Effects of Exercise and/or Diet on Plasma Insulin and Glucose Levels in Obese Men

by

Brenda Lynn Rice

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Dr. R. Ross	
Dr. R. Hudson	

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Please fax to Graduate Studies @ 545 6015

Abstract

Objective: We tested the hypothesis that a combination of diet and either aerobic (DA; N=11) or resistance (DR; N=11) exercise would have effects on plasma insulin and glucose levels that were greater than diet alone (DO; N=9) in upperbody obese men.

Research Design and Methods: Insulin and glucose levels were measured after an overnight fast and following a 75 gram oral glucose challenge (OGTT). Whole body visceral adipose tissue (VAT), subcutaneous adipose tissue (SAT) and skeletal muscle (SM) were measured by magnetic resonance imaging (MRI) pre- and post-treatment (16 weeks).

Results: The daily energy deficit induced by diet (~1,060 kcal, $p<0.05$) was not different between groups ($p>0.05$). The reduction ($p<0.05$) in body weight (~12kg), VAT (~37%), and SAT (~24%) volume (liters) was not different between treatments ($p>0.05$). SM was maintained in the DA and DR groups, but was significantly reduced (~7%) in the DO group ($p<0.05$). Peak $\dot{V}O_2$ (liters) significantly improved in the DA group alone (~14%). Muscular strength increased by ~20% in the DR group. Independent of treatment, fasting plasma glucose levels and OGTT-glucose area did not change ($p>0.05$). However, fasting plasma insulin levels, OGTT-insulin area, and insulin to glucose area ratio (IGAR) decreased within all treatments ($p<0.05$). However, the relative reduction in OGTT-insulin area and IGAR

were significantly ($p<0.05$) greater within the DA (46% and 41%) and DR (44% and 40%) treatments when compared to DO (18% and 16%).

Conclusion: These findings support the hypothesis that moderate weight loss induced by the combination of diet and either aerobic or resistance exercise has effects on OGTT- insulin levels as well as IGAR that are greater than diet alone in obese men. As no treatment differences were observed for reductions in VAT, SAT or total adipose tissue (AT), it is likely that the beneficial effects of exercise are mediated through adaptations in SM known to occur in response to the treatments prescribed.

Key words: insulin, glucose, diet, exercise, weight loss, magnetic resonance imaging

Co-Authorship

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List of Abbreviations

ASAT	Abdominal subcutaneous adipose tissue
AT	Adipose tissue
BMI	Body mass index
CT	Computed tomography
CVD	Cardiovascular disease
DA	Diet in combination with aerobic exercise
DO	Diet only
DR	Diet in combination with resistance exercise
EP-AT	Extra-peritoneal adipose tissue
FFAs	Free fatty acids
FG	Fast twitch glycolytic muscle fibers
FOG	Fast twitch oxidative glycolytic muscle fibers
FSAT	Femoral adipose tissue
IGAR	Insulin area to glucose area ratio
IP-AT	Intra-peritoneal adipose tissue
MRI	Magnetic resonance imaging
NIDDM	Non-insulin dependent diabetes mellitus
OGTT	Oral glucose tolerance test
RQ	Respiratory quotient
SAT	Subcutaneous adipose tissue
SD	Standard deviation
SM	Skeletal muscle
SO	Slow twitch oxidative muscle fibers
VAT	Visceral adipose tissue
$\dot{V}O_2max$	Maximal oxygen consumption
WHR	Waist-to-hip circumference ratio

1.0.0 INTRODUCTION

Obesity, particularly abdominal obesity, is associated with many metabolic complications including decreased insulin sensitivity and impaired glucose tolerance.[1] It is reported that both of these metabolic conditions are putative markers for non-insulin dependent diabetes mellitus (NIDDM).[2] Although not all obese individuals develop NIDDM,[2] approximately four out of five people with NIDDM are significantly overweight.[3] In addition to the association between obesity and these metabolic disturbances, it is reported that participation in regular physical activity is associated with a reduced occurrence of NIDDM.[4,5] Indirectly, these findings suggest that exercise may also be associated with improvements in insulin sensitivity and glucose tolerance. Taken together, these observations suggest that obesity reduction and exercise may be integral components of a strategy designed to normalize metabolic risk factors, in particular, insulin sensitivity and glucose tolerance.

It is commonly reported that diet-induced weight reduction is associated with improvements in insulin sensitivity and glucose tolerance.[6] Studies employing either oral glucose tolerance tests (OGTT) or euglycemic clamps reported reduced insulin and glucose levels and increased insulin sensitivity with a moderate weight reduction in both healthy individuals[7,8]

and those with NIDDM.[9] In addition, many studies have reported an association between exercise and improved insulin sensitivity, independent of weight loss and changes in body composition.[10-13] These changes are observed following both aerobic[10,12] and resistance[11,13] exercise programs. However, whether a training induced increase in insulin sensitivity is a chronic training effect or a residual effect of the last exercise session is unclear.[14] It is reported that improvements in insulin sensitivity are reversed within 3-6 days following exercise.[14] Since the majority of studies measured post-treatment insulin levels less than 36 hours after the final exercise session, the relationship between exercise and insulin sensitivity remains unresolved.[14]

Although not firmly established, it is generally accepted that the improvements in insulin sensitivity induced by exercise or weight loss are mediated by independent mechanisms. Whereas weight reduction may improve insulin sensitivity and glucose tolerance through reduced systemic[15] and portal circulation free fatty acid (FFA) concentrations and increased GLUT 4 activity,[15,16] it is reported that exercise may be associated with these changes through adaptations in skeletal muscle (SM) morphology. These adaptations may include an increase in the percentage of fast-twitch oxidative glycolytic fibers (FOG),[17] capillarization,[18] and oxidative enzyme

activity.[19] Thus, it is reasonable to assume that the combination of the two treatments would demonstrate a greater increase in insulin sensitivity when compared to either modality alone.

Few studies have investigated the influence of diet in combination with exercise versus diet alone on insulin and glucose variables.[9,12,20] In general, it is reported that diet combined with aerobic exercise training is associated with significantly greater improvements in insulin sensitivity compared to diet alone.[9,12,20] However, post-treatment insulin and glucose testing was performed less than 48 hours after the last exercise session in two of the three investigations.[12,20] Absent from the literature are studies comparing the effect of diet in combination with resistance training on insulin sensitivity with that of diet alone.

Based on these observations, we tested the hypothesis that the combination of diet and either aerobic or resistance exercise is associated with greater improvements in plasma insulin and glucose levels compared to diet alone in obese men. A whole body, multislice magnetic resonance imaging (MRI) protocol was employed to determine the associations between concurrent changes in subcutaneous adipose tissue (SAT), visceral adipose tissue (VAT), SM and carbohydrate metabolism.

2.0.0 REVIEW OF THE LITERATURE

2.1.0 Association between adipose tissue distribution, insulin sensitivity and glucose tolerance

It is well established that obesity is associated with several metabolic disturbances including insulin resistance and glucose intolerance, and that these risk factors are putative markers for NIDDM.[1,21,22] Evidence suggests that adipose tissue distribution rather than obesity per se is the stronger predictor of these metabolic complications (Figure 1).[23] In the 1980s several prospective studies confirmed that abdominal obesity, characterized by waist-to-hip circumference ratio (WHR), was associated with the greatest risk of developing NIDDM and cardiovascular disease (CVD).[24,25] Indeed, Ohlson et al.[24] in a study of 792 men reported that the incidence of diabetes mellitus was 16.6 times higher in the upper 5% of the distribution of the WHR compared to the lowest quintile.

In 1982, Kissebah et al.[21] provided the first cross-sectional evidence supporting an association between adipose tissue topography and insulin-glucose aberrations. They reported that women with abdominal adiposity had significantly higher plasma insulin and glucose levels in response to an oral glucose challenge compared to those with a gluteal-femoral adipose tissue distribution.[21] It is reported that a gender difference exists with

1930s: Initial observations that obesity is related to altered insulin and glucose levels (Newburgh et al. 1930)

1950s: Vague made the clinical observation that upper body obese individuals had a greater prevalence of diabetes compared to lower body obese persons (Vague, 1956)

Early 1980s: Prospective and cross sectional studies reported that WHR is associated with insulin sensitivity and NIDDM (Kissebah et al., 1982; Ohlson et al., 1985)

Late 1980s & 1990s: The advent of CT and MRI enabled researchers to separate abdominal AT into VAT and abdominal SAT to study the effects of each depot on insulin-glucose variables (Sparrow et al., 1986)

Figure 1. A time line outlining the progression in research on the association between obesity, insulin resistance and NIDDM.

respect to the distribution of adipose tissue.[26] In general, women are characterized by a gluteal-femoral adipose tissue distribution whereas men have a preponderance of adipose tissue in the abdominal region.[26] Consistent with this observation, Krotkiewski et al.[26] reported that after matching for total adiposity, men had higher fasting and OGTT-insulin and glucose levels compared to women.

In the late 1980s and early 1990s, the use of magnetic resonance imaging and computed tomography (CT) provided additional insight into the association between adipose tissue (AT) distribution and metabolic risk. In particular, subdivision of abdominal adipose tissue into VAT and SAT depots revealed that in obese individuals, the VAT depot was significantly correlated with plasma insulin and glucose levels.[27,28]

2.1.1 VAT and metabolic risk

Sparrow et al.[27] in 1986, were the first to demonstrate an association between VAT measured by CT and glucose tolerance. Subsequently, there have been numerous studies on the relationship between VAT and glucose metabolism.[28-31] From these studies it is clear that VAT is independently correlated with glucose tolerance in obese men and women between 25 and 76 years of age.[27,28,30,31] However, the independent association between VAT and insulin sensitivity in obese individuals is not as clear. Whereas it is

observed that VAT is significantly correlated with insulin levels independent of obesity,[28,31-33] evidence to the contrary is also reported.[29,30,34] Furthermore, it is reported that VAT is differentially associated with insulin and glucose levels in obese and non-obese individuals since VAT is not significantly correlated with these metabolic variables in non-obese subjects.[28,31] Although not firmly established, the equivocal findings may be due to differences in study design, in particular, subject characteristics and methodologies employed to determine total adiposity.

It is reported that VAT is the strongest correlate of insulin and glucose levels in obese subjects,[28,30,31] however, total adiposity per se is the best predictor of insulin and glucose levels in non-obese men[28] and women.[31] Although an explanation for the different relationships between VAT and insulin and glucose levels in obese and non-obese individuals remains unresolved, differences in the relative accumulation of VAT may be a factor. That VAT is not a significant correlate with insulin-glucose variables may be explained by the relatively small VAT accumulation in non-obese individuals. This evidence suggests that a sufficient accumulation of VAT is required to see a significant association between this AT depot and metabolic variables.

A second explanation for the discrepant findings of the independent

influence of VAT on insulin levels may be related to differences in the methodologies employed to measure total adiposity. Previous investigations used body mass index (BMI) or hydrostatic weighing as a measure of obesity.[28,30,34] Attempts to separate the influence of VAT on insulin and glucose levels, from that of obesity, are confounded by the fact that obesity per se includes VAT. The independent influence of VAT on metabolic variables would be better resolved by controlling for whole body SAT rather than obesity per se. Ross et al.[35] determined the association between VAT and insulin and glucose responses independent of whole body SAT measured by MRI. This was the first investigation to determine the relationship between VAT and insulin and glucose variables independent of all other AT depots. Their findings support the notion that VAT is an independent predictor of both OGTT- insulin and glucose levels in obese women.[35]

2.1.2 Mechanisms associating VAT with insulin sensitivity and glucose tolerance

The mechanism that would explain the association between VAT, insulin resistance and glucose intolerance is not clear. It is hypothesized that FFAs mobilized from VAT (omental and mesenteric adipocytes) are drained into the portal circulation leading to both hepatic gluconeogenesis

and reduced insulin clearance.[36] The decrease in hepatic insulin uptake may be a result of reduced insulin binding, internalization of insulin receptors and decreased insulin degradation, particularly in those with a preponderance of VAT (Figure 2).[36,37] The increased mobilization of FFAs from VAT is explained by the regional differences in the lipolytic sensitivity of various AT depots. As a result of greater β-adrenergic receptors and little α-adrenergic inhibition in VAT this tissue is more sensitive than SAT to catecholamine stimulated lipolysis.[38] In addition, AT localized within the abdomen is less sensitive to the anti-lipolytic effects of insulin, resulting from a lower insulin receptor binding affinity compared to SAT (Figure 3).[39] Consequently, VAT is easily mobilized which may result in elevated FFA concentrations within the portal circulation.

2.1.3 SAT and metabolic risk

As reported previously, obesity is associated with insulin resistance and glucose intolerance.[1,21] Since SAT represents ~85% and ~93% of total adipose tissue in obese men and women respectively it is reasonable to assume that this AT depot influences these metabolic variables.[40] Indeed, it is reported that SAT is a major storage site for the mobilization of plasma FFAs, the influence of which on peripheral insulin sensitivity is well

