Separate Effects of Diet- and Exercise-Induced Weight Loss on Insulin Sensitivity

by

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Abstract

Objective: The purpose of this study was to 1) evaluate the effects of equivalent diet- or exercise-induced weight loss on insulin sensitivity in upper body obese men and 2) determine whether exercise in the absence of weight loss is associated with improvements in insulin sensitivity.

Research Design and Methods: Forty-one obese men were assigned randomly to one of four groups: control (C, n=8), diet weight loss (DWL, n=10), exercise weight loss (EWL, n=11), and exercise weight stable (EWS, n=12). Insulin sensitivity was assessed with the hyperinsulinemic euglycemic clamp technique (40umol/min/m^2). Visceral (VAT), subcutaneous (SAT), and skeletal muscle (SM) tissue were measured by magnetic resonance imaging (MRI). The treatment period for all groups was 12 weeks.

Results: Weight loss (~7.5kg) in the DWL and EWL groups was not different ($p>0.10$). Reductions in VAT (~26%) and SAT (~17%) were not different ($p>0.10$) between the DWL and EWL groups. Improvements in peak VO_2 were observed in the EWL and EWS groups only ($p<0.01$). During the 4-h euglycemic clamp, improvements ($p<0.05$) in rates (mg/min-kg) of total (5.9 ± 3.5 vs. 5.7 ± 4.0) and nonoxidative (5.1 ± 5.4 vs. 5.9 ± 4.7) glucose disposal were not different ($p>0.10$) in the DWL and EWL groups respectively. Improvements in total (2.8 ± 3.7) and nonoxidative (2.6 ± 3.7) glucose disposal were also observed within the EWS group ($p<0.05$). No change in any variable was

observed in the C group ($p>0.05$).

Conclusions: Equivalent diet- or exercise-induced weight loss has similar beneficial effects on insulin sensitivity. Exercise without weight loss significantly improves insulin sensitivity in obese men.

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
C	Control
CA	Carnitine acyltransferase
CVD	Cardiovascular disease
DWL	Diet weight loss
EWL	Exercise weight loss
EWS	Exercise weight stable
FG	Fast glycolytic
FOG	Fast oxidative glycolytic
IRS-1	Insulin receptor substrate 1
LPL	Lipoprotein lipase
MRI	Magnetic resonance imaging
NIDDM	Non-insulin dependent diabetes mellitus
NPRQ	Non-protein respiratory quotient
OGTT	Oral glucose tolerance test
PI 3-kinase	Phosphatidylinositol 3-kinase
RQ	Respiratory Quotient
SAT	Subcutaneous adipose tissue
SD	Standard deviation
SM	Skeletal muscle
SO	Slow oxidative
VAT	Visceral adipose tissue
VO_2 max	Maximal oxygen consumption
WHR	Waist-to-hip ratio

INTRODUCTION

According to a recent U.S. National Health and Nutrition Examination Survey, 55% of men and women are overweight, a condition which substantially raises their risk of morbidity and mortality.[1] As the second leading cause of preventable death in the U.S.,[1] obesity poses a major public health challenge. While there is agreement concerning the health risks associated with obesity, there is less agreement regarding its management.

There is strong evidence that weight loss in overweight individuals reduces risk factors for diabetes and cardiovascular disease. Specifically, it is firmly established that weight loss mediated by caloric restriction is associated with improvements in glucose and insulin metabolism in men and women.[2-6] It is unclear, however, whether equivalent weight loss as a result of increased energy expenditure through exercise produces the same effects. That is, it is not known whether the method of inducing a negative energy balance influences the metabolic benefits associated with weight loss.

It has been reported previously that exercise, when combined with diet, induces a greater amount of fat loss than equivalent diet-induced weight loss.[7] It is unknown whether this increased fat loss resulted in a preferential reduction of abdominal fat, the region which conveys the greatest metabolic health risk.[8] If in fact exercise-induced weight loss induces a greater amount of fat loss compared to equivalent diet-induced weight loss, this would potentiate greater improvements in insulin sensitivity and glucose tolerance.[8]

Whether the changes in muscle morphology which are reported to accompany exercise training such as increased GLUT4 transporters,[9] oxidative enzyme capacity,[10] blood flow,[11] and the percentage of fast oxidative-glycolytic (FOG) fibres[10] augment the improvements in insulin sensitivity and glucose tolerance mediated by weight loss is not known. Therefore, given the independent effects of exercise, it is hypothesized that exercise-induced weight loss will have a greater effect on insulin sensitivity and glucose tolerance than equivalent diet-induced weight loss.

