advocated as a method for controlling the insulin resistance associated with the disease.

Exercise Modality and Insulin Sensitivity

Varying modalities of exercise have resulted in improved insulin sensitivity. Moderate-intensity aerobic exercise interventions observed reductions in insulin resistance in both normal and diabetic patients (Mourier et al., 1997, Magkos, Tsekouras, Kavouras, Mittendorfer & Sidossis, 2008). HIT interventions have also resulted in increased insulin sensitivity in both young, healthy subjects (Babraj et al., 2009, Richards et al., 2010, Metcalfe et al., 2012) and sedentary, obese subjects (Nassis et al., 2005, Whyte, Gill & Cathcart, 2010, Whyte, Ferguson, Wilson, Scott & Gill, 2013).

Resistance training has also been demonstrated as an effective exercise modality in increasing insulin sensitivity, but research has primarily been implemented on subjects with either impaired glucose tolerance or fully developed T2D (Dunstan, Puddey, Beilin, Burke, Morton & Stanton, 1998, Hansen, Landstad, Gundersen, Torjesen & Svebak, 2012). Further research has studied the combined effects of aerobic exercise and resistance training on subjects with T2D, observing improvements in insulin resistance

were greater in comparison to resistance exercise alone (Koo et al., 2010, Jorge et al., 2011), possibly due to the increased energy expenditure as discussed previously (Magkos et al., 2008). An earlier study observed changes in insulin with maximal eccentric contractions in healthy males (King, Feltmeyer, Baldus, Sharp & Nespor, 1993).

Recently, research has demonstrated a short-term periodized resistance training program significantly decreases insulin resistance in overweight men (Ahmadizad, Ghorbani, Ghasemikaram & Bahmanzadeh, 2014). Thus, the impact of exercise on improved insulin resistance through increased insulin sensitivity has been well-demonstrated, but further research on the main mechanisms responsible for improving insulin resistance through resistance training is necessary to develop the most effective program.

HIT and Insulin Sensitivity

Exercise has been demonstrated as an effective method of increasing insulin sensitivity (King et al., 1987, Prigeon, Kahn & Porte, 1995, Babraj et al., 2009, Whyte et al., 2010, Earnest et al., 2012, Metcalfe et al., 2012, Racil et al., 2013, Richards et al., 2013, Whyte et al., 2013). Several mechanisms induced by exercise may contribute to increased insulin sensitivity, including; a) increases in GLUT4, a glucose transporter protein (Wallberg-Henriksson et al., 1988, Goodyear et al., 1991, Brozinick et al., 1994, Gao et al., 1994, Hansen et al., 1995, Lund et al., 1995, Kristiansen et al., 1996), b) reductions in fatty acid mobilization (Santamauro et al., 1999, Schenk et al. 2009) and c)

counteraction of lipid-induced insulin resistance (Schenk et al., 2005, Schenk et al., 2009, Little et al., 2011).

The effects of exercise on insulin resistance instigated research into the effects of training duration and intensity on physiological adaptations. Early studies focused on interventions with moderate-intensity training for 30-120 min, with varying results. Yfanti et al. (2011) observed a 17.2% insulin-stimulated glucose uptake after 12 weeks of aerobic endurance training five times a week. A study on young men regularly exercising 4-6 ds a week at 55-91% HR_{max} observed an increase in insulin sensitivity at 12 h after the last bout of exercise, but at 84 h post-exercise the effect on insulin sensitivity had diminished with no changes in glucose effectiveness or acute insulin response to glucose (Prigeon et al., 1995). The lack of change in any alternative mechanisms prompted the researchers to contribute the subsequent decrease in glucose tolerance entirely to the decline in insulin sensitivity.

Further research has observed significant effects on insulin resistance after a HIT program. This research has produced varying results on the effects of HIT on insulin resistance. A six-week reduced-exertion HIT exercise intervention resulted in a 28% increase in insulin sensitivity of healthy sedentary men, but not women (Metcalf et al., 2012). Insulin resistance in young obese females was also improved to a greater extent after 12 weeks of HIT versus moderate-intensity interval training (Racil et al. 2013). 12 weeks of HIT resulted in significant improvements in insulin resistance at both 24-hr and 72-hr after the final session, suggesting both an acute and long-term effect on insulin resistance (Earnest et al., 2012). Later studies observed HIT significantly improved

insulin sensitivity and glucose uptake after a minimal two weeks of training in young healthy males (Babraj et al., 2009) as well as sedentary obese men (Whyte et al., 2010).

The potential benefits of an acute bout of exercise on insulin sensitivity have contributed to the recent influx in this area of research. Expanding the knowledge of the effects of an acute exercise bout on insulin sensitivity may provide insight for improving accuracy of exercise prescription for persons with insulin resistance and/or T2D. Magkos et al. (2008) found a curvilinear relationship between energy expenditure and insulin sensitivity and concluded a minimum energy expenditure of 900 kcals was required to increase basal insulin sensitivity after a single exercise bout. The same study also observed the greatest decrease in insulin resistance in subjects with the highest basal insulin resistance, suggesting a dose-effect of exercise on subsequent increases in insulin sensitivity.