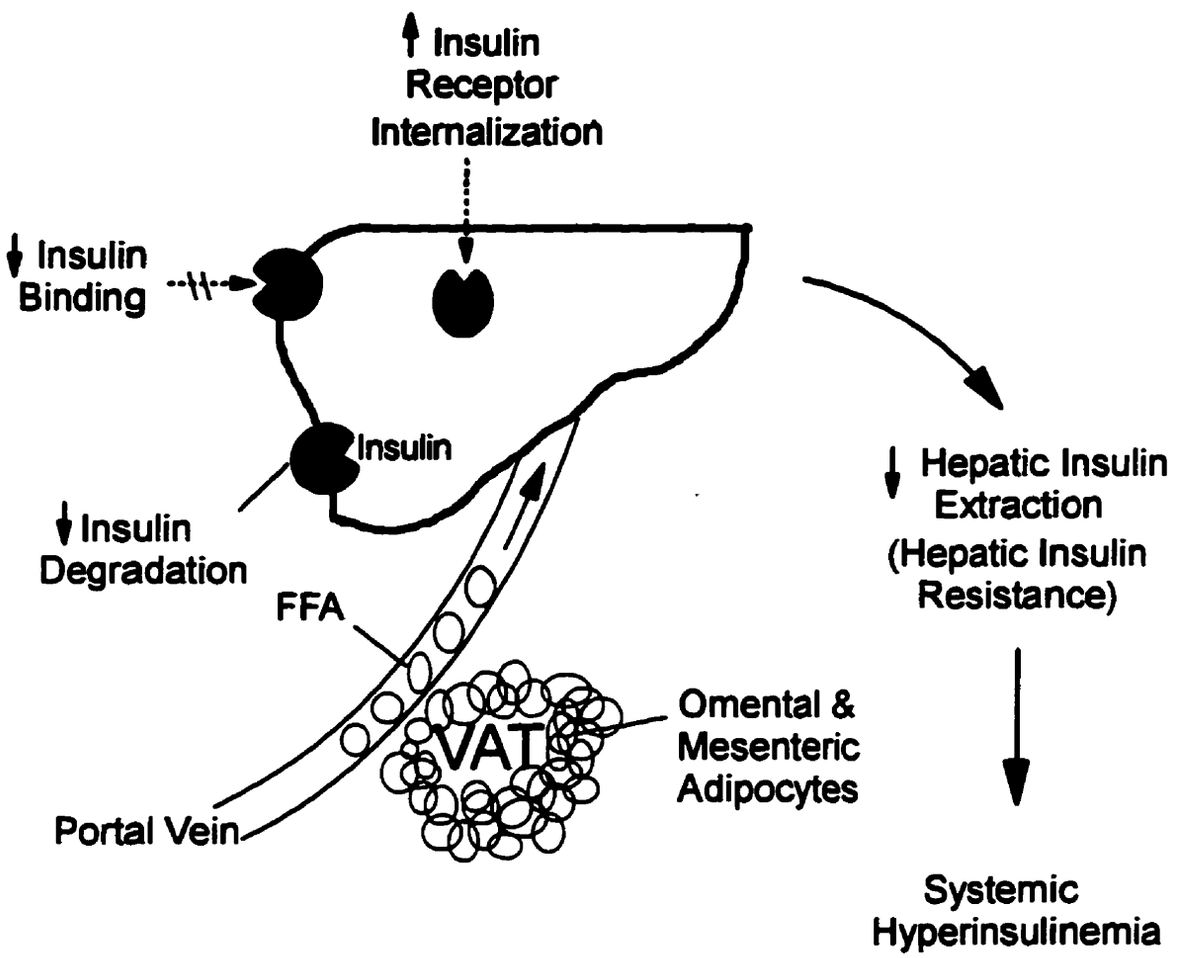
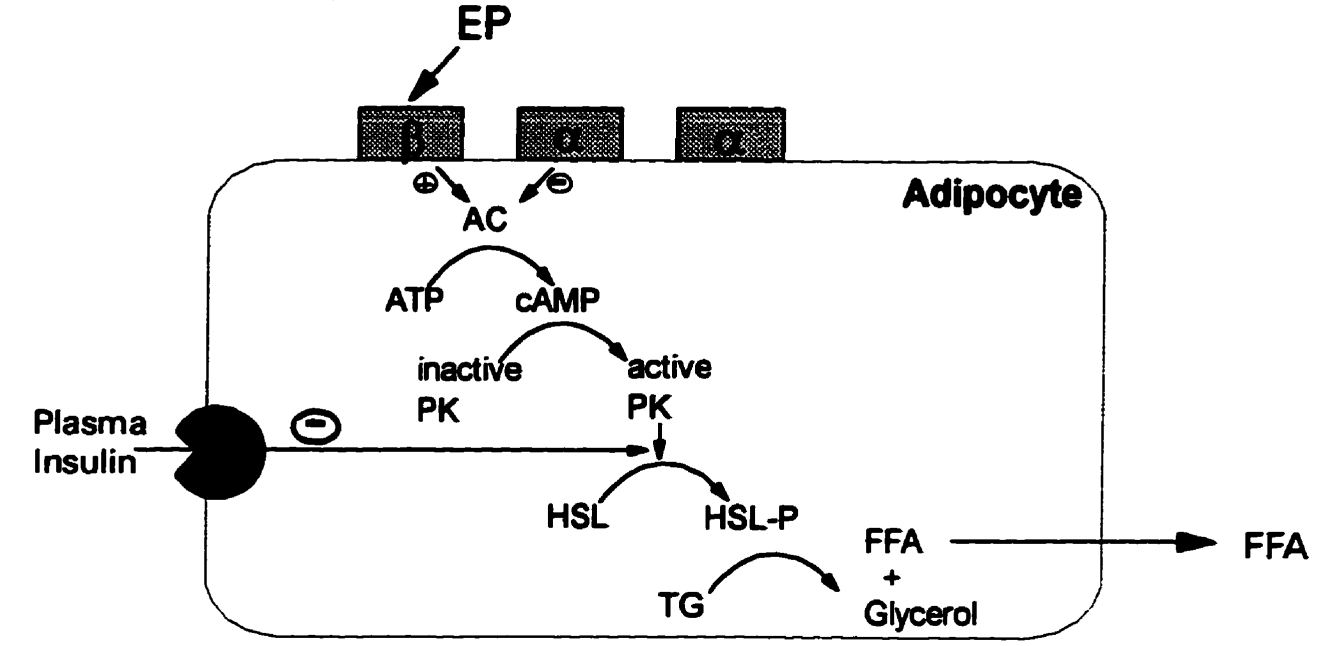


Figure 2. Proposed mechanism explaining the association between visceral adipose tissue and hepatic insulin resistance. VAT= visceral adipose tissue, FFA= free fatty acids

A) Subcutaneous Adipose Tissue



B) Visceral Adipose Tissue

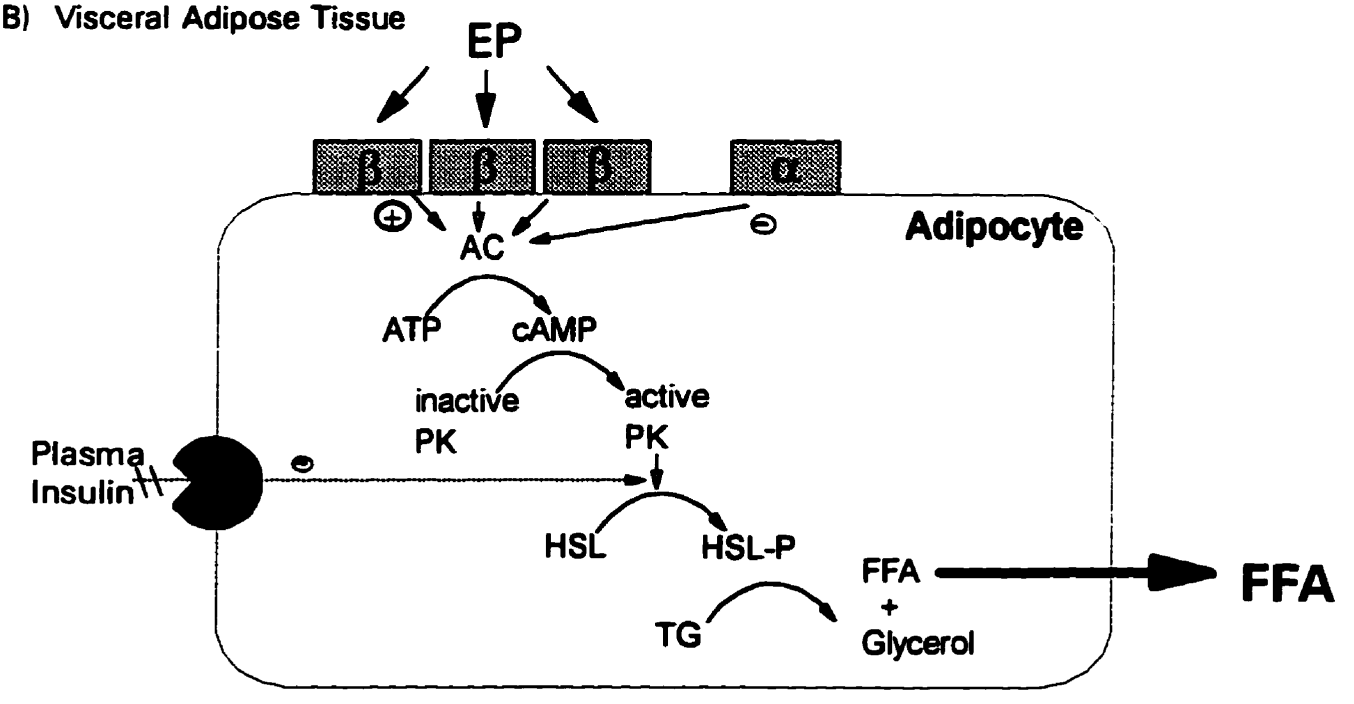


Figure 3A. Schematic representation of the lipolysis within subcutaneous adipose tissue (SAT).

Figure 3B. Visceral adipose tissue (VAT) is characterized by a preponderance of β -adrenergic receptors as well as diminished insulin receptor binding compared to SAT resulting in an increased free fatty acid (FFA) mobilization. EP= epinephrine, AC= adenylate cyclase, ATP= adenosine triphosphate, cAMP= cyclic adenosine monophosphate, PK= protein kinase, HSL= hormone sensitive lipase, TG= triglyceride, α,β = adrenoceptors

known.[41,42] However, the independent association between whole body SAT and insulin and glucose variables in obese individuals has not been fully established. Ross et al.[35] recently reported significant correlations between whole body SAT and both fasting and OGTT- insulin area in obese women. However, whole body SAT did not remain significantly related to insulin levels after controlling for VAT.[35]

Although whole body SAT is not a significant correlate of insulin-glucose variables in obese individuals after controlling for VAT, it is possible since SAT is not a homogeneous tissue that a regional consideration may provide different results. Abdominal SAT (ASAT) is more sensitive to the lipolytic action of catecholamines than gluteal-femoral SAT (FSAT).[43] This state is more prominent in women than men and has been observed both at rest and during exercise.[43] Indeed, reports have shown that ASAT is a stronger correlate of insulin levels than FSAT.[28,34] Although several investigations[28,31,33,35] have not observed an independent association between ASAT and elevated insulin levels, two studies have shown this.[34,44] Abate et al.[34] reported that independent of total adiposity, ASAT was a stronger predictor of insulin sensitivity in men than VAT. This observation was subsequently confirmed in a cohort of NIDDM men with a wide range of adiposity.[44] However, Abate et al.[34,44] assessed total adiposity with

hydrostatic weighing, a method that includes abdominal SAT in its' measurement.

2.1.4 Mechanisms associating SAT with insulin sensitivity and glucose tolerance

The mechanisms responsible for the association between SAT and insulin-glucose variables are not firmly established. It is proposed that FFAs mobilized from subcutaneous adipocytes may be involved by suppressing glucose utilization in skeletal muscles (Figure 4).[41,42] In 1963, Randle et al.[41,45] proposed that FFA oxidation causes an increased intra-mitochondrial ratio of acetyl CoA/CoA in rat heart and diaphragm muscles. This inhibits pyruvate dehydrogenase which in turn leads to elevated citrate concentrations. The rise in citrate level has an inhibitory effect on phosphofructokinase leading to accumulation of glucose-6-phosphate and a subsequent inhibition of hexokinase. The final result in this chain of events is a decreased glucose uptake into the cell.[41,45] Randle et al.[45] also suggested that the release of FFAs from adipocytes for oxidation in SM may be a cause of peripheral insulin insensitivity, due to the diminished responsiveness of the GLUT-4 transport system to the action of this hormone. More specifically, it is reported that FFA-induced insulin insensitivity may be related to a decrease in GLUT-4 expression on the

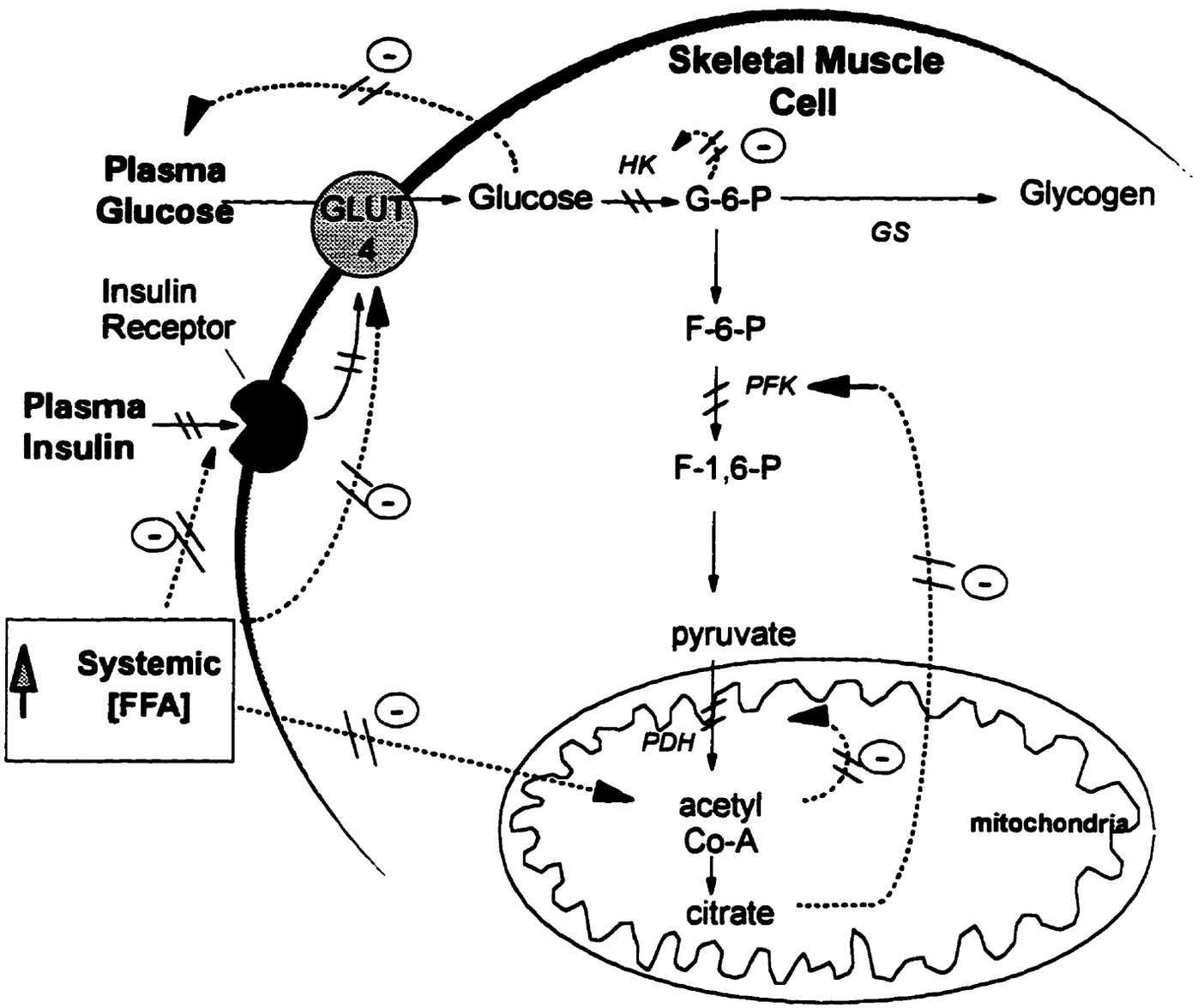


Figure 4. Proposed mechanism to explain the association between subcutaneous adipose tissue, decreased glucose uptake and peripheral insulin resistance. FFA= free fatty acids, PDH = pyruvate dehydrogenase, PFK= phosphofructokinase, HK= hexokinase, ·····► = proposed inhibition

plasma membrane or reduced intrinsic activity of this glucose transporter.[46]

Support for Randle's glucose-fatty-acid cycle has also been shown in humans. An inhibited glucose disposal in SM during hyperinsulinemic euglycemic conditions was reported in response to elevated FFA levels following lipid infusion in men[42,47] and women.[42] However, other studies did not observe an inhibitory effect of FFAs on insulin-mediated glucose disposal.[48] Reasons for these discrepant findings are unclear.