In an attempt to further clarify the separate effects of exercise, independent of weight loss, an exercise weight stable group will be incorporated into the study design. Previous studies reported that both aerobic[3,4,12-14] and resistance exercise[8,13,15] without weight loss results in improvements in insulin sensitivity. However, there are limitations to these studies which have confounded the findings associated with exercise alone. First, a number of studies[15-17] neglected to control for changes in body composition, which suggests that improvements observed in insulin sensitivity may have been influenced by concomitant weight loss. Second, numerous studies have measured the effects on insulin sensitivity and glucose tolerance immediately following the last exercise bout.[3,4,13,15,16,61] Therefore it is uncertain whether exercise has additional effects upon insulin sensitivity after controlling for repeated bouts of training.

Thus, the purposes of this study were twofold: to evaluate the effects of equivalent diet- or exercise-induced weight loss on insulin sensitivity and

glucose tolerance in upper body obese men, and to determine whether exercise without weight loss is associated with improvements in the same metabolic variables.

2.0.0 REVIEW OF LITERATURE

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

It is well established that obesity is associated with insulin resistance and glucose intolerance, and that these risk factors are putative markers for cardiovascular disease (CVD) and non-insulin dependent diabetes mellitus (NIDDM).[18] Whereas the prevalence of hypertension and hypercholesterolemia, and the incidence of mortality from heart disease and stroke are markedly declining in the U.S., the prevalence of diabetes has risen to 8.4% and 7.7% in men and women respectively over the age of 20 years.[19] Although not all obese individuals develop NIDDM,[20] approximately four out of five people with NIDDM are significantly overweight.[21] In addition to the association between obesity and these metabolic disturbances, the health risks associated with obesity relate not only to total adiposity, but also to the regional distribution of adipose tissue (AT).[22]

It was first observed in 1956 that the distribution of adiposity is a stronger correlate of metabolic risk than total obesity.[23] Vague noted an increased prevalence of diabetes, gout, and atherosclerosis in upper body obese individuals versus lower body obese individuals.[23] Upper body obesity is characterized by an abdominal fat distribution, as measured by waist-to-hip ratio (WHR), and is distinct from lower body obesity which is characterized by a gluteal-femoral fat distribution. Several prospective studies confirmed during the

1980s that upper-body obese individuals were at the greatest risk when abdominal obesity proved to be the strongest correlate of developing NIDDM and CVD (Figure 1).[18,23-27] In 1982, Kissebah et al.[18] reported that women with abdominal obesity had higher plasma insulin and glucose responses to an oral glucose challenge than to those with gluteal-femoral obesity. It was also reported in a study of 792 men that the incidence of diabetes mellitus was 16.6% higher in subjects with the highest waist-to-hip ratio (WHR) than to those with the lowest.[27]

The differentiation of AT within the abdominal region is also of critical importance when relating upper-body obesity to metabolic risk factors. This has been aided by the application of computerized topography (CT) and magnetic resonance imaging (MRI) in the late 1980's and early 1990's. Because it has allowed researchers to divide abdominal AT into subcutaneous and visceral depots, it is possible to make a clear distinction between them when discussing the relationship between the metabolic complications of obesity and adipose tissue distribution.

2.1.1 Mechanisms associating upper body adipose tissue distribution with metabolic risk

Excessive release of free fatty acids (FFA) and glycerol from adipocytes into the circulation in the obese state is responsible for the majority of adverse metabolic consequences of obesity, particularly for insulin resistance.[28] Since excess abdominal fat in upper-body obese persons gives rise to high plasma

1930's: Initial observations that obesity is related to metabolic risk factors (Newburgh et al,[24] 1939)

1950's: Clinical observation that upper-body obese individuals had a greater prevelance of diabetes and atherosclerosis compared to lower-body obese persons (Vague,[23] 1956)

Early 1980's: Epidemiological and cross-sectional studies reported that WHR is associated with insulin sensitivity, NIDDM, plasma lipids, and CVD (Kissebah et al,[18] 1982, Ohlson et al,[27] 1985)

Late 1980's & 1990's: 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 plasma lipids, lipoproteins, insulin and glucose (Sparrow et al,[25] 1986)

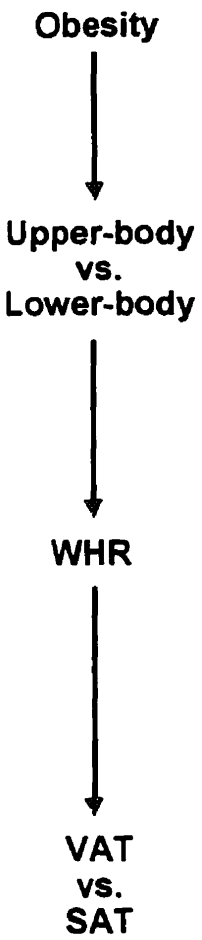

Figure 1. A time line outlining the progression in research on the association between obesity, insulin resistance, non-insulin diabetes mellitus (NIDDM), hyperlipidemia, and cardiovascular disease (CVD). WHR, waist-to-hip circumference ratio; VAT, visceral adipose tissue; SAT, subcutaneous adipose tissue.
(Adapted from Rice[45])