Richards et al. (2010) observed no significant changes in insulin sensitivity or glucose uptake 72 h after an acute bout of SIT. Similarly, Whyte et al. (2013) observed no significant changes in insulin sensitivity or glucose uptake 24 h after an acute bout of SIT. However, an earlier study implemented a five d exercise intervention that resulted in worsened insulin sensitivity immediately post-exercise (IPE), then improved insulin sensitivity and glucose uptake one and three ds post-exercise in trained middle-aged subjects (King, Baldus, Sharp, Kesi, Feltmeyer & Riddle, 1995). The discrepancy in observed effects of an acute bout of HIT on insulin sensitivity as well as the interim between the exercise session and post-exercise measurements necessitate further research into the effects of an acute bout of HIT on insulin sensitivity at several post-exercise time points.

More recent work observed an increase in insulin sensitivity and plasma glucose concentrations 72 h after the last training bout in a six-week reduced-exertion HIT intervention (Metcalf et al., 2012) as well as a two-week reduced-intensity HIT intervention (Babraj et al., 2009). The reduced-exertion protocol included 1-2 all-out sprints lasting 10-20 seconds per exercise session (Metcalf et al., 2012). Work by Whyte et al., (2010) observed significant improvements in insulin sensitivity, but not plasma glucose concentrations, 24 h after a two-week SIT intervention. However, improvements in insulin sensitivity were no longer significant 72 h after the intervention (Whyte et al., 2010), indicating the study observed similar effects on insulin sensitivity at differing post-exercise time points than both Babraj et al. (2009) and Metcalf et al. (2012). As mentioned previously, Earnest et al. (2012) saw improvements in insulin resistance at both 24 and 72 h post-exercise. Contradictory results as these warrant further research to determine how much of a role the length of a training program versus single bout has in the effectiveness of exercise on insulin sensitivity.

Research done by Richards et al. (2010) is one of the only studies that has observed the effects of an acute bout of high intensity sprint training on insulin sensitivity in healthy sedentary subjects, but it had major limitations. First, basal insulin sensitivity in the single bout group was unexpectedly higher in comparison with the short-term SIT group. The difference in mean basal insulin sensitivity between groups was considered insignificant, but approached statistical significance ($P=0.059$). Therefore, it is possible the elevated basal insulin sensitivity in the single bout group decreased the likelihood of an additional increase compared to the SIT group (Richards et al. 2010). The possibility of altered results suggests significant changes in insulin sensitivity may have been

observed in subjects with lower (normal) basal insulin sensitivity after an acute bout of high intensity interval training; further research is necessary to conclude the effects of an acute bout on insulin sensitivity.

Another major limitation of Richards et al. (2010) study was the inconsistency of the ratio of men to women in each training group. As mentioned previously, Metcalfe et al. (2012) observed a 28% increase in insulin sensitivity in the male training group and no improvements in the female training group 72 h post-exercise intervention. The single bout group consisted of two males and seven females and the SIT group was made up of five males and seven females. Sex differences in response to training (Esbjornsson-Liljedahl, Sundberg, Norman & Jansson, 1999, Esbjornsson-Liljedahl, Bodin & Jansson, 2002) could have created further variability in the results, as the single bout group had a higher proportion of women. Thus, changes in insulin sensitivity after an acute bout of sprint training may be altered, or possibly increased to significance, without the combination of men and women as subjects. This inconsistency in the study design warrants further investigation with subjects of the same sex.

A majority of the current literature on high intensity training involve similar exercise protocols. Reduced exertion training included a wide range of 1-2 (Metcalfe et al., 2012) or 8-12 (Skleryk, Karagounis, Hawley, Sharman, Laursen & Watson, 2013) repeated sprints for 10-20 seconds while SIT included 4-6 anaerobic Wingate tests (Babraj et al., 2009, Richards et al., 2010, Whyte et al., 2010, Whyte et al., 2013). As mentioned previously, the only studies that have observed the effects of an acute bout on insulin sensitivity are Richards et al. (2010) and Whyte et al. (2013) which both included 4 Wingate tests. The supramaximal exercise protocol implemented did not induce

significant changes in insulin sensitivity or glucose uptake 24 h (Whyte et al., 2013) or 72 h (Richards et al., 2010) post-exercise, leading the researchers to conclude an acute bout of SIT does not impact insulin sensitivity. Although research has determined four intervals of supramaximal exercise does not affect insulin sensitivity, the effect of short-duration reduced-exertion HIT on insulin sensitivity and glucose uptake is inconclusive, and the importance of quantity of bouts with SIT or HIT has yet to be determined (Metcalf et al., 2012, Skleryk et al., 2013). The effect of increasing the number of intervals in an acute bout of exercise must be investigated to determine if quantity of repetitions per bout also impacts the effects of exercise on insulin sensitivity and glucose concentrations. The current study will assess if an acute bout of HIT consisting of 8 x 30 second intervals against 100% peak workload achieved during a VO_{2peak} will alter insulin sensitivity and/or plasma glucose concentrations, as well as the length of the effect.

Previous studies observing the effects of an acute exercise bout on insulin sensitivity in healthy subjects only measured insulin sensitivity and glucose uptake at 24 h (Whyte et al., 2013) 48 h (Cartee, Young, Sleeper, Zierath, Wallberg-Henriksson & Holloszy, 1989) and 72 h post-exercise (Richards et al., 2010), with the exception of one study that measured both variables at one, three, five and seven ds after exercising for five ds consecutively (King et al., 1995). King et al. (1995) observed improved insulin sensitivity and glucose concentrations through 72 h post-exercise. The length of the effects of an acute bout of HIT on insulin sensitivity remains unclear and thorough investigation is necessary to further expand the understanding of the role of exercise on insulin resistance as well as the physiological mechanisms associated with it.