2.1.5 SM and insulin sensitivity in obesity

SM is the primary site for insulin-mediated glucose uptake in the post-absorptive state.[49,50] In obese individuals, particularly upper body obese, SM is characterized by a decreased oxidative capacity, as a result of a high percentage of fast-twitch glycolytic (FG) muscle fibers, decreased capillarization, and reduced activity of oxidative enzymes.[51,52] Krotkiewski et al.[53] observed that WHR was positively correlated with percentage of FG fibers and negatively correlated with capillary density. It is reported that a high percentage of FG fibers is associated with increased insulin and glucose levels, while capillary density is positively related to insulin sensitivity.[53] These associations suggest that muscle fiber type and capillarization may be involved in the development of insulin insensitivity.[53]

Consistent with a decrease in oxidative enzyme activity and a high

percentage of FG muscle fibers, obese individuals have a high respiratory quotient (RQ) when compared to lean subjects.[53] As an indirect measure of substrate metabolism, a high RQ describes a greater utilization of glucose and a reduced reliance on fats as an energy source. Indeed, it is reported that a decreased capacity for SM fat oxidation may predispose obese individuals to increased deposition of intra-muscular triglycerides.[52] It is suggested that these changes in muscle fiber type, capillarization and oxidative capacity are attributed to lack of physical activity which is commonly associated with obesity.[51]

2.2.0 Association between physical activity, insulin sensitivity and glucose tolerance

Recent prospective studies have investigated the relationship between physical activity and the incidence of NIDDM in large cohorts of both men and women.[4,5] In an 8 year follow up study of 87,253 healthy women age 34-59, it was reported that vigorous exercise performed at least once per week was associated with a 33% reduction in the age-adjusted risk of developing NIDDM compared to those who exercised less than once per week.[4] Relative risk was computed as the rate of occurrence of NIDDM in a specific category of physical activity divided by the incidence rates in those individuals who exercised less than once per week. After adjusting for both

age and BMI, the risk reduction remained significant but was reduced to 16%.[4]

Similarly, a 5 year follow up of 21,270 healthy men revealed a 22% reduction in risk for the development of NIDDM after adjustment for both age and BMI in response to physical activity at least once per week compared to sedentary individuals.[5] In addition, it was observed that the age-adjusted risk decreased with increased frequency of exercise revealing a dose-response relationship. The age-adjusted relative risk of developing NIDDM was 23% lower in those who exercised once weekly, 38% lower following 2-4 exercise sessions per week and 42% lower after 5 or more sessions per week in comparison to those who exercised less than once a week.[5] The beneficial effects of exercise were most pronounced among obese men who also had the highest incidence of NIDDM.[5] These observations suggest that exercise may be important in the prevention of NIDDM as well as improving insulin sensitivity and glucose tolerance.

In agreement with the observations of these prospective studies, cross-sectional investigations have confirmed the association between physical exercise and OGTT-insulin levels or insulin sensitivity measured by euglycemic clamp.[54,55] Rodnick et al.[54] reported that physically trained male runners demonstrated an OGTT- insulin response that was significantly

lower compared to sedentary controls matched for age and BMI. Glucose clamp data revealed a significantly greater insulin sensitivity and lower hepatic glucose production in the trained men versus the controls.[54] The trained subjects had 53% less body fat and a 50% higher maximal oxygen uptake ($\dot{V}O_2$max) than the controls.

2.2.1 Exercise prescription

Although evidence suggests that exercise reduces the incidence of NIDDM, the ideal modality, intensity, duration and frequency that would provide the greatest benefits is unknown. The American College of Sports Medicine recommends dynamic exercise involving large muscle groups for 20 minutes or longer, at least 3 times per week at an intensity of 60% $\dot{V}O_2$max or greater in order to improve cardiorespiratory capacity.[56] Although this exercise prescription was designed for healthy populations, it has been extrapolated to include those with NIDDM.[2] It is also reported that for reduced risk of CVD, energy expenditure through physical activity must be greater than 150 kcal/day with no further risk reduction associated with an expenditure above 400 kcal/day.[57] Whether the same exercise prescription is effective for reducing risk of NIDDM has not been established.

2.2.2 Mechanisms associating exercise training with insulin-glucose variables

It is unlikely that short term physical activity (12-16 weeks) in the absence of weight loss is associated with reductions in either VAT or SAT. Thus, the improvements in insulin sensitivity and glucose tolerance associated with routine exercise are more likely related to changes in SM mass or morphology.

An increase in SM mass may be associated with an enlarged glucose storage area and an increased number of insulin receptors available for binding.[58] It is hypothesized that this would lead to enhanced insulin clearance and improved peripheral insulin sensitivity. However, there are equivocal findings with respect to the association between SM mass and insulin-glucose variables. Whereas it is reported that percent SM mass, estimated from anthropometric measures, is positively correlated with insulin sensitivity,[59] other studies failed to observed an association between CT measured muscle area and plasma insulin and glucose levels.[27] Thus, the influence of SM mass per se on insulin-glucose variables is unresolved.

In addition to changes in SM mass, various morphological adaptations may occur in response to regularly performed exercise which may be associated with improved insulin sensitivity. These adaptations may include

fiber type conversion, and changes in the biochemistry and hemodynamics of SM.[17,19,60] It is reported that muscle fibers are heterogeneous and can be grouped according to their potential for insulin stimulated glucose utilization as well as their expression of glucose transport proteins.[61] FOG and slow-twitch oxidative (SO) fibers have greater levels of most oxidative enzymes, GLUT-4 transporters, and hexokinase when compared to FG fibers.[61] Although there is no evidence that FG or FOG fibers can be converted to SO fibers, it may be possible for the conversion of FG to FOG muscle fibers by exercise training in humans.[62] This adaptation would be associated with an increased level of oxidative enzymes, leading to an improvement in the oxidative capacity of the muscle.

Glucose transport is the rate-limiting step in skeletal muscle glucose utilization.[63,64] The glucose transporter which is most plentiful in skeletal muscle is GLUT-4.[61] It is translocated from an intra-cellular compartment to the sarcolemma where it facilitates glucose uptake when stimulated by insulin or muscle contraction.[61] An increase in the level or activity of SM GLUT-4 transport proteins may be associated with improved peripheral insulin sensitivity and glucose tolerance. Hemodynamic changes including enhanced insulin-stimulated muscle blood flow, and increased capillarization may also be associated with regular exercise training.[60] These changes may

improve glucose disposal by increasing the supply of both insulin and glucose to the muscle.[60]

Taken together, these observations suggest that strategies are needed to improve insulin sensitivity and glucose tolerance in obese individuals. It has already been established that whole body SAT, VAT and SM may be associated with insulin insensitivity in this population. Therefore, it is reasonable to suggest that diet-induced weight loss and exercise training may be effective treatments to improve these metabolic variables.

2.3.0 Influence of diet-induced weight reduction on insulin sensitivity and glucose tolerance

A recent review reported that diet-induced weight reduction is an effective means of increasing insulin sensitivity and reducing plasma insulin levels in healthy obese individuals.[6] From these studies, it would appear that a moderate weight loss of ~6-13 kg, is associated with a 26-53% improvement in insulin sensitivity, a 16-37% reduction in OGTT-insulin levels and an 8-12% reduction in OGTT-glucose levels in both men and women.[7,8,65-67,69,70] Although the majority of studies observed improvements in insulin and glucose variables, others have reported no reductions in insulin area despite a decrease in fasting plasma insulin levels,[71,72] or no

change in glucose tolerance despite an enhanced insulin response to an oral glucose load.[8,73] A rationale that would explain the equivocal findings is not clear. However, in several studies the normal pre-treatment glucose tolerance may explain the absence of improvement in OGTT-glucose levels.

2.3.1 Diet-induced changes in VAT, SAT and SM

Visceral Adipose Tissue

As previously stated, it is proposed that FFAs mobilized from VAT lead to hepatic gluconeogenesis and decreased hepatic insulin clearance.[36] Although a reduction in VAT should reduce portally drained FFAs, the portal concentration of FFAs has not been measured in vivo. In fact, studies have shown that a diet-induced weight loss of ~12-18kg is associated with a ~35% reduction in VAT in men[74] and women.[74,75] It is reasonable to assume that the concentration of portal FFAs would also be reduced likely improving hepatic insulin sensitivity. This would be consistent with the findings of decreased systemic FFA levels following SAT reduction which will be discussed below.

Subcutaneous Adipose Tissue

The reduction of SAT, in particular ASAT, may be associated with decreased levels of FFAs in the systemic circulation improving peripheral insulin sensitivity and glucose utilization. Indeed, following a 12.4 kg

weight reduction in 13 obese insulin resistant women with polycystic ovary syndrome, it was observed that ASAT, measured by skinfolds, decreased by 28% and FFA levels were reduced by 32%.[15] Insulin sensitivity measured by hyperinsulinemic euglycemic clamp more than doubled.[15] Analysis revealed that the variance in insulin sensitivity post-treatment was best explained by ASAT and FFA levels.[15] Thus, it was concluded that the preferential reduction in ASAT and FFA concentration may be associated with the improved insulin sensitivity.[15]

Skeletal Muscle

In addition to the mechanisms associated with AT reduction, it is also reported that weight loss increases the activity of muscle GLUT-4 transporters.[16] Friedman et al.[16] observed a significant increase in glucose disposal and a two-fold improvement in insulin-stimulated glucose transport following a 43 kg weight reduction in 7 healthy obese individuals and those with NIDDM. Although no changes were observed in the level of GLUT-4 transporter proteins, it is reported that the activity of these transporters increased.[16]

2.4.0 Influence of exercise on insulin sensitivity and glucose tolerance

Evidence suggests that an acute bout of exercise increases insulin sensitivity in healthy obese individuals and in those with NIDDM.[76,77] This

improvement in insulin sensitivity may last for a period of ~5 days.[14] This is important to consider when measuring the influence of chronic exercise training versus acute exercise on insulin and glucose variables, since testing less than 5 days after the last exercise session may be measuring acute exercise effects.

The effects of chronic exercise on insulin sensitivity and glucose tolerance is not clear. Studies have shown that both aerobic[10,12] and resistance[11,58,78] exercise training are effective in increasing insulin sensitivity, measured by hyperinsulinemic euglycemic clamp or OGTT-insulin response. In these same studies glucose tolerance was improved[10,11,58] or maintained.[12,78] However, within many of these investigations there was no attempt to control for changes in weight or body composition.[58,78] Furthermore, it is unclear whether the improved insulin and glucose levels were residual effects of the last exercise session or true training effects[14] since many studies assessed post-treatment metabolic variables less than 3 days after the last exercise bout.[10-12,58,78] Consistent with this observation, Segal et al.[79] demonstrated that aerobic exercise training was not associated with improvements in insulin sensitivity regardless of a 27% improvement in $\dot{V}O_2$max. In this investigation, the authors controlled for changes in body composition and the effects of the last exercise session. Subjects trained

for 12 weeks on a cycle ergometer for 4 hours a week at ~70% $\dot{V}O_2$max. The limited muscle mass involved in this form of training in contrast to many other studies that employed cycling, walking and jogging may be a possible explanation for these discrepant findings, since less involved skeletal muscle mass would suggest less metabolically active tissue. In addition, the authors suggested that the refeeding of calories immediately following exercise to ensure weight maintenance may be associated with the reduced non-oxidative glucose disposal.[79] Indeed, it has been reported that increased caloric intake is related to a reduction in insulin-stimulated glucose storage rate.[80]

2.4.1 Exercise-induced changes in SM morphology

As discussed previously, the proposed mechanisms associated with an improvement in insulin sensitivity after chronic exercise training include changes in SM morphology and an increase in SM mass.

SM morphology

Aerobic training is related to many SM morphological adaptations which may be associated with improved insulin sensitivity (Figure 5). Evidence suggests that aerobic training increases the percentage of FOG muscle fibers[17] and GLUT-4 levels.[81-83] It is reported that GLUT-4 levels are positively correlated with whole body glucose disposal.[81] In addition,

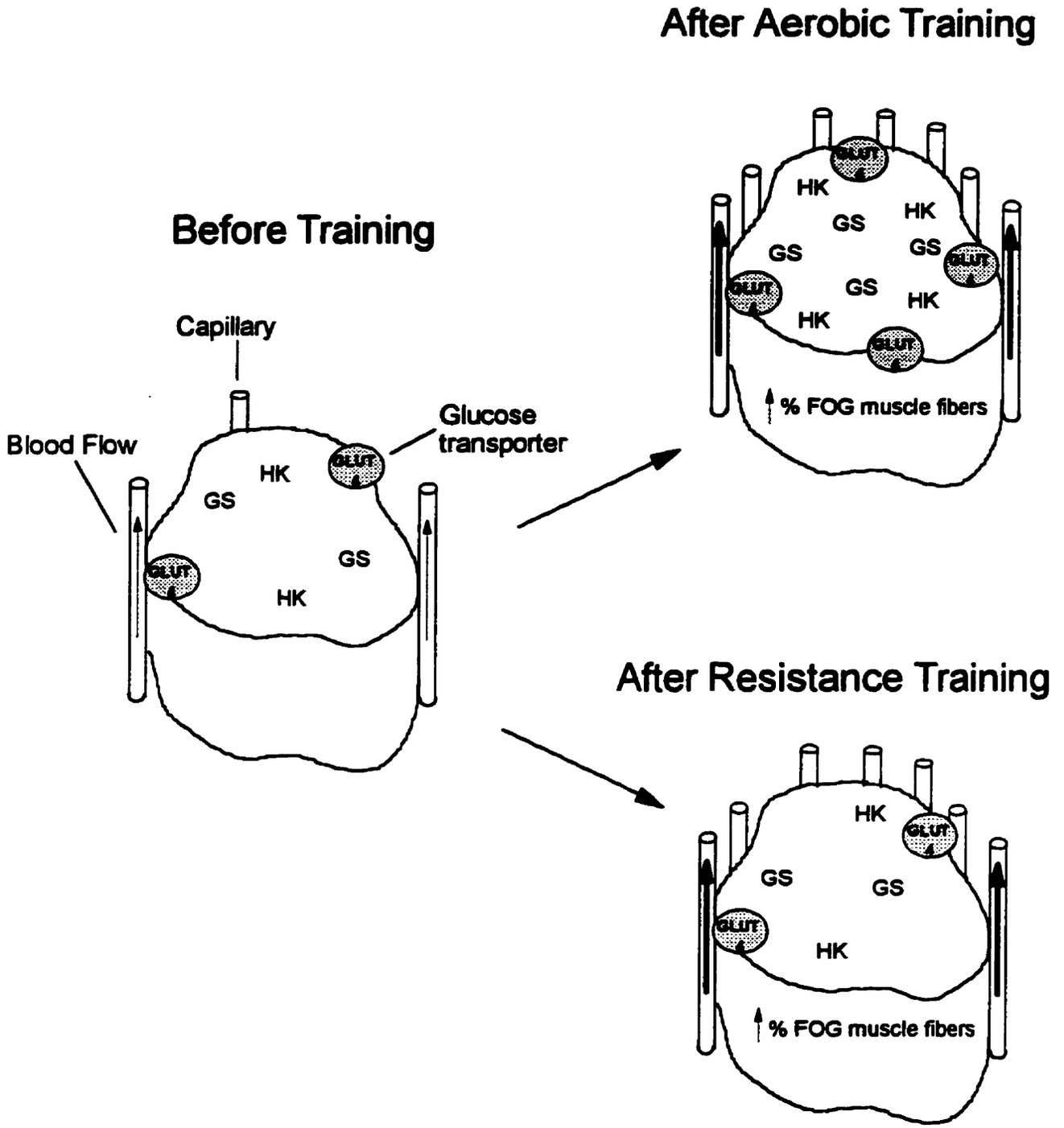


Figure 5. Schematic diagram of aerobic or resistance exercise induced changes in skeletal muscle morphology. Changes following aerobic training include an increase in muscle fiber capillary density, percentage of fast twitch oxidative fibers (FOG), blood flow, GLUT-4 transporter level, glycogen synthase (GS) and hexokinase (HK) activity. After resistance training, changes include an increase in capillary density, percentage of FOG fibers, and blood flow.