FFA levels and turnover,[30] this can only be possible if abdominal adiposity is either more metabolically active than other adipose regions or if the absolute mass of adipose tissue accumulated in this region contributes significantly more to plasma FFA levels than does adipose tissue in the appendicular regions. Indeed, individuals having relatively high waist-to-hip ratios are more likely to exhibit the metabolic complications of obesity.[29] In accord with this concept, Jensen et al[31] reported that upper body obese women but not lower body obese women had higher FFA turnover rates than obese women with low waist-to-hip ratios.

2.1.2 Visceral adipose tissue (VAT) and metabolic risk

Sparrow et al[25] were the first to demonstrate an association between CT-measured VAT and glucose tolerance. Since then, many studies have validated the independent association of VAT with glucose intolerance.[25,32,33] Although VAT has been reported as the strongest correlate of insulin and glucose levels in obese subjects,[33] total adiposity has been shown to be the best independent predictor of insulin and glucose levels in non-obese men[32] and women.[34] Since VAT accumulation in non-obese individuals is relatively small, it is possible that a critical threshold level of VAT is required for its influence on insulin and glucose variables to be observed.

It is also possible that the independent influence of VAT on metabolic variables cannot be separated from that of total adiposity, as total adiposity includes the VAT depot. The independent influence of VAT on insulin and

glucose variables would be better resolved after controlling for whole body SAT rather than total adiposity per se.[35] Ross et al[35] were the first to report that VAT remained significantly related to oral glucose tolerance test (OGTT) insulin and glucose variables after controlling for whole body SAT in obese women.

2.1.3 Mechanisms associating VAT with increased risk

It is currently hypothesized that individuals with high VAT accumulation are at an increased risk of developing insulin resistance and hyperglycemia because mesenteric and omental adipocytes in the VAT depot are resistant to the antilipolytic effect of insulin and highly sensitive to the stimulation of lipolysis by catecholamines.[36] Moreover, metabolites from omental and mesenteric adipocytes go directly to the liver through the portal circulation where they can lead to a reduction in insulin sensitivity of hepatocytes and increased hepatic gluconeogenesis.[37] The decrease in hepatic insulin sensitivity is caused by a decrease in hepatic insulin extraction and may be a result of reduced insulin binding, internalization of insulin receptors and decreased insulin degradation, particularly in those individuals with a preponderance of VAT (Figure 2).[38]

An elevated concentration of FFAs in the portal circulation occurs due to an elevated sensitivity of VAT to catecholamine stimulated lipolysis. The elevated sensitivity to lipolysis exhibited by VAT, as opposed to other adipose tissue depots, is proposed to be the result of a preponderance of β_3-adrenergic receptors with little α-adrenergic inhibition.[18] Other research has shown that VAT, when compared to SAT, exhibits a threefold lower sensitivity to the