Conclusions

Knowledge of the metabolic impact of acute exercise on insulin sensitivity has strong potential application to the general population looking to improve health without spending hours each week exercising. The purpose of this study was to determine the effect of an acute bout of high intensity interval training (8 x 30 s sprints) on insulin sensitivity and glucose uptake for four days in young, healthy, overweight/obese sedentary men. The time course was selected to allow for comparison to results of previous studies (Cartee et al., 1989, King et al., 1995, Richards et al., 2010) with an additional measurement at four days post-exercise to provide further details on the length of the effects of an acute HIT bout on insulin sensitivity. Overweight/obese sedentary men were used as the study sample to represent a population at higher risk for developing insulin resistance and T2D later in life. Determining the length of the effects on insulin will aid in giving specific exercise prescription to those at risk for developing insulin resistance and T2D. This study will investigate the hypotheses that insulin sensitivity and glucose tolerance will be improved at days two, three and four post-exercise, with final measurements at day four approaching baseline measures.

CHAPTER III

METHODS

Subjects

10 young (age 20.9 ± 2.0 y) overweight/obese males (BMI 29.3 ± 2.2 , body fat $21.1 \pm 4.3\%$) with a sedentary status ($\text{VO}_{2\text{peak}}$ 29.7 ± 4.2 mL/kg/min) defined as having not participated in regular exercise beyond daily physical activity more than twice a week for 30 min or more in the last 12 months were recruited for this study. Seven subjects were overweight and three were obese according to BMI classifications. All subjects were recruited with flyers posted on Iowa State University's campus or by word of mouth to participate in the study. Subjects gave written consent of participation in the study. Inclusion criteria were: male, age 18-25, BMI ≥ 25.0 kg/m², sedentary lifestyle, non-smoker, and euglycemia. Exclusion criteria were: known cardiovascular disease, NIDDM, family history of type 1 diabetes, current use of medications known to affect the insulin or glucose response to glucose ingestion, or injury that may have limited performance during the peak test and exercise trial.

Study Design

Five d prior to the exercise trial, subjects arrived to the lab in the morning after a 12-h fast. Subjects were asked to refrain from consuming alcohol 48 h before arrival to the lab. Subjects were also asked to refrain from exercising 7 d prior to arriving at the lab and to refrain from exercise through the completion of the study. Upon arrival to the lab,

subjects read and signed the informed consent form. Height and weight were measured and recorded. Subject body mass and height were used to calculate BMI to determine inclusion in the study. Percent body fat was estimated using a handheld bioelectrical impedance analysis device (Omron Healthcare fat loss monitor, Lake Forest, IL). Subjects then completed the long form of the International Physical Activity Questionnaire (IPAQ) to estimate normal physical activity habits and a medical history form to confirm no presence of cardiovascular disease, NIDDM, or family history of type 1 diabetes. A cannula was inserted into a vein in the antecubital region, then a baseline blood sample was taken five min after insertion. Subjects then drank 75 g of glucose dissolved into 10 fl oz of water and performed a fasting oral glucose tolerance test (OGTT) to determine basal glucose and insulin levels and confirm euglycemia. After completion of the OGTT, subjects were introduced to the exercise protocol and subjects completed a VO_{2peak} test on an Excalibur stationary cycle ergometer (Lode, Groningen, Netherlands). Subjects were then given a pedometer (HJ-321 Tri-Axis, Omron Healthcare, Hoofddorp, Netherlands) to track steps taken daily for the five d between the VO_{2peak} test and exercise trial. Subjects were verbally instructed to maintain a similar diet to that of the day prior to the familiarization session throughout the course of the study.

Five d after the VO_{2peak} test and baseline OGTT, subjects arrived at the lab in the morning after a 12-h fast. The subjects completed a single-bout of high intensity interval training (HIT) described below. Subjects then reported to the lab, fasting, at 48, 72 and 96 h post-exercise trial to perform a fasted OGTT to determine the time course of insulin action (Fig 1). Fasting blood samples were taken prior to each OGTT to determine basal glucose and insulin concentrations.

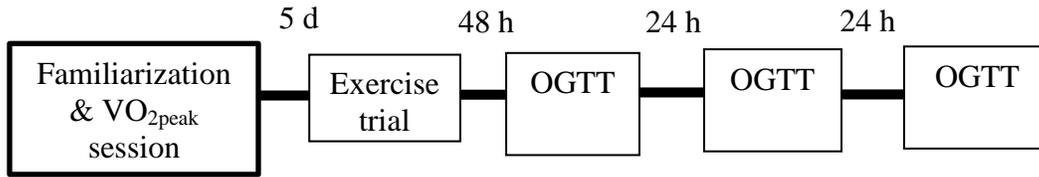


Figure 1. Study flow.

Exercise Trial

Prior to starting the trial, subjects performed an exhaustive incremental cycling test to determine VO_{2peak} , which has been previously described (Burgomaster, Hughes, Heigenhauser, Bradwell & Gibala, 2005). The test was performed on an Excalibur stationary cycle ergometer (Lode, Groningen, Netherlands) and oxygen uptake was monitored with an indirect calorimeter (Moxus Metabolic Systems, Pittsburgh, PA). The test began with a three min warm-up at 50 W, then workload was increased 25-50 W every two min until exhaustion. Workload was increased slower in subjects with a smaller body frame, and increased in 50 W increments for those subjects with a larger body frame and greater capability of producing power. VO_{2peak} was established as the highest value achieved during a 30-s collection period.