hexokinase activity increases, facilitating glucose transport into the muscle and glycogen synthase activity improves thereby increasing the storage of glucose into muscle glycogen.[19,81]

Hemodynamic changes in SM have also been observed after aerobic training. Cross sectional studies have shown that athletes have enhanced insulin-stimulated muscular blood flow when compared to sedentary individuals.[60] Furthermore, it is reported that endurance training enhances skeletal muscle capillarization.[18] Various studies have reported an association between muscle capillary supply and fasting insulin levels supporting the hypothesis that the improvement in insulin sensitivity may be due to a decreased diffusion distance between the capillary and muscle fiber.[84,85]

Resistance exercise training has been associated with fiber type adaptations as well. It is reported that 8 weeks of high intensity resistance training increased FOG and decreased FG muscle fiber percentage in both men and women.[86] In addition, studies have reported an increase in the capillary to fiber ratio after a resistance training program.[87,88] However, little is know on the association between resistance training and GLUT-4 levels, hexokinase or glycogen synthase activity.

SM mass

Miller et al.[58] speculated that an increased SM mass following training may be associated with a decreased OGTT- insulin response. This is based on the observation that an increase in lean body mass was correlated with a decreased insulin area ($r=0.89$, $p<0.05$) after a 10 week high-resistance weight training program in non-obese men. In contrast to this proposed mechanism, others have speculated that an increased muscle mass likely plays only a minor role in improving insulin sensitivity.[78] It is suggested that even if an increase in lean body mass of 1.2 to 2.3 kg were entirely attributed to increased muscle cell mass, this would only represent a 5-8% increase in total muscle mass assuming that muscle comprises 40% of lean body mass.[58,78] This magnitude of increase would not be large enough to entirely account for the 20% improvement in glucose disposal[78] and the 19% reduction in insulin area[58] observed after resistance training in these studies. Thus, whether SM mass influences OGTT- insulin levels or insulin sensitivity measured by glucose clamp remains unclear.

2.5.0 Influence of diet and exercise-induced weight loss on insulin sensitivity and glucose tolerance

Since both diet and exercise may increase insulin sensitivity through independent mechanisms, it is reasonable to assume that the combination of

the two would be associated with greater improvements in insulin sensitivity when compared to either treatment alone. In fact, few studies have investigated the combined effects of diet and exercise versus diet alone.[9,12,20] Inspection of Table 1 reveals that aerobic exercise was the principle training modality employed. In general, it is observed that DA was associated with significantly greater changes in insulin levels than compared to DO in NIDDM,[9,20] and healthy obese[12] men and women. Dengel et al.[12] conducted the only investigation to compare the effects of DO versus DA on insulin sensitivity and glucose tolerance in obese men. The findings demonstrate that the combination of DA was associated with significantly greater reductions in insulin response following an oral glucose challenge (DA:42%; DO:21%). In addition, the DA group demonstrated significantly greater glucose disposal during a glucose clamp (DA:22%, DO: no change) when compared to DO.[12] The exercise training included walking, jogging or stationary cycling 3 days per week, at an intensity of 50-85% of heart rate reserve. Initially, all subjects exercised for ~10 minutes and gradually progressed up to 40 minutes per session.[12]

The results are potentially confounded by two factors. First, it is unclear how accurately weight reduction was monitored in this study, since the 10 month treatment only elicited an ~8.5 kg decrease in body weight in

Table 1. Studies comparing the effects of diet only versus diet in combination with aerobic exercise training on insulin and glucose variables

Reference	Comparison	Method	Duration	Subjects	Wt. Red	Diet	Type Exercise	Relative Reduction in Fasting Insulin	Relative Reduction in Insulin Area	Relative Increase in Hepatic Insulin Sensitivity	Relative Increase in Peripheral Insulin Sensitivity	Relative Reduction in Fasting Glucose	Relative Reduction in Glucose Area
Bogardus et al. (1984)	DO vs DA (plus light RT)	EC	12 wk	N=18 Niddm Males & Females (non-obese)	DO= -10kg DA= -11Kg	consumed 450 kcal/m2	- DA- light resistance training, walk, jog, swim, bike	DO= - 33.1% DA=- 37.7%	N/A	DO= + 25% DA= + 25%	DO= no change DA= +30%	DO= -20.3% DA= -19.8%	N/A
Yamanouchi et al. (1995)	DO vs DA	EC	6-8 wk	N=24 Niddm Males & Females (obese)	DO= - 4.2kg DA= -7.8kg	consumed 1000-1600 kcal/day	- DA- walk 10,000 steps per day	DO= no change DA= - 45.6%	N/A	N/A	DO= no change DA= +51%	DO= -13.6% DA= -14.7%	N/A
Dengel et al. (1996)	DO vs DA	EC/OGTT	10 mon	N=28 Males (obese)	DO= -8.8 kg DA= -8.5 kg	energy deficit = 300-500 kcal/day	DA -bike, walk, jog	DO= no change DA= - 31%	DO= - 21% DA= - 42%	N/A	DO= no change DA= +22%	DO= no change DA= no change	DO= -16% DA= - 20.8%

DO= diet only; DA= diet and aerobic exercise; EC= euglycemic hyperinsulinemic clamp; OGTT= oral glucose tolerance test; NIDDM= non-insulin diabetes mellitus; wk=week; mon= month; N/A= not available

both diet groups at a caloric reduction of 300-500 kcal per day.[12] This level of energy restriction should have been accompanied by a 11-18 kg body weight loss. Second, Dengel et al.[12] conducted all post-treatment metabolic measurements less than 36 hours after the last exercise session, which may suggest that the observed change in insulin levels may have been a residual effect of exercise.[14]

To our knowledge the effects of DR versus DO on insulin sensitivity and glucose tolerance in men or women have not been studied. However, Ryan et al.[13] reported that 4 months of DR was related to a greater increase in insulin sensitivity compared to resistance training alone in postmenopausal women. The subjects were not well matched however, because the pre-treatment BMI (30.3 kg/m^2) of the diet and resistance training group was significantly different from the BMI (23.2 kg/m^2) of the resistance training alone group.[13]

2.6.0 Summary

It is observed that diet alone is an effective treatment for improving both insulin sensitivity and glucose tolerance in obese individuals. Furthermore, reports indicate that exercise training in the absence of change in body weight or body composition may be related to decreased insulin response to a glucose challenge and increased insulin sensitivity. However,

the association between diet in combination with either aerobic or resistance training versus diet alone on glucose metabolism has not been established. Therefore, the principle purpose of this study was to assess the effects of diet alone and diet in combination with aerobic or resistance exercise on changes in OGTT-insulin and glucose levels in obese men. Furthermore, we employed a whole body MRI model in an attempt to distinguish between the respective contribution of changes in SAT, VAT, and SM mass to improvements in carbohydrate metabolism.

3.0.0 MANUSCRIPT

The following chapter of this thesis has been submitted for publication and is presented in a format consistent with that required by the journal. For simplicity the references for the manuscript are included in Chapter 4.0.0.

Effects of Exercise and/or Diet on Plasma Insulin and Glucose Levels in Obese Men

INTRODUCTION

Diet induced weight loss is associated with improvements in insulin sensitivity[8,67,70] and glucose tolerance[8,67] in both men and women.[8,70] It is also reported that aerobic[10,12] or resistance[11,13] exercise is associated with a decreased insulin response to an oral glucose load[11,12] or increased insulin sensitivity[10,13] independent of weight loss and changes in body composition. However, in many of the exercise studies insulin response was determined less than 72 hours after the final exercise session[10,11] and thus, it is unclear whether the reduction in insulin levels are true training effects, or residual effects of the last exercise bout.[14] Consistent with this observation Segal et al.[79] reported that aerobic exercise training is not associated with improved insulin sensitivity after controlling for the effects of the last exercise bout and changes in body composition.

Although not firmly established, it is generally accepted that the principal mechanisms by which weight loss and exercise influence insulin sensitivity differ. Whereas weight loss may improve insulin sensitivity and glucose tolerance through reduced systemic and portal circulation free fatty acid (FFA) concentrations, and increased GLUT-4 activity,[15,16] it is reported that exercise may be associated with these changes through adaptations in skeletal muscle (SM) morphology. These adaptations may include an increase in the percentage of fast twitch oxidative (FOG) fibers,[17] capillarization,[18] and oxidative enzyme activity.[19] Taken together, these

observations suggest that the combination of weight loss and exercise would have effects on insulin metabolism that are greater than weight loss alone. Indeed, Dengel et al.[12] recently reported that diet-induced weight loss and aerobic exercise were associated with significantly greater reductions in oral glucose tolerance test (OGTT) insulin values compared to diet alone in healthy obese men.

In this study we tested the hypothesis that the combination of diet and either aerobic or resistance exercise is associated with greater improvements in plasma insulin and glucose levels compared to diet alone in obese men. We employed a whole body magnetic resonance imaging (MRI) protocol to determine the associations between concurrent changes in subcutaneous adipose tissue (SAT), visceral adipose tissue (VAT), SM mass and carbohydrate metabolism.

METHODS

Subjects. Forty obese but otherwise healthy men were recruited from the general public and gave their fully informed consent to participate in this study. Entry criteria required that the men be non-smokers, upper-body obese [body mass index (BMI, kg/m^2) >27, waist-to-hip circumference ratio (WHR) >0.95], weight stable (± 2 kg) for 6 months prior to enrollment, taking no medication known to affect the study variables, and consume on average fewer than two alcoholic beverages per day. Pre-participation screening included a medical examination and a 5 hour oral glucose tolerance test.

The subjects were randomly assigned to one of three treatment groups; diet only (DO), diet and aerobic exercise (DA) or diet and resistance exercise (DR). Eight men did not complete the study; thirty-one complied with the study requirements, 9 in the DO group, 11 in the DA group and 11 in the DR group. The descriptive characteristics for all groups are given in Table 1. The three groups were not different with respect to the anthropometric, MRI, or metabolic variables. This study was conducted in accordance with the ethical guidelines of Queen's University.

Anthropometric measurements. Body weight was measured on a balance scale calibrated to 0.1 kg. Barefoot standing height was measured to the nearest 0.1 cm using a wall mounted stadiometer. Circumference measurements were acquired according to the procedures described in the

Anthropometric Standardization Reference Manual.[68] Circumference measurements were taken by the same investigator pre- and post- treatment at the following sites: biceps, forearm, chest, hip, proximal thigh, calf, and waist at the level of the last rib. Body fat distribution by anthropometry was estimated using the WHR.

Tissue measurement by MRI. Magnetic resonance images were obtained with a Siemens 1.5 T whole body scanner (Erlangen, Germany). A T1-weighted, spin-echo sequence with a 210 ms repetition time and 15 ms echo time was used to acquire all the MRI data. The total time required to obtain all MR images for each subject was ~25 min. The protocol followed for MR image acquisition is described in detail elsewhere.[89] Briefly, six data sets (7 images per set) were obtained while the subject lay in the magnet in a prone position, arms straight above the head (Figure 1). Transverse images (10-mm thickness) were obtained every 40 mm over the whole body. For all subjects a total of 41 images were acquired. All image data were transferred to a stand-alone Indigo2 computer (Silicon Graphics Inc., Mountain View, CA) and analysed using software developed within our laboratory (Slice-O-Matic Inc., Montreal).

Calculation of tissue areas and volumes. The model used to segment adipose and lean tissues is illustrated in Figure 2. The threshold selected for adipose tissue was based on an analysis of a sample of typical images and their grey level histograms. Once the appropriate threshold was selected,

each image was reviewed using an interactive slice editor program which allowed for verification and, where necessary, correction of the segmentation result. Corrections were made by superimposing the original grey level image on the binary segmented image using a transparency mode. Tissues were labelled by assigning them different colour codes. Whole body SM and SAT were calculated using all 41 images. Because it is proposed that abdominal adiposity is associated with metabolic complications, this region was subdivided into VAT and abdominal SAT (ASAT) depots. VAT and ASAT volumes were derived using 5 abdominal images extending from one below to four above the L4-L5 intervertebral space; femoral subcutaneous adipose tissue (FSAT) was determined using 18 images extending from the femoral head to the foot. Since it has been hypothesized that the complications associated with the accumulation of VAT are related to the portally drained depots (omental and mesenteric) located in the peritoneal cavity, we subdivided VAT into intraperitoneal (IP-AT) and extraperitoneal (EP-AT) compartments using a method previously described.[90]

Measurement of plasma glucose and plasma insulin levels. A 5 hour, 75 g oral glucose tolerance test was administered the morning after an overnight fast. Blood samples were collected from the antecubital vein at 0, 60, 120, 180, 240, and 300 minutes post glucose ingestion. The glucose oxidase method (Beckman Glucose Analyser, Fullerton, CA) was used for

plasma glucose measurement. Plasma insulin was measured by a double anti-body radioimmunoassay.[91] Glucose and insulin areas under the curve were determined using a trapezoid model. The insulin to glucose area ratio (IGAR) was used to represent a crude index of peripheral insulin sensitivity. Post- treatment OGTT measurements were obtained 5-13 days after the last exercise session. Coefficients of variation for the blood chemistry measurements were: insulin 4.5-7.6% and glucose 2.0-3.5%

Dietary protocol. The Harris-Benedict equation[92] multiplied by a factor of 1.5 was used to estimate each subjects energy requirements.[93] This energy intake was followed for a 2 week baseline period. For the 16 weeks following the baseline period energy intake was reduced by 4.18 MJ/day (1000 kcal/day). All subjects were required to limit dietary fat intake to less than 30% of total energy intake. All foods were self-selected and no supplements were prescribed. Daily diet records were kept and submitted weekly for analysis to ensure adherence to the dietary protocol. After the 16 week treatment the energy intake for weight maintenance was recalculated by deriving the average daily energy intake obtained from the diet records and adding to that number the energy value associated with the weight loss (assuming 32.2 MJ/kg, 3500 kcal/lb). The derived energy intake value was prescribed for 2 weeks.