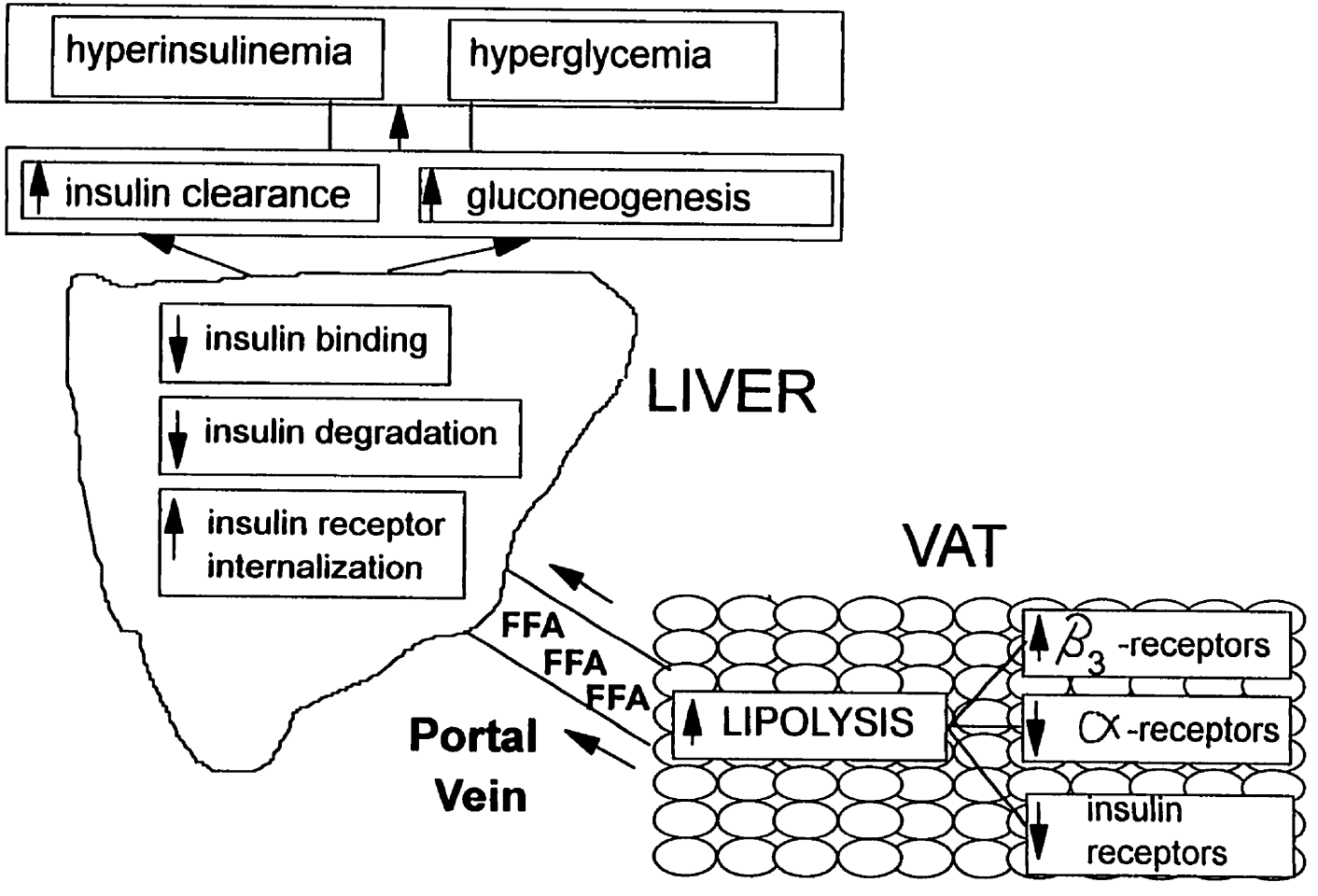

Figure 2. Mechanism of VAT-mediated effects on hepatic insulin sensitivity (adapted from Rice[49])

antilipolytic effect of insulin due to a diminished density of insulin receptors in obese men.[39,40] Therefore, an exaggerated antilipolytic response occurs in VAT which may result in elevated plasma FFAs which enter the portal circulation. The hyperinsulinemia observed in individuals with android obesity is not, however, solely due to a VAT-mediated increase in FFA to the hepatic circulation.

2.1.4 Subcutaneous adipose tissue (SAT) and metabolic risk

Despite the independent influence of VAT on insulin resistance, it is not clear as to whether VAT is the strongest predictor. Since SAT accounts for approximately 85% and 93% of total adipose tissue in men and women respectively,[41] it is reasonable to assume that the larger mass of this adipose tissue depot influences insulin and glucose variables. Indeed, Ross et al[35] reported that whole body SAT was significantly correlated with both fasting and OGTT insulin area in obese women. Whole body SAT did not remain significantly correlated however after controlling for VAT.

Since abdominal SAT is more lipolytically active than gluteal-femoral SAT in response to catecholamine stimulation,[42] it is possible that abdominal SAT is a stronger correlate of insulin and glucose variables than whole body SAT. Abate et al[29] found that abdominal SAT was a stronger predictor of insulin resistance than VAT. In support of Abate's findings, Carey et al[43] found a strong association between abdominal adiposity, for which SAT accounts for the largest component,[29] and insulin resistance. Recently, in a study of healthy men and women with a wide range of adiposity, Goodpaster et al[44] reported that

abdominal SAT had as strong an association with insulin resistance as VAT. In addition, abdominal SAT correlated with insulin resistance after adjusting for visceral adiposity, for which the converse was not found. Therefore, current findings suggest that abdominal SAT is also a potent indicator of insulin resistance and that this association needs to be explored further.