Five d after VO_{2peak} testing, subjects arrived at the lab after a 12-h fast for the exercise trial. The protocol consisted of 8 x 30 s intervals on a stationary cycle ergometer (Lode, Groningen, Netherlands) with a 4-min recovery period between intervals. Power output was set at the maximum workload achieved during the VO_{2peak} (256 ± 21 W). During the 4-min recovery period between tests, subjects cycled at a low cadence (50

rpm) against a light resistance (50 W) to reduce venous pooling in the lower extremities and minimize the risk of syncope (Burgomaster et al., 2005). Subjects were verbally encouraged during the exercise trial, and instructed to keep pedaling rate above 90 RPM during the 30-s intervals. Ratings of perceived exertion (Borg, 1982) were recorded immediately following each 30 s bout.

Body Composition Measures

Body mass and height were measured on standard lab scales (Table 1). Measurements of body fat were obtained through bioelectrical impedance analysis (Omron Healthcare fat loss monitor, Lake Forest, IL). Body mass index was calculated with measures of height and weight with the standard equation:

$$\text{BMI} = (\text{weight in kg}) / (\text{height in meters})^2$$

Table 1. Subject characteristics.

Characteristic	Mean (\pm SE)
age (y)	20.9 \pm 2.0
body mass (kg)	97.28 \pm 11.60
height (m)	1.82 \pm .06
BMI (kg/m²)	29.32 \pm 2.18
% body fat	21.14 \pm 4.25
VO₂peak (ml/kg/min)	29.72 \pm 4.25
RER at VO₂peak	1.11 \pm 0.07

Values are mean \pm SE.

OGTT and IG Index

A cannula was inserted into a vein in the antecubital region, then 5 ml of blood was drawn five min after insertion. After each blood sample, the cannula was flushed with 5 ml of 0.9% NaCl solution. Subjects consumed a drink which contained 75 g of glucose mixed into 300 ml of water in under 10 min. 1 ml of blood was drawn prior to each blood sample to remove any remaining NaCl solution from the cannula, and 5 ml of blood was sampled at 30, 60, 90 and 120 min after the drink was ingested. Blood samples were collected into sodium fluoride tubes and placed on ice immediately after collection. Blood samples were then centrifuged at 3800 RPM for 10 min and plasma was withdrawn from sample. The samples were then frozen at -80° F for 12 wk until data collection was completed.

Insulin sensitivity was determined using the IG Index, calculated with the following formula:

$$\text{IG Index} = \text{glucose}_{\text{AUC}} \times \text{insulin}_{\text{AUC}}$$

Where $\text{glucose}_{\text{AUC}}$ and $\text{insulin}_{\text{AUC}}$ are calculated glucose AUC (mmol/l.min) and insulin AUC (converted from pmol/l to $\mu\text{mol/l}$) during the OGTT (Mondon, Dolkas & Reaven, 1983). The IG Index is an inverse measure of insulin sensitivity which uses the response of both glucose and insulin to an oral load of glucose. Thus, a decrease in the IG Index reflects increased insulin sensitivity through a diminished glucose and/or insulin response to an oral glucose load (Mondon et al., 1983).

Blood Analysis

Blood samples were collected into tubes and placed on ice immediately after collection. Blood samples were then centrifuged at 3800 RPM for 10 min and plasma was withdrawn from sample. Duplicates of each sample were then frozen at -80°C for 12 wk until data collection was completed. Plasma glucose concentrations were determined in duplicate with a commercially available enzymatic UV spectrophotometric glucose assay reagent kit (Sigma-Aldrich Inc., Milwaukee, WI) with absorbance read at 340 nm on a spectrophotometer (Beckman DU 640). Insulin was measured in duplicate using a Quantikine solid-phase sandwich enzyme-linked immunoassay (ELISA) (R&D Systems, Minneapolis, MN) with absorbance set to 450 nm on a spectrophotometer (FLUOstar Galaxy). All samples from a subject were analyzed in the same assay run to avoid inter-assay variability. Any samples with a CV above 15% were repeated. Areas under the curve for glucose and insulin were calculated with the trapezoidal model.

Statistical Analysis

The influence of HIT on glucose and insulin concentration at 5 different time points (0, 30, 60, 90, 120 min) was analyzed with 2-way analysis of variance (ANOVA) with repeated measures (pre-exercise vs d 2, 3 and 4 post-exercise). The influence of HIT on areas under the curve for glucose concentration and insulin concentration at each time point was analyzed with 1-way ANOVA with repeated measures, then compared with a multiple comparisons versus baseline procedure (Holm-Sidak method). The influence of HIT on insulin sensitivity was analyzed with 1-way ANOVA with repeated measures.

Any significant results were then compared with the Holm-Sidak method. All data were tested for normality (Shapiro-Wilk). Significance was set at $P < 0.05$. All statistical analyses were carried out using SigmaPlot12.5 software (Systat Software Inc., San Jose, CA).