Aerobic exercise protocol. In addition to energy restriction, 11 men performed aerobic exercise 5 d/wk. Initial duration of each exercise period

was ~19 min and gradually progressed to a maximum duration of 60 min based on individual capabilities. The exercise intensity was followed with automated heart rate monitors (Polar USA, Inc., Stamford CT). Intensity of exercise progressed from 50% to 85% of maximum heart rate which was determined during a maximum oxygen uptake ($\dot{V}O_2max$) test. The subject determined the mode of exercise which varied between walking on a motorized treadmill, stationary cycling or stair stepping using the StairMaster 4000 (Tri-Tech Inc., Tulsa, OK). All exercise sessions were by appointment and monitored by a physical educator.

Resistance exercise protocol. In addition to the energy restriction, 11 men performed resistance exercise 3 d/wk. Training sessions began with a 5-10 min warm-up of low intensity stationary cycling and 5 min of static stretching. Resistance training was executed on seven Nautilus (Nautilus Inc., Deland, FL) weight training stations. The resistance training program consisted of 1 set of the following 7 exercises: leg extension, leg flexion, superpullover (latissimus), bench press, shoulder press, triceps extension, and biceps curl. Subjects performed between 8 and 12 repetitions to failure for each exercise. Once subjects could successfully perform 12 repetitions, the load was increased. Sit ups for the abdominal muscles were performed each session. Verbal encouragement by the exercise supervisor was given to ensure that the subjects performed to volitional fatigue. Each resistance exercise session lasted ~ 30 min.

$\dot{V}O_2$max. Maximal oxygen consumption was determined during a ramp treadmill test prior to and following the treatment. Standard open-spirometry techniques were employed with a Beckman metabolic cart (Sensormedics Inc., Fullerton, CA).

Statistical analysis. All data were tested for skewness. Log and square root transformations were used to correct insulin variables and VAT. The untransformed data is presented in tables. Data are presented as mean $\pm$ standard deviation (SD). A 2-way analysis of variance, group (DO, DA, DR) by time (pre, post) was employed to evaluate main treatment effects and interactions on all dependent variables. Significant differences were analysed using a Scheffé post hoc comparison technique. Paired t-tests were used to assess within group changes for all dependent variables. Unpaired t-tests were used to determine changes between variables. Bonferonni adjustments ($p < 0.017$) were used for all t-tests. Regression analysis was used to determine whether changes in insulin variables were related to either changes in anthropometric or MRI variables. Data were analysed using SYSTAT.[94]

RESULTS

Adherence to the diet and exercise program. For the DA group, attendance at the exercise sessions averaged 92% (range 74%-99%). The mean duration of each session was 37.0 $\pm$ 7.0 min and the exercise intensity was 77.0 $\pm$ 4.0 % of maximum predicted heart rate. The DR group attended 96% of the exercise sessions (range 85%-100%). The average diet-induced energy deficit (~4.5 MJ, 1060 kcal/d) and contribution of dietary fat (~22%) to the total caloric intake were not different between groups ($p > 0.05$).

Change in cardiovascular and strength performance. The improvement in peak $\dot{V}O_2$ from 3.1 $\pm$0.6 L/min to 3.5 $\pm$0.7 L/min (14%) was significant ($p < 0.05$) for the DA group alone. Muscular strength increased significantly ($p < 0.05$) in both the upper (12%) and lower (20%) body in the DR group (Figure 4).

Change in anthropometric variables. The changes in selected anthropometric variables are given in Table 2. Significant ($p < 0.001$) within group reductions were observed for all groups for BMI (~12%) and waist circumference (~10%). WHR decreased (~5%) in the DA and DR groups alone ($p < 0.01$). Without exception, the changes in anthropometric variables were not different ($p > 0.05$) between groups.

Change in MRI variables.

Adipose tissue and skeletal muscle. The changes observed in adipose tissue (AT) and SM variables are given in Table 2. Independent of treatment, the relative reductions in VAT (~37%) were significantly greater than whole body SAT (~24%) (Figure 3). Within the VAT depot, both IP- and EP-AT were significantly ($p<0.001$) reduced. However, independent of treatment, the relative decrease in IP-AT (~41%) was greater ($p<0.01$) than EP-AT (~25%). For the DA and DR groups alone, the relative decrease observed for ASAT (~31%) was greater ($p<0.01$) than that observed for FSAT (~21%). Whereas SM was preserved in the DA and DR groups ($p>0.05$), a 7% reduction ($p<0.001$) in whole body SM was observed within the DO group.

Change in metabolic variables.

Fasting. Independent of treatment, no significant ($p>0.05$) reductions were observed for plasma glucose levels (Table 2). For plasma insulin, significant decreases ($p<0.05$) were observed within all groups (Figure 4). Although not statistically significant, a trend toward a significant group by time interaction was revealed when the reduction in fasting plasma insulin for the DO (~19%) group was compared to the DA (~38%) and DR (~36%) groups ($p=0.09$).

Oral glucose tolerance test. OGTT-glucose area was not significantly reduced within any group ($p>0.05$). However, insulin area

decreased in all groups ($p<0.01$). Post hoc analysis revealed that by comparison to the DO group (18%), the reduction in insulin area was significantly ($p<0.05$) greater in the DA (~46%) and DR (~44%) groups (Figure 5). Accordingly, IGAR significantly decreased in all groups ($p<0.05$), however, the reduction in IGAR within the DA (~41%) and DR (~40%) groups was greater than that observed for the DO group (~16%).

Relationship between anthropometric, MRI and metabolic variables.

For both pre-treatment and change score values, no significant correlations ($p>0.05$) were observed between the metabolic variables, and either the anthropometric or MRI variables.

DISCUSSION

We tested the hypothesis that the combination of diet and either aerobic or resistance exercise has effects on plasma insulin and glucose levels that are greater than diet alone in obese men. These findings demonstrate that, despite no change in glucose tolerance, all treatments were associated with reductions in both fasting and OGTT-insulin levels. However, the reductions observed within both exercise groups were significantly greater compared to diet alone. Accordingly, the decrease in IGAR, a crude measure of insulin sensitivity, was significantly greater within the DA and DR groups as compared to the DO group.

Within the DO group both fasting and OGTT-insulin levels decreased by approximately 18%. This is consistent with others who report similar reductions in response to a 10 kg weight loss in men[10,66,73] and women.[7] The decrease in OGTT-insulin was responsible for the concomitant decrease in IGAR as glucose tolerance was not affected by weight loss. These observations support the notion that diet-induced weight loss is associated with a corresponding improvement in the biological effect of insulin. In other words, less insulin is required to dispose of a given quantity of glucose post-weight loss. The mechanism by which diet-induced weight loss improves insulin sensitivity is not clear. It is generally assumed that reductions in body fat are associated with corresponding reductions in systemic FFA concentration which would have a positive influence on

peripheral insulin sensitivity (muscle)[95] and/or pancreatic secretion.[97] It is also possible that reductions in VAT would result in a corresponding reduction in portal FFA concentrations which would improve hepatic insulin extraction. Plasma FFA concentration was not measured in the present study, however, it is reasonable to assume that the reductions observed for SAT (~24%) and VAT (~32%) are associated with a corresponding decrease in both systemic and portal circulation of FFAs. Although the association between VAT and portal FFA concentrations has not been measured in vivo, Holte et al.[15] reported a 32% reduction in systemic FFA levels in response to a 12 kg weight loss in insulin-resistant women with polycystic ovary syndrome. The reduction in FFA concentration was associated with a significant improvement in insulin sensitivity.[15] In addition to the influence of body fat reduction, it is also possible that diet-induced weight loss may result in adaptations in SM per se, however, this is unlikely since we observed a decrease in MRI-SM (~7%) combined with an absence of change in peak $\dot{V}O_2$ in response to DO. This suggests that improvements in OGTT-insulin response are probably not explained by changes in muscle morphology. Thus, it is more likely that the improvement in insulin response following diet induced weight loss in this study is mediated through reductions in both VAT and whole body SAT.

Whether the addition of exercise to a regimen of energy restriction has added benefits with respect to insulin and glucose metabolism has not

been clearly established. Dengel et al.[12] recently reported that for a group of age and weight matched obese men, the combination of diet and aerobic exercise resulted in a 42% decrease in OGTT- insulin area which was significantly greater than the 21% reduction observed within the DO group. Furthermore, glucose disposal during hyperinsulinemic euglycemic clamp increased by 22% in response to the DA treatment and was unchanged in the DO group.[12] These observations are similar to the findings reported here wherein a 46% reduction in OGTT- insulin levels, in response to DA was significantly greater than the 18% reduction observed for the DO group. Taken together these observations suggest that, in response to a 10kg weight loss, the combination of diet and aerobic exercise is associated with a 2 fold greater reduction in OGTT-insulin levels compared to diet alone.[12]

In the present study, and that of Dengel et al.[12], the reductions in weight and fat mass (adiposity) were not different between the DA and DO treatments suggesting that the added benefit of exercise is mediated through mechanisms other than reductions in body weight and/or total adiposity. Accordingly, it is likely that the greater reduction in insulin levels are associated with morphological adaptations in SM known to occur in response to aerobic exercise. In both studies, peak $\dot{V}O_2$ increased by ~14% in the DA group.[12] Previous studies have observed that a 10-16% increase in peak $\dot{V}O_2$ is associated with increases in GLUT-4 levels,[83] capillarization,[18] and hexokinase activity.[83] Indeed, it is reported that GLUT-4 levels are

positively correlated with whole body glucose disposal[81] while capillarization is correlated with serum insulin concentration.[84] It has also been proposed that aerobic training enhances insulin action through an increase in muscular blood flow,[60,81] and percentage of FOG muscle fibers.[62] Furthermore, glycogen synthase activity increases in response to aerobic training and is positively correlated with non-oxidative glucose disposal which is thought to be the main path for improved peripheral insulin sensitivity after exercise training.[9,81] Finally, it has been reported that a greater lean body mass could be associated with increased glucose storage and improved insulin binding resulting in enhanced insulin clearance.[58] Although SM glycogen content was not measured in this study, the maintenance of SM mass may suggest that glycogen storage capacity was preserved.

In this study we also observed that diet in combination with either aerobic or resistance exercise was associated with a preferential reduction in ASAT (~32%) compared to FSAT (~21%). This is consistent with the observation that the lipolytic activity of abdominal subcutaneous adipocytes during exercise is increased by comparison to femoral adipocytes in men and women.[43] That ASAT is preferentially reduced in response to exercise may confer an additional metabolic benefit as it has recently been reported that ASAT is a strong, independent predictor of insulin sensitivity in men.[34]

The results of the present investigation demonstrate the synergistic effect of diet and exercise (aerobic or resistance) on OGTT- insulin levels.

However, it is important to note that the influence of exercise on insulin sensitivity is clearly transient, since it is reported that improved insulin sensitivity associated with exercise is significantly reduced within 5 days after the cessation of exercise.[98] Therefore, for the beneficial metabolic effects of exercise to be maintained, physical activity must be performed on a regular basis. It is important to note that exercise performed in the present study was well tolerated. That is, aerobic exercise 5 days/week for ~40 minutes, or resistance training 3 days/week for ~ 30 minutes may not be ideal, but both regimens were associated with reduced insulin levels when combined with diet.

To our knowledge this is the first study to compare the effects of diet and resistance exercise versus diet alone on insulin and glucose metabolism. The reductions observed in OGTT-insulin and IGAR in response to DR were significantly greater than those observed in response to DO. Our results are in agreement with those of Ryan et al.[13] who reported that a 50% improvement in strength was associated with a corresponding reduction (43%) in insulin response during a hyperglycemic clamp in healthy obese women following DR. Moreover, in that study resistance training in the absence of weight reduction was associated with a 16% improvement in insulin response.[13] Taken together, these findings strongly support the utility of resistance exercise as a modality for improving insulin sensitivity.

Consistent with the DA group, the added benefit of DR is likely

explained by adaptations in SM morphology. As observed in response to aerobic training, resistance training is also reported to be associated with SM changes which include an increased percentage of FOG muscle fibers,[86] and an increased capillary to fiber ratio.[88] In addition, SM mass was maintained after the 16-week resistance training program unlike the DO group.

In summary, the results of this study demonstrate that the addition of either aerobic or resistance exercise to a diet regimen is associated with reductions in OGTT-insulin levels that are greater when compared to diet alone. In conjunction with the observation that diet in combination with exercise is more effective than diet alone for the maintenance of weight loss,[96] it is prudent to recommend that routine exercise be included within a therapeutic strategy designed to improve insulin sensitivity and maintain weight loss.

Table 1
Descriptive characteristics of subjects[1]

Variable	DO group (n=9)	DA group (n=11)	DR group (n=11)
Anthropometry			
Age (y)	44.4 ± 6.1	47.6 ± 6.4	38.8 ± 13.0
Weight (kg)	99.1 ± 11.2	101.6 ± 12.3	109.6 ± 16.8
BMI (kg/m^2)	31.9 ± 2.8	32.5 ± 3.6	33.6 ± 4.1
WHR[2]	0.96 ± 0.04	0.99 ± 0.09	0.98 ± 0.08
Waist circumference (cm)[3]	106.9 ± 7.3	112.7 ± 8.3	112.6 ± 10.4
MRI-measured			
Total AT (L)	34.2 ± 7.9	35.0 ± 7.1	39.3 ± 10.4
Subcutaneous AT (L)	27.1 ± 7.0	27.1 ± 6.6	32.8 ± 8.6
ASAT (L)	6.6 ± 2.1	7.2 ± 2.2	8.5 ± 2.7
FSAT (L)	11.8 ± 2.9	11.1 ± 3.0	14.4 ± 3.3
Visceral AT (L)	4.6 ± 1.6	4.6 ± 1.4	3.9 ± 2.3
Intraperitoneal (L)	3.6 ± 1.4	3.4 ± 1.2	3.0 ± 1.9
Extraperitoneal (L)	0.9 ± 0.3	1.0 ± 0.3	0.8 ± 0.4
Skeletal Muscle (L)	34.7 ± 3.6	33.2 ± 4.3	35.2 ± 4.8
Metabolic			
Fasting Glucose (mmol/L)	5.8 ± 0.6	5.7 ± 0.4	5.8 ± 1.3
Fasting Insulin (pmol/L)	97.4 ± 18.3	143.8 ± 90.4	152.6 ± 55.4
Glucose Area (mmol/L*5hr)	29.8 ± 3.3	28.8 ± 4.7	31.4 ± 11.9
Insulin Area (pmol/L*5hr)	1522.2±488.8	1980.8±1127.3	2114.3 ± 777.6

[1] Mean ± standard deviation. DO, diet only; DA, diet and aerobic exercise; DR, diet and resistance exercise; BMI , body mass index; WHR, waist-to-hip circumference ratio; MRI, magnetic resonance imaging; AT, adipose tissue; ASAT, abdominal subcutaneous adipose tissue; FSAT, gluteal-femoral adipose tissue.
[2] Calculated by using last rib waist circumference.
[3] Waist circumference at the last rib.