2.1.5 Mechanisms associating SAT with increased risk

Although SAT is not as metabolically active as VAT, its contribution to systemic FFA flux should nonetheless be greater due to its size alone since abdominal SAT mass is about twice that of VAT.[45]

The possibility that a high level of systemic FFAs might play a key role in the development of insulin resistance in obesity was first proposed by Randle et al.[36] more than 30 years ago. In 1963, Randle et al.[46] hypothesized that FFAs mobilized from SAT suppress glucose utilization in the skeletal muscle through the inhibition of the pyruvate dehydrogenase complex. Randle's hypothesis proposes that an increased provision of FFAs for respiration inhibits glucose oxidation in muscle and impairs the responsiveness of this tissue to insulin. The final result in this chain of events is a decreased uptake of glucose into the cell. It also suggests that increased intramuscular and/or adipose tissue lipolysis, coming from VAT or abdominal SAT (ASAT), leads to a conversion of glucose to FFA oxidation. This is not consistent however with elevated respiratory quotients in obese subjects.[47]

Randle et al.[37] reported that a diminished responsiveness in the skeletal

muscle GLUT-4 transport system occurs due to the amplified levels of plasma FFA from adipose tissue. More specifically, it is reported that FFA-induced insulin insensitivity may be related to a decrease in GLUT-4 expression on the plasma membrane or reduced intrinsic activity of the transporter.[48] Studies examining this interaction have shown that FFAs inhibited glucose uptake in a dose-dependent fashion throughout the physiological range of plasma FFA concentrations from 50-800umol/L in both healthy subjects and obese subjects with NIDDM. It was also reported that those studies that did not observe this inhibition did not give sufficient time for fat plus insulin infusion (only 2hrs in most studies).[49-51] Thus, there is strong evidence that physiological elevations of plasma FFA levels lowers peripheral insulin sensitivity in a dose-dependent fashion.

More recently, an opposite perspective to the traditional glucose-fatty acid cycle proposed by Randle and colleagues[52] has been put forward. According to Wolfe's hypothesis,[52] the rate of lipolysis may have some effect on the availability of glucose, via a fatty acid-mediated inhibition of plasma glucose uptake and also by supplying glycerol for gluconeogenesis, but has no effect on glucose oxidation (Figure 3). Randle's cycle proposes that fatty acids inhibit intracellular glucose oxidation. However, no evidence exists that after glucose is in the cell, there is any impairment of glucose oxidation by fatty acids.[52] Thiebaud et al[53] reported that glucose uptake and oxidation were both reduced when the fatty acid concentration was high. However, they did not