Physical Activity Measures

Results from the IPAQ were calculated to determine the activity level of either low (< 500 MET-min/wk) moderate (500-999 MET-min/wk) or high (≥ 1000 MET-min/wk) for physical activity (Patterson, 2005). Steps per d gathered from the pedometers were used to calculate mean steps per d for each subject. The mean steps per d were then compared to the preliminary pedometer indices (Tudor-Locke & Bassett, 2004) to determine the subject's activity level. The pedometer indices are as follows: i) < 5000 steps/d – sedentary lifestyle index; ii) 5000-7499 steps/d – low active; iii) 7500-9999 steps/d – somewhat active; iv) ≥ 10000 steps/d – active; v) > 12500 steps/d – highly active.

CHAPTER IV

RESULTS

High Intensity Interval Training

One subject failed to complete the final interval due to nausea, for a total of 79/80 intervals completed (>98% adherence).

Blood Variables

Insulin and glucose responses at baseline, 48 h, 72 h, and 96 h post-exercise are shown in Table 2. IG index and AUC for glucose and insulin are shown in Fig 2. There was a significant within-subject effect for session on mean glucose at 72 h (7.1 ± 0.2 vs 6.5 ± 0.2 mmol/L, $P=0.044$, $\beta=0.444$) and 96 h (7.1 ± 0.2 vs 6.4 ± 0.2 mmol/l, $P=0.042$, $\beta=0.444$) post-exercise. Within-subject glucose concentration at 60 min was significantly lower at 72 h post-exercise (7.1 ± 0.7 vs 8.2 ± 0.6 mmol/L, $P=0.033$) and 96 h post-exercise (6.9 ± 0.7 vs 8.2 ± 0.6 mmol/L, $P=0.023$) compared to baseline. However, values did not differ significantly at 48 h post-exercise compared to baseline (7.6 ± 0.7 vs 8.2 ± 0.6 mmol/L).

No significant differences were observed from baseline to any post-exercise trials in glucose or insulin AUCs (Fig 2). Glucose AUC approached significance at 48 h ($P=0.065$), 72 h ($P=0.064$) and 96 h ($P=0.059$) post-exercise compared to baseline. High intensity interval training improved insulin sensitivity in 7 subjects and worsened it in 3 subjects. The IG Index was significantly lower at 48 h post-exercise compared with

baseline (10128 ± 3910 vs 4867 ± 2080 units $P=0.013$), demonstrating improved insulin sensitivity at 48 h post-exercise compared to baseline. There were no significant changes in IG index at 72 or 96 h post-exercise measurements compared to baseline.

Table 2. Plasma glucose concentration (mmol/L) in response to a 75-g oral glucose tolerance test before (baseline) and after high intensity interval exercise.

Timepoint	Baseline	48 h post	72 h post [†]	96 h post [†]
0	5.2 ± 0.2	5.8 ± 0.4	5.2 ± 0.1	5.3 ± 0.2
30	7.8 ± 0.7	8.4 ± 0.4	7.6 ± 0.5	8.1 ± 0.4
60	8.2 ± 0.6	7.6 ± 0.7	$7.1 \pm 0.7^*$	$6.9 \pm 0.7^*$
90	7.5 ± 0.7	6.7 ± 0.6	6.6 ± 0.8	6.5 ± 0.8
120	6.5 ± 0.7	5.7 ± 0.6	5.8 ± 0.8	5.2 ± 0.6

Data shown are mean \pm SEM. * $P < 0.05$ for the session x time interaction effect versus baseline, [†] $P < 0.05$ for the session effect versus baseline.

Table 3. Plasma insulin concentration (pmol/L) in response to a 75-g oral glucose tolerance test before (baseline) and after high intensity interval exercise.

Timepoint	Baseline	48 h	72 h	96 h
0	7 ± 5	11 ± 11	3 ± 3	10 ± 10
30	255 ± 48	188 ± 53	266 ± 78	334 ± 69
60	242 ± 56	194 ± 61	317 ± 64	207 ± 67
90	212 ± 62	203 ± 74	148 ± 69	172 ± 70
120	133 ± 65	126 ± 60	145 ± 69	97 ± 64