Table 2
Changes in selected anthropometric, magnetic resonance imaging (MRI) and metabolic variables.[1]

Variable	DO (n=9) ABS	%	DA (n=11) ABS	%	DR (n=11) ABS	%
Anthropometry						
Weight (kg)	-12.1±3.4[3]	-12.1	-11.6±3.7[3]	-11.4	-13.2±4.1[3]	-12.3
BMI (kg/m^2)	-3.9±1.1[3]	-12.1	-3.7±1.0[3]	-11.4	-4.1±1.4[3]	-12.3
WHR[2]	-0.02±0.03	-2.4	-0.05±0.04[3]	-4.7	-0.05±0.02[3]	-4.6
Waist Circumference(cm)	-8.8±3.9[3]	-8.1	-12.9±4.0[3]	-11.4	-11.9±3.9[3]	-10.6
MRI						
Total AT (L)	-8.5±2.9[3]	-24.9	-9.5±4.4[3]	-27.3	-10.6±3.3[3]	-28.7
Subcutaneous AT (L)	-6.5±2.2[3]	-24.0	-5.9±2.9[3]	-22.1	-8.0±2.8[3]	-25.7
ASAT (L)	-1.6±0.6[3]	-25.1	-2.1±0.8[3]	-29.2	-2.7±0.9[3]	-33.9
FSAT (L)	-2.6±0.7[3]	-22.4	-2.3±1.4[3]	-20.9	-2.8±1.6[3]	-20.7
Visceral AT (L)	-1.5±0.9[3]	-31.5	-1.8±1.0[3]	-39.4	-1.4±0.7[3]	-40.4
Intraperitoneal (L)	-1.3±0.8[3]	-35.0	-1.5±0.9[3]	-43.3	-1.2±0.6[3]	-44.4
Extraperitoneal (L)	-0.2±0.1[3]	-18.1	-0.3±0.2[3]	-27.3	-0.2±0.1[3]	-28.0
Skeletal Muscle (L)	-2.5±1.0[3]	-7.3	+0.2±1.0	+0.7	+0.3±2.1	+1.0
Metabolic						
Fasting Glucose (mmol/L)	+0.0±0.4	0.0	-0.2±0.3	-2.9	-0.1±0.7	+0.3
Fasting Insulin (pmol/L)	-19.0±18.9[3]	-18.6	-54.7±46.2[3,4]	-38.1	-60.7±52.4[3,4]	-35.5
Glucose Area (mmol/L*5hr)	-0.7±3.3	-1.9	-3.0±3.8	-9.0	-2.9±4.9	-6.5
Insulin Area (pmol/L*5hr)	-250.2±211[3]	-17.9	-913.0±539[3,4]	-46.0	-997.1±637[3,4]	-43.8
IGAR	-8.4±7.9[3]	-16.5	-26.1±10.7[3,4]	-41.2	-31.7±23.2[3,4]	-39.9

[1] Mean absolute change (ABS), percent change (%). DO, diet only; DA, diet and aerobic exercise; DR, diet and resistance exercise; BMI , body mass index; WHR, waist-to-hip circumference ratio; AT, adipose tissue; ASAT, abdominal adipose tissue; FSAT, gluteal-femoral adipose tissue; IGAR, insulin to glucose area ratio.
[2] Calculated by using last rib waist circumference.
[3] Significant within-group differences $p<0.05$ (paired t-test with Bonferroni modification)
[4] Significantly different from DO $p<0.05$.

MRI PROTOCOL

Protocol (Abdomen)

T1-weighted, spin-echo pulse sequence
Each image = 10 mm thickness, 40 mm spaces
TR = 210 ms ; TE = 17 ms ; 1/2 NEX
FOV = 48 cm x 36 cm (Rectangular)
Matrix = 256 x 256
Each acquisition = 7 images
Time = 26 seconds (breathold)

Protocol (Appendicular)

T1-weighted, spin-echo pulse sequence
Each image = 10 mm thickness, 40 mm spaces
TR = 210 ms ; TE = 17 ms
FOV = 48 cm x 36 cm
Matrix = 256 x 256
Each acquisition = 7 images
Time = 43 seconds

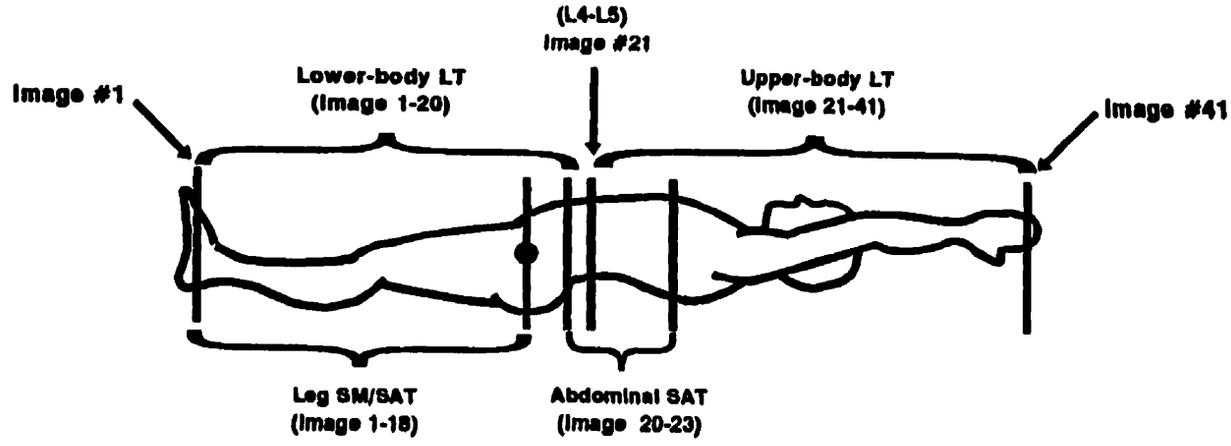


Figure 1. MRI protocol. A T1 weighted, spin-echo sequence with a 210ms repetition time and 17ms echo time was used to acquire all MRI data. The abdominal protocal was used to acquire 3 sets of 7 images; two sets extended from L4-L5 to the upper thorax region, and one extending from L4-L5 to the appropriate level of the femoral head. The other 3 acquisitions were obtained using the appendicular protocol.

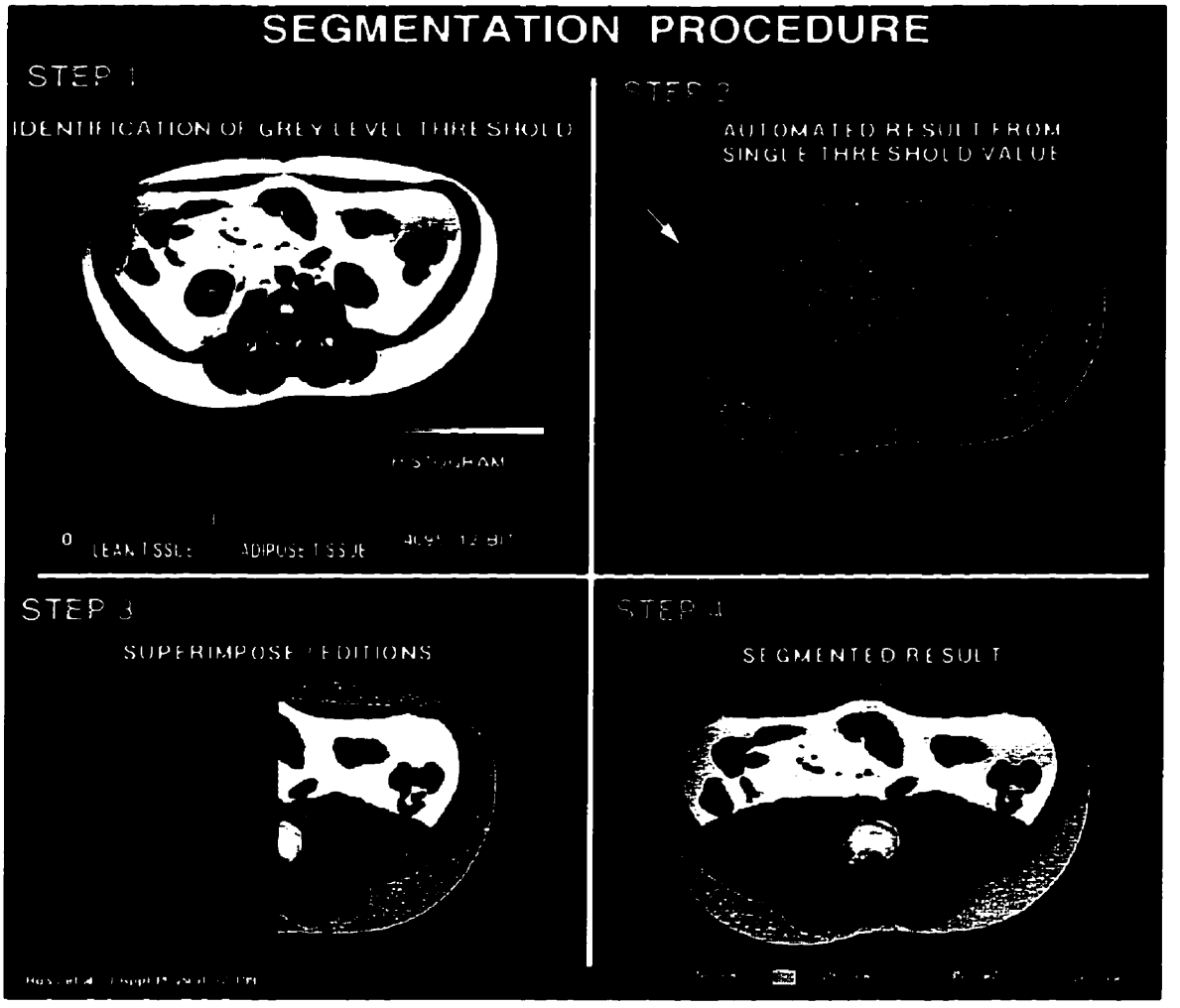


Figure 2. Calculation of lean and adipose tissue area and volume: Step 1, the threshold is selected for AT and LT based on the analysis of a sample of typical images and their respective grey level histograms; Step 2, each slice is reviewed using an interactive slice editor program which allows for verification, and where necessary, correction of the segmentation result; Step 3, the original grey level image is superimposed on the binary segmented image using a transparency mode; Step 4, a completed example of an axial image that has been segmented with the various tissues identified using separate colour codes.

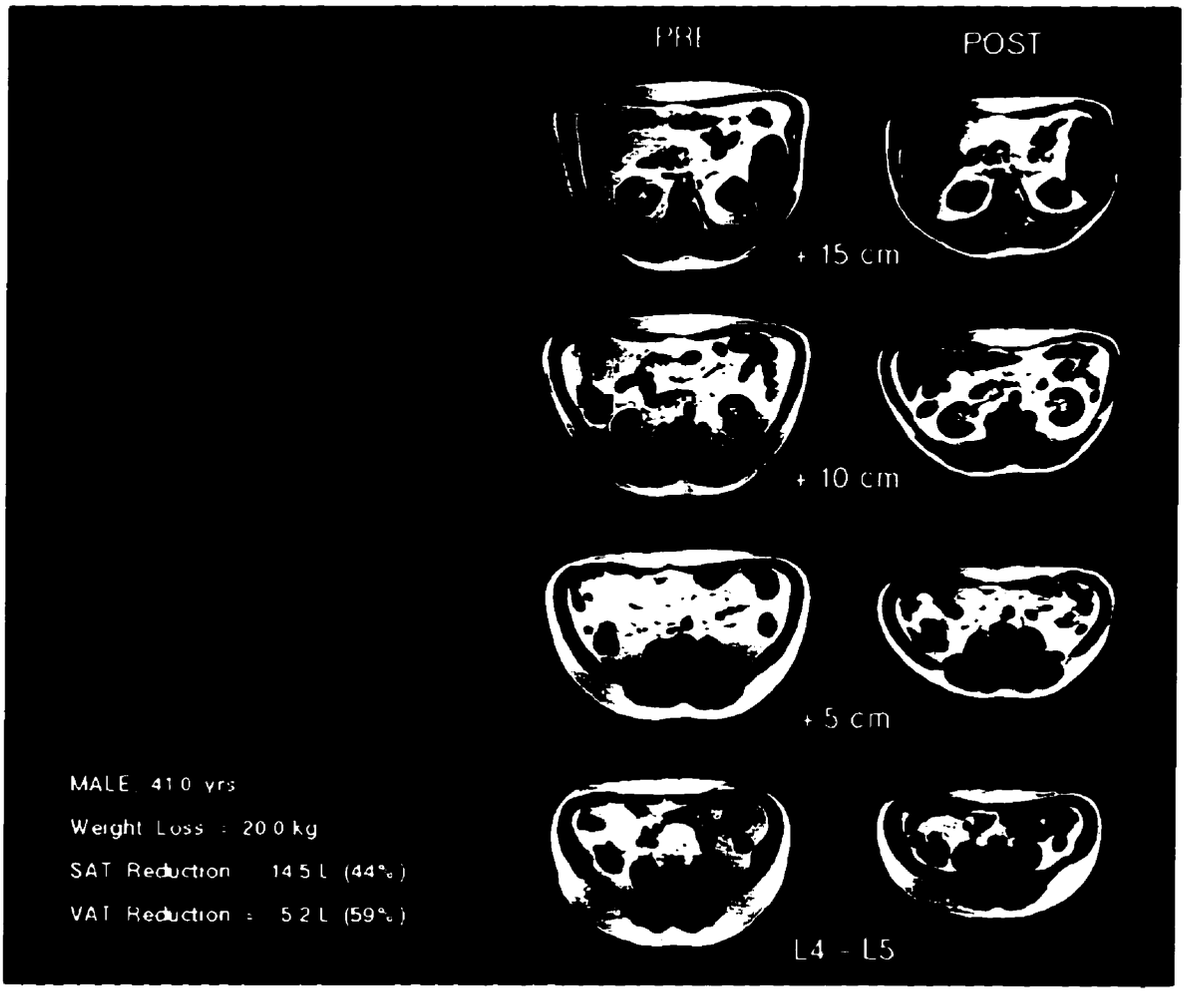


Figure 3: A typical example of the reductions observed for SAT and VAT for a series of MR images throughout the abdomen.