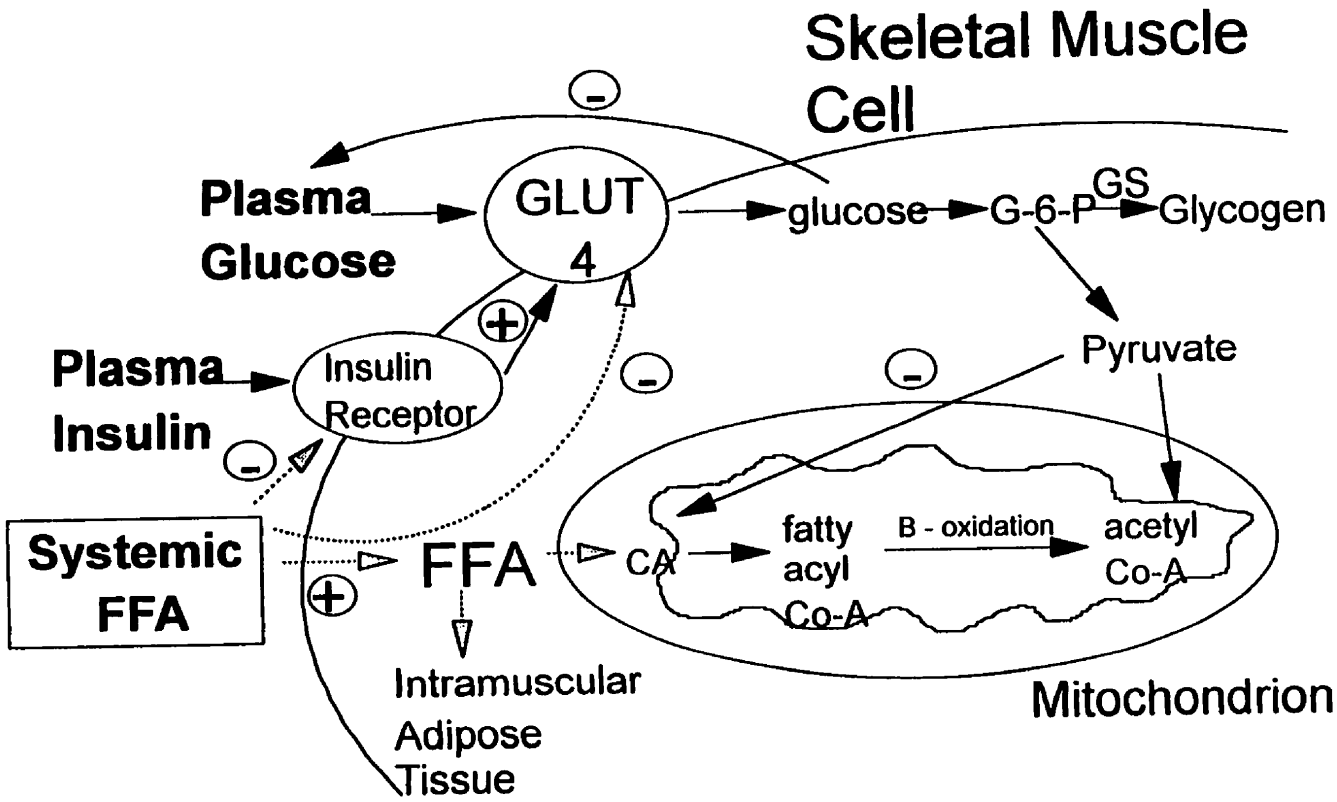

Figure 3. Mechanisms associated with glucose uptake and FFA inhibition. FFA= free fatty acids, G-6-P= glucose-6-phosphate, GS= glycogen synthase, ⋯⋯► = proposed FFA-mediated mechanisms (adapted from Rice[45])

report the percentage of glucose oxidized which showed no impairment at high fatty acid concentrations.[52]

In contrast to Randle's cycle, it is proposed that the rate of glycolysis, determined by the intracellular availability of glucose-6-phosphate, is the predominant factor determining the rate of glucose oxidation.[52] In addition, it is hypothesized that increased glucose oxidation inhibits fatty acid oxidation by limiting FFA transport into the mitochondria by inhibiting carnitine acyltransferase (CA). Whereas there is a close coupling between glucose availability and oxidation, fatty acids are generally available in greater quantities than are required for oxidation. Therefore, in contrast to Randle's cycle, an increased uptake of fatty acids coupled with a decreased capacity for oxidation should favour increased fat deposition in skeletal muscle of obese individuals. This is consistent with reports that muscle of obese individuals has a decreased CT attenuation, which is indicative of an increased storage of intramuscular fat.

2.1.6 Skeletal muscle and insulin resistance

Impaired glucose uptake in skeletal muscle is a feature of all insulin resistant states in NIDDM and obesity. Since skeletal muscle is the primary site for insulin-mediated glucose uptake in the postabsorptive state,[54] the mechanisms by which skeletal muscle become resistant to insulin with obesity is the focus of much investigation. Skeletal muscle of obese individuals, particularly upper body obese, is characterized by decreases in muscle capillarization and blood flow, a reduced percentage of fast-twitch oxidative

glycolytic fibres (FOG), fewer oxidative enzymes, and an overall decrease in oxidative capacity.[55]

Krotkiewski et al.[47] observed that WHR was positively correlated with the percentage of fast-twitch glycolytic (FG) fibres and negatively correlated with capillary density. In rats, it has been reported that FG fibres have lower levels of insulin receptor binding compared with slow-twitch oxidative (SO) fibres[56] and are associated with increased insulin and glucose levels. Thus, lower levels of SO fibres in obese subjects may result in an overall decrease in insulin-stimulated glucose uptake. Similarly, capillary density[47] and blood flow[11] have been reported to be positively associated with insulin sensitivity. A high WHR is also associated with a decrease in oxidative enzyme activity and a high respiratory quotient (RQ) when compared to lean subjects.[47,57] 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. Consistent with this observation, decreases in activities of muscle citrate synthase, a marker enzyme of the Kreb's Cycle, and muscle carnitine palmitoyl transferase, the carrier enzyme responsible for transport of FFA into the mitochondria, favour increased fat deposition in skeletal muscle and may contribute to insulin resistance.[57] In fact, it is reported that a decreased capacity for skeletal muscle fat oxidation contributes to increased deposition of intra-muscular triglycerides in obese individuals.[44,52,57]

2.1.7 Skeletal muscle glucose transport and insulin sensitivity

Under basal, sedentary conditions, glucose transport in skeletal muscle is regulated primarily by insulin.[54] Insulin stimulates the translocation of GLUT4 isoform transporters from their intracellular vesicles to the plasma membrane, thereby greatly increasing the plasma membrane concentration of glucose transporters and the rate at which glucose can be transported into the cell.[58,59] Physical exercise (muscle contractions) has also been reported to stimulate glucose uptake, independently and in addition to insulin-mediated effects, through the translocation of GLUT4 transporters. Evidence for two distinct pools of GLUT4 transporters suggests that muscle contractions and insulin cause stimulation of glucose uptake by two separate pathways (Figure 4).[54]