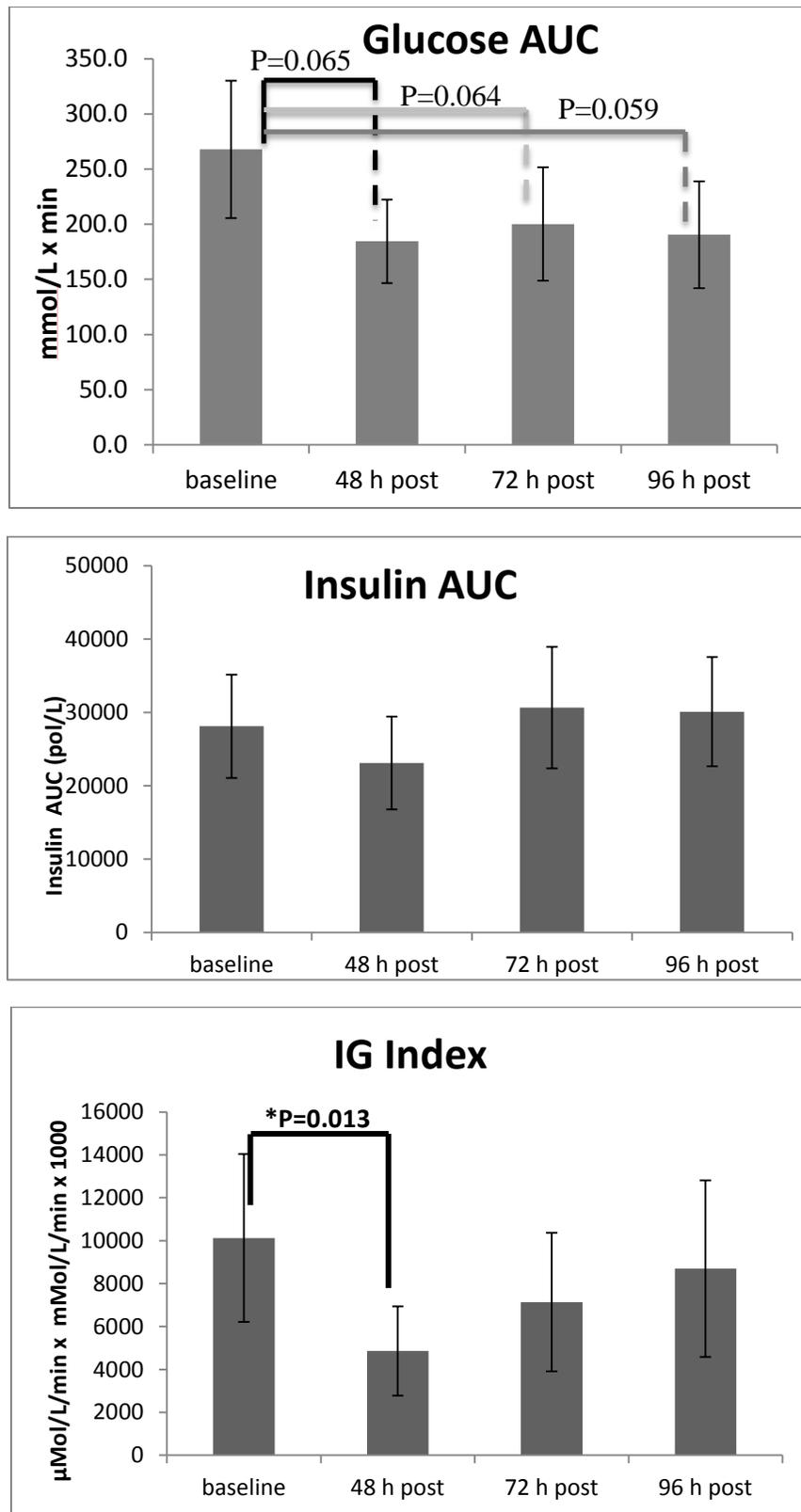


Figure 2. Response to a 75-g oral glucose load in glucose and insulin AUC, and IG Index at Baseline and 48 h, 72 h and 96 h post-exercise. * $P < 0.05$ for between sessions.

Physical Activity Measures

International Physical Activity Questionnaire indicated that four subjects had low, two had moderate, and four had high physical activity levels (Table 4) based on self-report (Patterson, 2005). Most physical activity was reported in the walking from place to place category of the transportation physical activity section of the IPAQ. Pedometers recorded number of steps taken per d for each subject for the five ds between the VO_{2peak} and the exercise trial. Average step count from pedometers indicated subjects were under 5000 steps per d (4005 ± 553 steps), which meets the criteria for the sedentary lifestyle index (Tudor-Locke & Bassett, 2004). Individually, nine subjects met the criteria for sedentary lifestyle, and one subject met the criteria for low active (Fig 3).

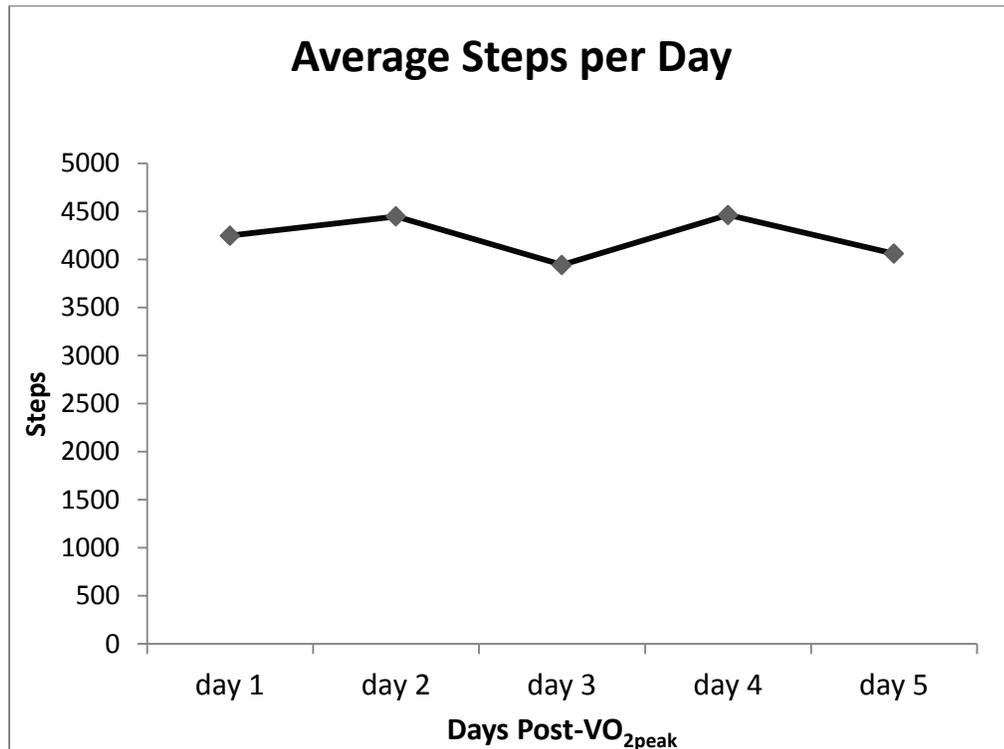


Figure 3. Average steps per d.