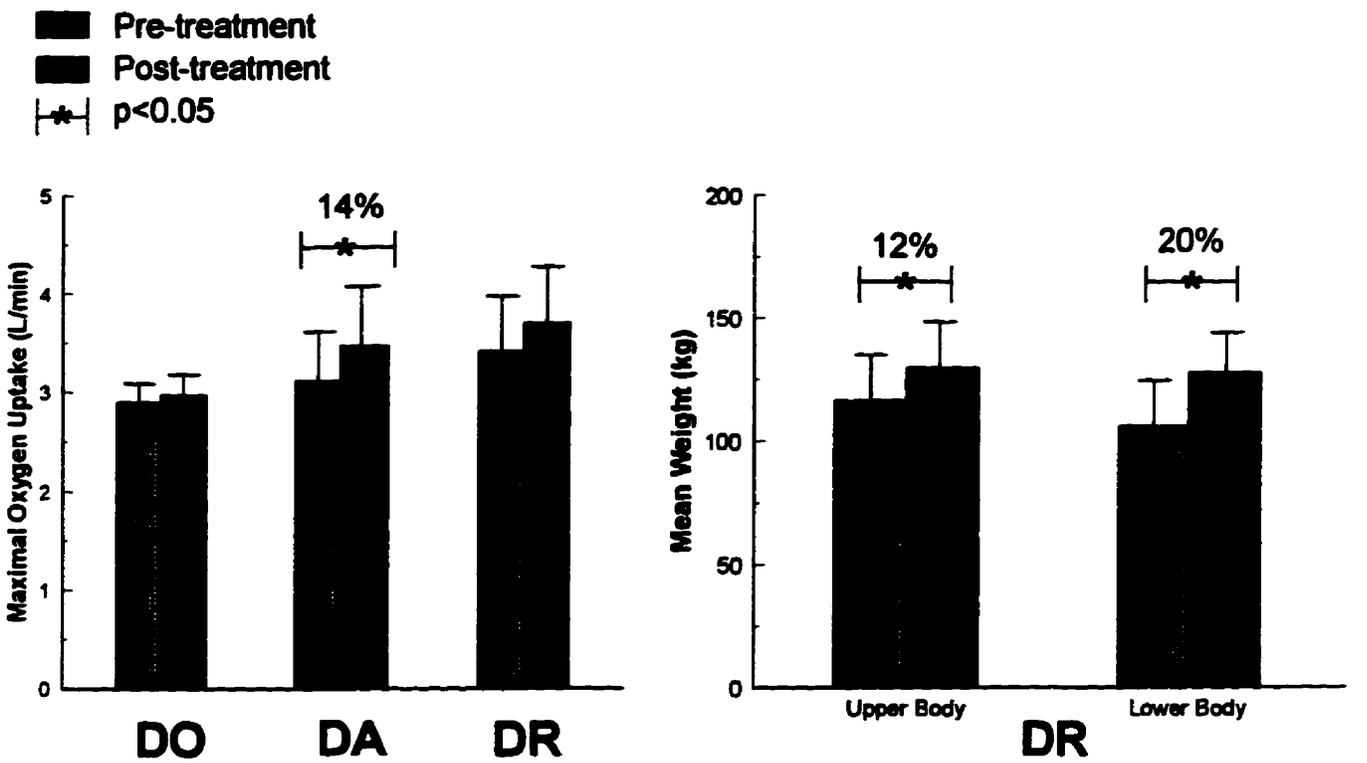


Figure 4. Improvements in maximal oxygen uptake and strength in obese men; * p<0.05

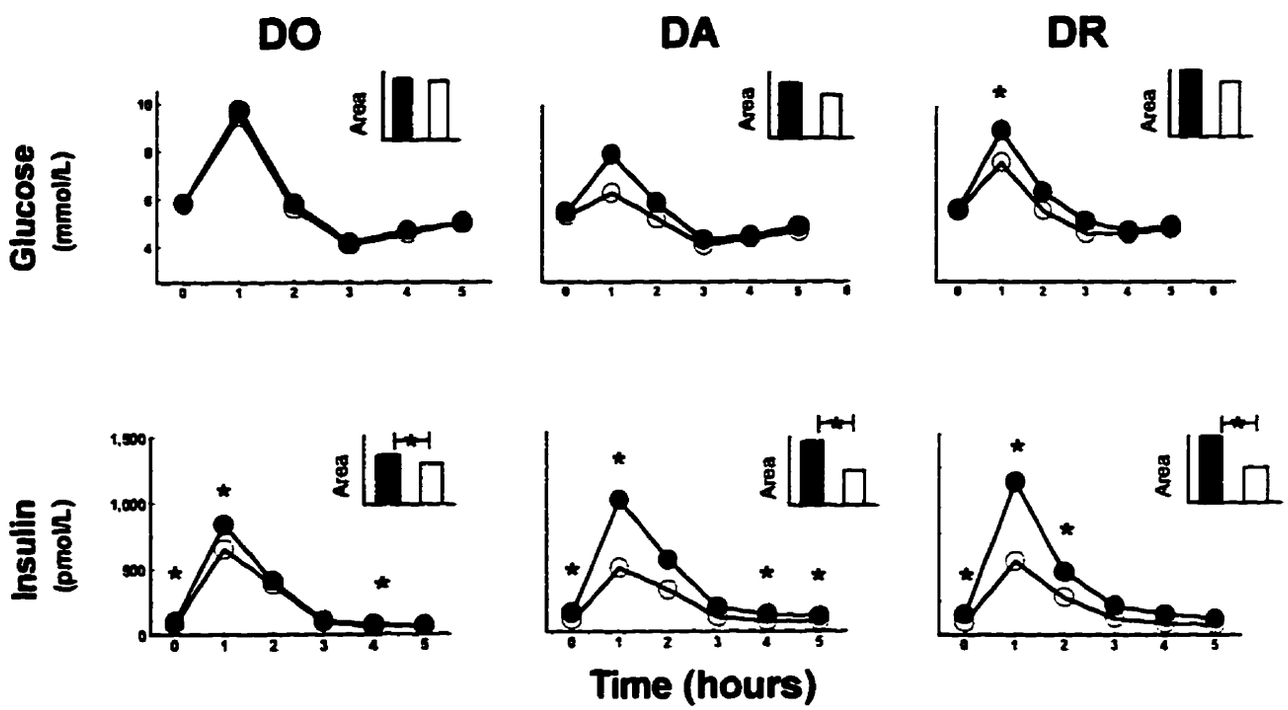


Figure 5. Plasma glucose and insulin values during an oral glucose tolerance test (75g) ; (●) pre, (○) post; *p<0.05

4.0.0 CONCLUSIONS

The findings of this study demonstrate that the combination of exercise and diet is associated with improvements in fasting and OGTT-insulin levels. However, the independent influence of exercise on insulin sensitivity and glucose tolerance remains unresolved. An experimental design to investigate this relationship should include two groups: an exercise group that is refed after each session, and an exercise group that would lose weight through caloric expenditure. This study would provide evidence to help resolve whether exercise per se has a positive influence on insulin sensitivity or glucose tolerance. In addition to controlling for weight loss, it would be beneficial to control for differences in daily activity level. Doubly-labeled water, a technique used to measure 24-hour energy expenditure, could be employed to provide information on energy expended outside of supervised exercise sessions.[100]

The oral glucose tolerance test, a measure of integrated insulin response to an oral glucose load, was a limitation of our study design since it does not distinguish between changes in hepatic or peripheral insulin extraction, or pancreatic insulin secretion. A more sophisticated technique such as a hyperinsulinemic euglycemic clamp should be employed in future studies to identify the independent contributions of both hepatic (with the addition of exogenous tritiated glucose) and peripheral insulin sensitivity. Concurrent with a euglycemic clamp, muscle biopsies would be useful in

providing information on morphological changes that occur in response to exercise. A study design incorporating these techniques would provide insight into the mechanisms that explain the influence of exercise on insulin sensitivity.

The optimal exercise intensity and duration required to influence insulin sensitivity and glucose tolerance is an issue that requires further study. Indeed, it is unclear whether low and high intensity exercise are equally effective for improving these metabolic variables. Furthermore, whether a training induced increase in $\dot{V}O_2max$ is necessary to increase insulin sensitivity is not fully established. In addition to exercise intensity, it would be useful to determine the most beneficial duration of exercise related to the greatest improvements in carbohydrate metabolism. It is unknown whether short and long exercise bouts are associated with comparable improvements in insulin sensitivity. This knowledge would enable the clinician to prescribe exercise of optimal intensity and duration to those who are insulin resistant and glucose intolerant.

It is reported that the addition of physical activity to a program of energy restriction is more effective than energy restriction alone for the maintenance of weight loss.[96] It is also observed that moderate weight loss (~12 kg) maintained over time is associated with significant long term improvements in fasting and OGTT- insulin response.[99] Therefore, consistent with the findings of the present study, it is suggested that an effective

treatment for the improvement of carbohydrate metabolism should include the combination of diet and exercise (aerobic or resistance). This may be a successful strategy for the reduction of insulin resistance and obesity, both of which are CVD risk factors and putative markers for NIDDM.

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Appendix A: Informed Consent

QUEEN'S UNIVERSITY

DIET AND EXERCISE STUDY

INFORMED CONSENT

The following brief is intended to provide you with the details you should be aware of prior to your consent as a participant in this research project. Please read the following information carefully and feel free to ask any question that you may have.

Objective of the study

In recent years a number of studies have clearly shown that a relationship exists between obesity and the development of numerous health problems including cardiovascular disease and diabetes. In fact, the relationship is strengthened if one considers the regional distribution of body fat (i.e where your body fat is located). Given the relationship between obesity with ill health, and the fact that obesity is a condition characterized by large amounts of body fat, it follows that an important component of an effective prevention program would be the ability to lose body fat. Hence the purpose of this research project will be to investigate different methods of changing body composition through diet and or exercise.

EXPLANATION OF PROCEDURES

Pre-participation screening

Prior to participation in this study you will be required to have a medical exam. The exam will be conducted by a medical doctor at the Kingston General Hospital. The examination will include a fasting blood sample that will be used to measure your glucose and fat levels, and the levels of certain hormones that may be related to fat metabolism. This procedure is explained in further detail on the last page of this form.

Diet and Exercise Protocol

The study will be 18 weeks in duration. The low calorie diet and exercise part of the study will last 16 weeks. The 16 week treatment period will be prefaced and followed by a 1 week weight maintenace period - hence 18 weeks in total. By volunteering to participate in this study, your name will be selected by chance and placed into one of the following five groups: control (no diet or exercise program), diet (diet only), diet plus aerobic exercise, diet plus strength training exercise and diet plus both aerobic and strength training exercises.

Diet Procedure

The diet will consist of regular foods that you will buy and prepare yourself. After a 1 week weight-maintenance period, the diet you follow will total approximately 1000 calories less than the amount you need to maintain your present weight. You will follow that diet for 16 weeks. After the 16 week period, you will be given a diet that will increase your total caloric intake to a level that will maintain your new weight. All aspects of the diet plan will be explained to you in detail. The session will take place at the beginning of the study, with several additional sessions planned throughout to help you follow the diet plan. If someone else shops for your food or prepares your meals, or if you share those tasks with someone else, that person is invited to meet with the dietitian as well. You will be required to record the food you eat each day for one week, 5 times during the the 18 week study. All of your meetings with the dietitian will be at the Fitness Center in the Physical Education building at Queen's.

Exercise Procedure - Aerobic Group

If you are a participant in this group, in *addition* to following the same diet procedures described above, you will be required to perform aerobic exercise (walk/run type exercise) 5 times per week. The aerobic exercise program will be designed to meet your abilities. The duration of the sessions will range from approximately 15 minutes at the beginning of the program to a maximum of 60 minutes by the end. Each exercise session will be supervised by a trained physical educator.

Exercise Procedure - Strength Training Group

If you are a participant in this group, in *addition* to following the same diet procedures described above, you will be required to perform strength training exercises using Nautilus equipment 3 times per week. As with the aerobic exercise group, the strength training exercises will begin at a very easy level and progress slowly. A total of 8 exercises will be performed each session assuring that all the major muscles of the body are used. Each exercise session will be supervised by a physical educator.

Although as a participant in this study you will follow all the appropriate safety precautions including a pre-participation medical exam, there are risks associated with exercise. These risks include a slight chance of fainting and a remote chance of heart attack. As indicated, all your exercise sessions will be supervised by a masters level physical educator. This person will be trained in emergency procedures including cardio-pulmonary resusitation (CPR).

Assessment of Body Composition

Magnetic Resonance Imaging

Magnetic resonance imaging is a new technique for imaging or creating pictures of body structures or organs. Magnetic resonance (MR) gives images in slices comparable to those produced by x-ray tomography or CT (CAT) scan. One of the primary advantages of MR is that it does not employ x-rays or other potentially harmful forms of radiation, contrary to ordinary radiography or nuclear medicine. Instead, a large magnet, a radio transmitter/receiver and a computer are used to gather chemical information from the body, and to produce images or pictures of internal anatomy. No harmful effects have been associated with MR under existing conditions of use.

It is important that you fill out the enclosed questionnaire. The purpose of the questionnaire is to identify any metallic pieces which would have been implanted during a surgery or would have been lodged in your body during an accident.

As mentioned, the MR procedure is very similar to a scanner examination. You will be placed on a table and you will be moved smoothly into the scanner. A loud-speaker within the magnet makes it possible for you to keep in constant contact with the staff. At all times the operator can see and hear you if you need help or have questions, and you can be removed from the machine if necessary. The scanning procedure takes 45 to 60 minutes. All MR images will be obtained at the Kingston General Hospital.

Bioelectrical Impedance

This is a very simple and safe procedure requiring no more than 5 minutes to complete. Laying on your back, 2 electrodes will be placed on the surface of your right hand and foot. Two of the electrodes will introduce an alternating current that you can't feel into the body, while the other 2 record the resistance. In order to obtain accurate results with this technique it is very important that you follow the following procedure prior to your assessment. Prior to the test you should not:

1) have eaten or consumed caffeine for the 4 to 5 hours immediately preceding the test,

2) have exercised or consumed alcohol for 24 hours.

Anthropometry/Summation of skinfolds

Many circumference and diameter measurements will be taken at numerous sites on the body. These measure can be used to derive estimates of body composition. In addition, through the use of skinfold callipers, skinfold thickness will

be measured at 10 different sites on your body. This is a simple procedure requiring no special preparation on your part.

Underwater weighing

Recognized by many researchers as the best method of measuring body composition (i.e. percent body fat), the intent of the procedure is to weigh you while you are submerged in water. In a seated position, you will be submerged in water (comfortable temperature) to the shoulder level. Approximately 10 times during the test you will be asked to put your head in the water, exhale completely, and hold your breath for 5 to 10 seconds while your body weight is measured. At any time during the procedure you can come out of the water by simply lifting your head.

With the exception of the MRI measurements, the anthropometric measurements (bioelectrical impedance, skinfolds and underwater weighing) will be obtained at the School of Physical and Health Education, Queen's University.

Assessment of Cardiovascular Fitness

In addition to body composition measurements we will measure your cardiovascular fitness by using either a stationary bicycle or a treadmill procedure. The work level will begin at a level you can easily accomplish and will be advanced in stages, depending on your capacity to do so. We may stop the test at any time because of signs of fatigue or you may stop when you wish to because of persinal feelings of fatigue or discomfort.