It was originally hypothesized that muscle of upper body obese individuals may be GLUT4 protein deficient. The finding of normal GLUT4 protein concentration in muscles of obese Zucker rats, however, has subsequently led to the speculation of a defect in GLUT4 translocation and/or activation by insulin-mediated signalling.[56] However, it is likely that the impaired insulin action associated with obesity originates from alterations in the expression or function of one or more of the cellular proteins that are components of the insulin receptor signalling pathway. Therefore, a blunted signal may lead to a block in the activation of glucose transporter function, or may occur in parallel with and independent effect of obesity on the glucose transport system. Although the complete sequence of insulin-stimulated glucose

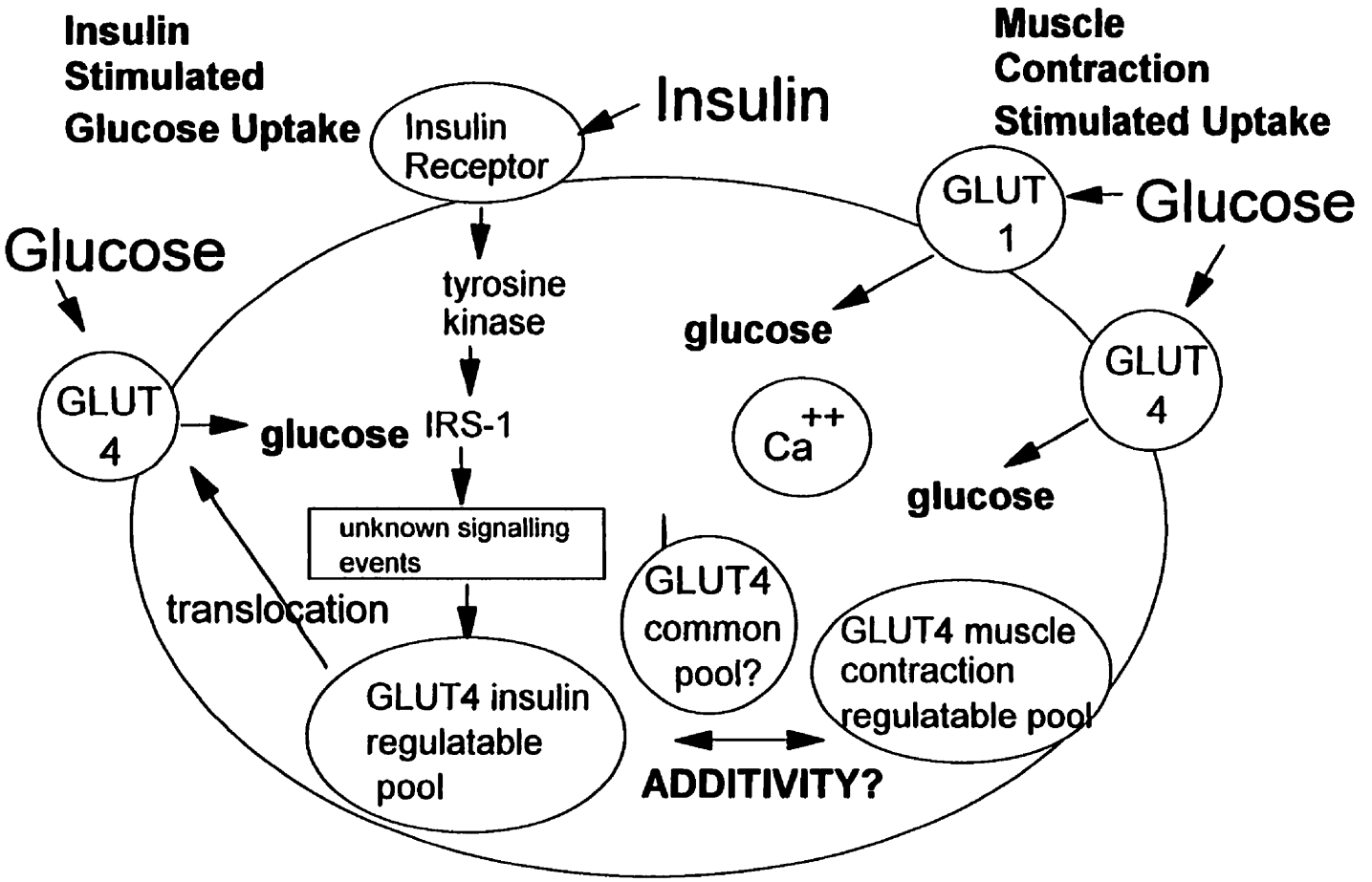

Figure 4. Mechanisms of insulin- and muscle contraction-induced glucose uptake (adapted from Cortright and Dohm[64])

transport still remains unclear, a model for insulin- and contraction-induced glucose transport in skeletal muscle has been described (Figure 4).[54] Briefly, when insulin binds to the α-subunit of its skeletal muscle receptor, it activates tyrosine kinase which immediately initiates a cascade of signalling events. The initial step in the cascade is tyrosine phosphorylation of the insulin receptor substrate 1 (IRS-1). Phosphatidylinositol 3-kinase (PI 3-kinase) is then phosphorylated and is believed to be involved in propagating many of the events which lead to the translocation of GLUT 4 to the cell surface membrane from its intracellular pool.