Table 4. *IPAQ and Pedometer Ratings, Length of Sitting.*

IPAQ Rating	Number of Subjects	MET-Mins/wk
Low	4	190 ± 81
Moderate	2	865 ± 72
High	4	4434 ± 1306

Pedometer Rating	
Sedentary	9
Low Active	1

Length of Sitting	
Hr/weekday	7.9

Values are mean ± SE.

Ratings of Perceived Exertion

Subjects reported RPE for the 30 s interval immediately after each interval.

According to the Borg Scale (Borg, 1982) average RPE for all intervals was “hard” (15 ± 2).

CHAPTER V

DISCUSSION

The main finding of this repeated measures experimental study in young, overweight males is that an acute bout of 8 x 30 s intervals results in significantly reduced glucose concentrations at 72 and 96 h post-exercise and improved insulin sensitivity at 48 h post-exercise. Further, the glucose AUC was trending towards improvement at 48, 72 and 96 h post-exercise. There were no significant differences between baseline and any post-exercise measures for plasma insulin concentration or AUC.

The improvement in glucose concentration at 72 and 96 h post-exercise may be attributed to an increase in GLUT-4 translocation to the plasma membrane. Previous studies have shown an increase in GLUT-4 translocation after an acute bout of moderate continuous exercise (Kennedy et al., 1999), six weeks of SIT (Bradley, Shaw, Worthington, Sheperd, Cocks & Wagenmakers, 2014), and two weeks of low-volume HIT (Little, Safdar, Wilkin, Tarnopolsky & Gibala, 2010, Hood, Little, Tarnopolsky, Myslik & Gibala, 2011). Research has also observed an increase in the size and number of intracellular GLUT-4 clusters following six weeks of SIT (Bradley et al., 2014), concluding exercise training results in increased GLUT-4 translocation.

The findings of decreased glucose concentration in the current study are similar to those of Babraj et al. (2009), who observed a reduction in glucose at 60 min during an OGTT two and three d after a two week short-duration HIT. In contrast, other studies have found no reduction in the glucose response 24 h after a single bout of SIT (Whyte

et al., 2013) or at 24 or 72 h after a two-week SIT intervention (Whyte et al., 2010), despite an improvement in insulin sensitivity index at 24 h post-intervention. The similar findings of the current study and previous research (Babraj et al., 2009) suggest the reduction in glucose after a two-week SIT intervention is partially due to a last-bout effect.

Glucose AUC in the current study was not significantly different at any post-exercise measures compared to baseline, but approached significance at all post-exercise time points ($P=0.065$, $P=0.064$, $P=0.059$ at 48, 72 and 96 h post-exercise). Previous studies have found similar results, observing significantly lower glucose AUC two and three ds following a two week SIT intervention (Babraj et al., 2009) as well as one and three ds after a five d exercise protocol (King et al., 1995). Dissimilarly, Whyte et al. (2013) observed no differences approaching significance or significant differences in glucose AUC at 24 h after a single bout of SIT. The inconsistency between the glucose AUC results from the current study and previous studies can be attributed to the significantly improved glucose uptake in the current study. Mean plasma glucose concentration was significantly lower at 72 and 96 h post-exercise, with reduced glucose concentration at 60 min during the OGTT at 72 and 96 h post-exercise. In comparison, Whyte et al. (2013) observed no differences in glucose concentration or glucose AUC 24 h after a single bout of SIT. Results from the current study as well as King et al. (1995) suggest that improvements in glucose concentration, AUC and insulin sensitivity post-exercise are largely attributed to an acute bout of exercise.

The current study found no significant differences between baseline and any post-exercise measures for insulin concentrations or AUC, but found significant differences in

insulin sensitivity at 48 h post-exercise compared to baseline. The findings on plasma insulin concentration and AUC are similar to Whyte et al. (2013), who found no significant differences 24 h after a single bout of SIT. King et al. (1995) detected similar improvements in insulin sensitivity to the current study, though improvements were extended to 72 h after five ds of exercise. In contrast to the current study, Whyte et al. (2013) observed no significant differences from baseline to 24 h post-exercise in insulin sensitivity. Further, Richards et al. (2010) observed no differences in insulin sensitivity index from baseline at 72 h (Richards et al., 2010) after a single bout of SIT.