Risks and Discomforts

The treadmill or bicycle test will involve risks comparable to any strenuous exercise situation. They include very rare instances of abnormal blood pressure, faintings, disorders of the heart beat, and heart attack. Every effort will be made to minimize them by preliminary medical examination and observation during the test.

Benefits to be expected

These test results will be used to help us give you the proper amount of aerobic exercise that is right for you, and, to check for any possible reasons why you should not participate in an exercise program. Quantification of your fitness level will also enable us to follow your improvement throughout the study.

Blood Chemistry Analysis

Fasting Blood Samples

At the beginning, after 8 weeks, and at the end of the 16 week study, you will have a fasting blood test in order to measure blood sugar, blood fats and hormones (including adrenal, thyroid and pancreatic hormones). This procedure will involve a venepuncture with a needle and the removal of about 30 ml (3 tablespoons) of blood. The only risk from this is possible local pain and bruising at the time of the blood test. In addition, at the beginning and end of the study, you will be given a glucose tolerance test. The purpose of this test is to determine your bodie's response to sugar.

Subject's Name: _____

I have been given an opportunity to ask any questions concerning the procedures. All of my questions regarding the research project have been satisfactorily answered. I understand that my test results will be considered confidential and will never be released in a form traceable to me, except to my family physician or myself. I do understand that I am free to deny consent if I so desire, and that I may withdraw from the study at any time. I understand that I may contact Dr. Robert Ross, 545-6583, or the head of the School of Physical and Health Education, Dr. Gavin Reid 545-2666, should I have any questions about the study. In addition, I release the principals and Queen's University from all claims arising out of my participation in this study that do not arise due to negligence.

Signature of Subject: _____

Witness: _____

Date: _____

Appendix B: Medical Questionnaire

QUEEN'S UNIVERSITY

DIET AND EXERCISE PROGRAM

MEDICAL QUESTIONNAIRE

Please follow the instructions for each section carefully, and answer every question unless otherwise indicated, or unless you choose not to.

1. **PERSONAL DATA (Please print)**

Name:	_____	Date:	_____
Home Address:	_____	Home Tel:	_____
City:	_____	Postal Code:	_____
Position:	_____		
Business Address:	_____	Business Tel:	_____
City:	_____	Province:	_____
Birth Date:	_____	Age:	_____

2. **MEDICAL HISTORY**

*N.B. There are two parts to medical and health history. Please complete your parts on page 1 and 2, and have your physician fill out pages 3, 4 and half of page 5.

		Yes	No
1.	Has your doctor ever said that you have heart trouble?	___	___
2.	Do you have pains in your chest?	___	___
3.	Do you often feel faint, or experience severe dizziness?	___	___
4.	Has your doctor told you that you have high blood pressure?	___	___
5.	Has your doctor ever told you that you have a bone or joint problem (arthritis) that might be made worse by exercise?	___	___
6.	Is there a good reason, not mentioned here, why you should not follow an exercise program, even if you'd like to?	___	___

7. Do you have, or have you had any of the following health problems or diseases?

		Yes	No	Comment
1)	Heart, Cardiovascular	___	___	_____
2)	Neurological	___	___	_____
3)	Respiratory (asthma, etc.)	___	___	_____
4)	Gastrointestinal (ulcers, etc.)	___	___	_____
5)	Genito-urinary	___	___	_____
6)	Endocrine (glandular)	___	___	_____
7)	Musculoskeletal (low back pain, etc)	___	___	_____

	Yes	No	Comment
8) Skin	___	___	_____
9) Gynaecological	___	___	_____
10) Other (Women - are you pregnant?)	___	___	_____

8. Please list any serious injuries suffered, or surgery undergone:

_____ Date:_____

_____ Date:_____

9. If you have undergone surgery, was any metal (ie. pins or screws to repair broken bones) left in your body?

_____

_____

10. Are you presently taking any medication including vitamin or mineral supplements? If yes, please specify what type, and reasons:

_____

9. If you have undergone surgery, was any metal (i.e. pins or screws used to repair bone fractures) left in your body?

_____

_____

10. Are you presently taking any medication including vitamin or mineral supplements? If yes, please specify what type, and reasons:

_____

11. Are you presently undergoing any physiotherapy, or any other sort of treatment? If yes, please specify:

_____

12. Are you presently under the care of a physician? If so for what?

_____

3. **MEDICAL REFERRAL**

To The Physician:

The applicant is considering participation in a research project that intends to investigate the effects of different methods of exercise, in combination with caloric restriction, on body composition. A brief that describes the details of the study is appended to the Medical Questionnaire. Should you have any questions regarding the participation of your patient in this project, please contact Robert Ross Ph.D., School of Physical and Health Education, Queen's University (545-6583/2666), or Robert Hudson M.D., Department of Endocrinology, Kingston General Hospital.

ACSM - Contraindications to Exercise Testing

Absolute Contraindications

1. A recent significant change in the resting ECG suggesting infarction or other acute cardiac events
2. Recent complicated myocardial infarction
3. Unstable angina
4. Uncontrolled ventricular dysrhythmia
5. Uncontrolled atrial dysrhythmia that compromises cardiac function
6. Third-degree A-V block
7. Acute congestive heart failure
8. Severe aortic stenosis
9. Suspected or known dissecting aneurysm
10. Active or suspected myocarditis or pericarditis
11. Thrombophlebitis or intracardiac thrombi
12. Recent systemic or pulmonary embolus
13. Acute infection
14. Significant emotional distress (psychosis)

Relative Contraindications

1. Resting diastolic blood pressure >120 mm Hg or resting systolic blood pressure >200 mm Hg
2. Moderate valvular heart disease
3. Known electrolyte abnormalities (hypokalemia, hypomagnesemia)
4. Fixed-rate pacemaker (rarely used)
5. Frequent or complex ventricular ectopy
6. Ventricular aneurysm
7. Cardiomyopathy, including hypertrophic cardiomyopathy
8. Uncontrolled metabolic disease (e.g., diabetes, thyrotoxicosis, or myxoedema)
9. Chronic infectious disease (e.g., mononucleosis, hepatitis, AIDS)
10. Neuromuscular, musculoskeletal, or rheumatoid disorders that are exacerbated by exercise
11. Advanced or complicated pregnancy

I. **REVIEW OF SYSTEMS**

a) Cardiovascular _____
b) Respiratory _____
c) Neurological _____
d) Gastrointestinal _____
e) Genitourinary _____
f) Endocrine _____
g) Musculoskeletal _____
h) Skin _____
i) Gynaecological _____

II. **PHYSICAL EXAMINATION**

Blood Pressure Supine ___RA___LA Bruits _____
Standing ___RA___LA Pulses _____
Evidence of chronic Lung Disease _____
Heart rate _____ _____
Heart sounds _____ Bone or Joint Abnormalities _____
_____

EKG interpretation, 12 lead, resting. **Enclose copy if available**

_____

III. **LABORATORY FINDINGS (NOT MANDATORY)** Date of Test(s): _____

Hb _____ Hct _____ RBC _____ WBC _____
Total Cholesterol _____ HDL _____ LDL _____
Triglycerides _____ Uric acid _____
Glucose _____ post dexicola 30 min _____ 1 hr _____ 2 hr _____
3 hr _____ 4 hr _____

IV. Additional Abnormalities you are aware of _____

_____

_____

V. Current medications and dosages _____

_____

_____

VI. Impression of above information _____

_____

_____

On the basis of your knowledge and medical evaluation of the applicant, you would recommend:

- participation in a fitness appraisal with supervision by physical education graduate _____
- participation only with physician in attendance _____
- participation not recommended _____

Signed_____M.D.

Name of Physician_____
(Please print or type)

Address_____

Telephone_____

Date_____

4. FAMILY MEDICAL HISTORY (Should be filled out by participant)

Have either of your parents or any brothers or sisters ever suffered from any cardiovascular disease (heart attack, high blood pressure, stroke, angina, etc.) or diabetes? If yes, please describe which relative, the type of problem, and the approximate age of the relative at the first diagnosis of the disease.

_____

_____

_____

5. SMOKING

Are you a: smoker _____

ex-smoker (stopped) _____

non-smoker (never smoked) _____

Enter average amount smoked per day in the last five years, or in the last five years prior to quitting:

cigarettes per day _____

pipes/cigars inhaled per day _____

pipes/cigars not inhaled per day _____

If you are an ex-smoker, how many years ago did you start? _____ quit? _____

6. **DIET**

Weight now: _____ 1 year ago: _____ at age 21: _____

What do you consider a good weight for you? _____

What is the most you've ever weighed? _____ at age? _____

Do you regularly eat:			Are these meals:		
	yes	no	light	moderate	heavy
Breakfast	_____	_____	_____	_____	_____
Lunch	_____	_____	_____	_____	_____
Dinner	_____	_____	_____	_____	_____
Snacks	_____	_____	_____	_____	_____

Have you ever dieted? _____ If yes, for what reasons? _____

_____

Are you presently on a diet? _____ If yes, what kind? _____

_____

Do you have any special dietary needs, e.g., vegetarian? _____

Do you drink alcoholic beverages? _____ If yes, how much?:

	none	occasional	often	drinks per week
Wine (4 oz.)	_____	_____	_____	_____
Hard Liquor (1 - 1½ oz.)	_____	_____	_____	_____
Beer (12 oz.)	_____	_____	_____	_____

7. **EXERCISE**

Are you currently involved in a regular exercise program? _____

Physical activity in your present occupation is:

none _____ light _____ moderate _____ heavy _____

How many hours per day are you presently active? (at work and play/or exercise)

none _____ 0 - ½ _____ ½ - 1 _____ 1 - 2 _____ 2 or more _____

Please list the moderate to vigorous activities (such as brisk walking, jogging, aerobics) that you are presently involved in and the # of times per week that you participate.

_____

_____

Please list the recreational or leisure activities (such as casual walking, etc.) you are presently involved in and the # of times per week.

_____

_____

What activity or activities would you prefer to be included for you in an exercise program (if you are not presently involved)?

_____

_____

If you have been involved in an exercise program in the past, and quit, or had difficulty participating regularly, what were the reasons?

_____

_____

8. **PERSONAL INTERESTS**

Please list in order of importance to you, what you would like to change in terms of your present lifestyle?

1. _____
2. _____
3. _____

What areas of health or fitness would you like to learn more about?

_____

_____

Appendix C: Anthropometric Data Collection Form

MRI DIET AND EXERCISE
ANTHROPOMETRIC DATA COLLECTION FORM

NAME:_____ **M F DATE:**_____ **TIME:**_____

WEIGHT:_____**kg AGE (yr.mo):**_____ **TEST #:**_____

ARM LENGTH:_____**(cm) STANDING HEIGHT:**_____**(cm)**

ACROMION HEIGHT:_____**(cm) SITTING HEIGHT:**_____**(cm)**

IMPEDANCE (ohms) **R:** Arm ___ Torso ___ Leg ___ Whole L___ R___

Xc: ___ ___ ___ ___ ___

SKINFOLDS (mm)

	1	2	3	$\bar{X}$
Chest	____	____	____	____
Tricep	____	____	____	____
Bicep	____	____	____	____
Mid-Axillary	____	____	____	____
Subscapular	____	____	____	____
Iliac	____	____	____	____
Abdomen	____	____	____	____
Thigh	____	____	____	____
Suprapatellar	____	____	____	____
Calf	____	____	____	____

NAME:_____ **DATE:**_____ **TIME:**_____

CIRCUMFERENCE MEASURES (cm):

Chest:_____ Hip:_____

Waist (standing): _____(L) _____Last Rib_____(U)

Waist (supine): _____Last Rib_____(U)

Bicep:	_____(R)	_____(L)	Thigh:	_____(PR)	_____(PL)
Forearm:	_____(R)	_____(L)		_____(MR)	_____(ML)
Calf:	_____(R)	_____(L)		_____(DR)	_____(DL)

Appendix D:Diet Record

Name: _____

Date: _____

FOOD DIARY

Food and Amount	Time	Calories	Fat(grams)
BREAKFAST			
LUNCH			
DINNER			
SNACKS			
Total			

Fat Calories = Fat(grams) x 9 _____

Daily Calorie Total = Total Calories _____

%Fat = Fat Calories / Total Calories _____

Appendix E: Aerobic Exercise Recording Sheet

AEROBIC TRAINING PROGRAM

Name: _____

Week	1	2	3	4	5	6
Date						
Activity						
Duration						
Intensity/Workrate						
Mean Heart Rate						

Week	7	8	9	10	11	12
Date						
Activity						
Duration						
Intensity/Workrate						
Mean Heart Rate						

Week	13	14	15	16
Date				
Activity				
Duration				
Intensity/Workrate				
Mean Heart Rate				

Appendix F: Resistance Exercise Recording Sheet

NAUTILUS TRAINING PROGRAM

TECHNIQUE: Select a weight with which you can obtain total momentary failure in between 8 and 12 repetitions. One repetition should take approximately 7 seconds.

POSITIVE – 2 seconds lifting / PAUSE – 1 second hold / NEGATIVE – 4 seconds lowering.

Perform each repetition smoothly and with good form.

Legend: Total Repetitions → 12/4 ← Exercise Weight

Name: _____

RECORD EXERCISE WEIGHTS AND TOTAL REPETITIONS FOR EACH EXERCISE (See Legend)

Exercise		Seat Pos.	Ht.	Week			Week			*	Week			Week			Week			Week			Week			Week		
LOWER BODY																											
Hip and Back																											
Compound Leg	Extension																										
	Press																										
Leg Curl																											
UPPER BODY																											
Super Pullover																											
Rowing																											
Double Chest	Cross																										
	Press																										
IHP	Abduction ← →																										
	Adduction → ←																										
Torso Arm																											
Double Shoulder	Lateral																										
	Overhead																										
Bicep																											
Tricep																											
Rotary Torso																											
Abdominal																											
4-way Neck	Lateral																										
	Anterior																										
	Posterior																										
Neck and Shoulder																											
Multi-Exercise	Heel Raises									*																	
	Wrist Rollers																										
SIT UPS	TOTAL REPETITIONS																										

SEE INSTRUCTOR

Appendix G: Formulae

Anthropometric Formulae

a) Body Mass Index:

$$BMI = \frac{weight\ (kilograms)}{height\ squared\ (meters\ squared)}$$

b) Waist-to-Hip Circumference Ratio:

$$WHR = \frac{waist\ circumference\ at\ last\ rib\ (centimeters)}{hip\ circumference\ (centimeters)}$$

Metabolic Formulae

a) Area Under the Curve (insulin and glucose areas):

$$AREA = \frac{t([x]_0 + [x]_5)}{2} + t([x]_1 + [x]_2 + [x]_3 + [x]_4)$$

Where, t = time
[x] = glucose or insulin concentration at hours 0 to 5

Units: Glucose Area (mmol/L · 5hr)
Insulin Area (pmol/L · 5hr)

b) Insulin-to-Glucose Area Ratio:

$$IGAR = \frac{insulin\ area\ (pmol/L \cdot 5hr)}{glucose\ area\ (mmol/L \cdot 5hr)}$$