The disparity between the findings from existing research on an acute bout of SIT and insulin sensitivity (Richards et al., 2010, Whyte et al., 2013) and the current study may be the result of differing populations. The subjects in the current study were 10 overweight/obese young men who were sedentary ($VO_{2peak}=29.7 \pm 4.3$ mL/kg/min) and represented a population at risk for insulin resistance. Subjects from Whyte et al. (2013) were also overweight/obese men, but appeared to be more fit ($VO_{2peak}=42.0 \pm 2.4$ mL/kg/min) compared to the subjects in the current study. Whyte et al. (2013) recruited subjects with less than two h per week of structured exercise, whereas the current study recruited subjects with less than one h per week. Although the difference is small, training status affects insulin response, as previous research (King et al., 1987) observed a smaller insulin response to a glucose stimulus in trained individuals compared to untrained individuals. Thus, level of subject fitness may explain the lack of difference in insulin or glucose response in Whyte et al. (2013) that was observed in the current study. Richards et al. (2010) used sedentary, overweight subjects similar to the current study, but the sample included 7 women and 2 men. Research has not been conclusive as to the

differences in insulin and glucose response to exercise between men and women , however, Metcalfe et al. (2012) observed an improved insulin sensitivity in men, but not women, 72 h after a 6-week reduced-exertion HIT intervention. Metcalfe et al. (2012) suggested the gender difference in insulin and glucose response to the HIT intervention may be due to a lesser glycogen reduction during a Wingate sprint in women compared to men (Esbjornsson-Liljedahl et al., 1999, Esbjornsson-Liljedahl et al., 2002). Therefore, it is possible the lack of improvement in insulin sensitivity in Richards et al. (2010) may have been due to a lesser response in women to the repeated Wingates used for the bout of SIT.

The difference in exercise protocol in previous research (Richards et al., 2010, Whyte et al., 2013) versus the current study may be partially responsible for the opposing results. Both studies on the effect of a single bout of SIT on insulin sensitivity utilized four repeated Wingate tests against a set braked resistance (Richards et al., 2010, Whyte et al., 2013). The current study consisted of 8 x 30 s high intensity intervals at a resistance set to maximum power output reached at VO_{2peak} . Although the power output in the current study was lower (256 ± 21 vs 518 ± 22 W), total work done was much greater in the current study (61.6 ± 4.8 vs 15.4 ± 0.7 kJ) than Whyte et al. (2013). These results suggest total work done greatly influences the effects of an acute bout of HIT on insulin and glucose response.

Limitations

There are several limitations in the current study. First, one of the ten subjects in the current study had fasting glucose concentrations at the start of each OGTT that were highly suggestive of impaired insulin response, or insulin resistance. Baseline fasting glucose was 115 mg/dL, and 120 min glucose was 200 mg/dL, suggesting the subject is diabetic (Standards of Medical Care in Diabetes, 2012). Previous research has observed improved glucose response post-exercise through increased GLUT-4 translocation (Goodyear et al., 1991, Kennedy et al., 1999). Other studies have observed improved insulin sensitivity immediately post-exercise (Bordenave et al., 2008) as well as 24 h after a 7-d exercise intervention (Winnick et al., 2008) in subjects with T2D. Results from the current study are similar to those previously mentioned, as glucose uptake and insulin sensitivity was improved in the subject with impaired glucose, despite markedly lower basal insulin sensitivity index. Despite the similar response to the exercise protocol, the hyperglycemia was inconsistent with the other subjects and statistical comparisons were run with and without the subject to confirm his data did not significantly alter results.

Another limitation of the current study was the varying IG index response to an acute bout of HIT. IG index improved in 7 subjects and worsened in 3 subjects from baseline to each post-exercise measure, resulting in the only significant difference at 48 h post-exercise compared to baseline. There are several reasons this may have occurred. The workload applied during the bout of SIT was based on peak workload reached during the VO_{2peak} test. However, the VO_{2peak} test is not a test of peak power, and it cannot be assumed that each subject's peak workload elicited the same intensity during the high

intensity intervals. Average RPE after each interval ranged from 13 to 17, which translates to an exercise between “somewhat hard” and “very hard”. Therefore, a workload not great enough to elicit any changes in GLUT-4 translocation would possibly explain a lack of improvement in insulin sensitivity in 3 subjects.

Sample size was another major limitation of the current study. Power was too low to reach significance in IG index at 72 or 96 h post-exercise with ten subjects. However, effect size was calculated at 0.28 for baseline to 72 h post-exercise, suggesting a similar study with a larger sample size could observe a significant difference in insulin sensitivity at 72 h post-exercise.

Subjects were instructed to maintain a diet similar to the day prior to starting the study throughout the study. However, diet was not recorded, and it is possible alterations in subjects/ diet may have affected glucose and insulin responses.

Finally, total time commitment is a major limitation of the current study. Total time for the acute bout of HIT was 41 min, including a warm-up and cool down. Lack of time has been identified as the major reason for physical inactivity in the adult population (Stutts, 2002), and the HIT session in the current study was of longer duration than the current recommendation of 30 min, 5 d a week for a total of 150 min weekly (U.S. Dept. of Health and Human Services, 2008). However, the current study observed improvements in insulin sensitivity at 48 h post-exercise and glucose concentrations at 72 and 96 h post-exercise. Thus, the length of improvements in insulin sensitivity and glucose uptake would allow individuals to complete two sessions of HIT a wk to acquire

improvements in insulin sensitivity, while decreasing total exercise time from 150 min to 82 min per wk.

Conclusion

In summary, an acute bout of 8 x 30 s high intensity intervals improves insulin sensitivity at 48 h post-exercise and plasma glucose concentrations during an OGTT at 72 and 96 h post-exercise. Further research is warranted to determine the feasibility of carrying out the HIT protocol from the current study outside of a laboratory setting. Additionally, similar studies investigating the effects of an acute bout of HIT on insulin sensitivity in women are necessary before suggesting HIT as a method of improving insulin sensitivity in both insulin-resistant men and women. Finally, the findings of the current study warrant continued research on the minimal duration and number of intervals required to elicit an improvement in insulin sensitivity and glucose concentrations.

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