Studies comparing lean subjects with healthy obese,[60] obese NIDDM,[60,61] and patients with impaired glucose tolerance[60] have reported that no significant differences exist between groups with respect to GLUT 4 content. In the obese Zucker rat in which both transporter expression and function can easily be measured, GLUT 4 levels were not altered[3,61] while GLUT 4 translocation was impaired.[3] More recently however, more sensitive techniques have allowed researchers to study glucose transporter translocation. Using a photo-labelling technique, Lund et al.[60] definitively determined that increases in insulin stimulated GLUT4 translocation fully accounted for the observed increases in glucose uptake. Thus, human obesity may be associated with a defect in GLUT4 translocation.

2.1.8 Skeletal muscle interstitial adipose tissue (SMIAT) and metabolic risk

Skeletal muscle interstitial adipose tissue is increased in obese compared

with lean men[44] and women[57] and has been found to be correlated with insulin sensitivity. Using CT, Simoneau et al[57] found that muscle with low attenuation was as strong a predictor of insulin resistance as VAT. Moreover, in a large cohort of men and women, Goodpaster et al[44] reported that muscle with an increased fat content was the strongest correlate of insulin resistance. Therefore defects in skeletal muscle lipid oxidation may also be involved in the mediation of insulin resistance.

Skeletal muscle is responsible for the majority of lipid oxidation and insulin-stimulated glucose utilization. As such, increased RQ values are observed in obese individuals during the basal state, signifying that a low ratio of fat to carbohydrate oxidation is occurring.[62] Consistent with this indirect evidence of low fat oxidation in muscle, an inverse correlation has been demonstrated between skeletal muscle lipoprotein lipase (LPL) activity and 24-h RQ.[62] Low muscle LPL activity would limit fatty acid or lipid oxidation and favour its deposition in adipose tissue. In addition, increased intramuscular triglyceride in obese individuals has been linked to reduced glucose storage and glycogen synthase activity in muscle.[63] Thus, it seems evident that defects of lipid oxidation also exist in individuals predisposed to developing insulin resistance. Whether a defect in glucose storage is the result or is the causative factor of increased SM interstitial adipose tissue remains unclear.

2.1.9 Summary

Upper body obese individuals are at the greatest risk of developing CVD

and NIDDM.[26,27] Upper body obesity can result from either excess abdominal SAT or VAT fat deposition. Although there is evidence that VAT is the strongest correlate of insulin and glucose levels in obese subjects,[33] it has recently been reported that abdominal SAT has as strong an association with insulin resistance as VAT.[44] It is hypothesized that an exaggerated lipolytic response occurs in VAT which may result in elevated plasma FFAs which drain into the portal circulation where they can lead to a reduction in insulin sensitivity of hepatocytes and increased hepatic gluconeogenesis.[37] In addition, FFAs mobilized from SAT suppress glucose utilization in skeletal muscle through a diminished responsiveness in the skeletal muscle GLUT4 transport system.[37] As well, an increased uptake of fatty acids coupled with a decreased capacity for oxidation favours increased fat deposition in skeletal muscle of obese individuals.[52]

Therefore the aim of improving insulin sensitivity and glucose tolerance is two-tiered. First, adiposity must be reduced by means of a negative energy balance. In particular, VAT, SAT and SMIAT depots must be targeted if treatment is to be effective. Second, weight loss should be the primary goal of attaining a negative energy balance as it has been documented to be an effective means of improving insulin sensitivity, glucose tolerance, and increasing skeletal muscle GLUT4 and lipid oxidation. Whether a differential effect on insulin sensitivity and glucose tolerance is observed after equivalent weight loss through calorie restriction or increased energy expenditure through

exercise is not known. In addition, it would be clinically useful to determine three important factors. How much weight loss is required to induce metabolic benefits? Does exercise per se have additional benefits and can exercise induce changes in body composition in the absence of weight loss?

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

It is commonly reported that weight loss results in metabolic improvements for conditions such as hyperglycemia,[64] hyperinsulinemia,[65] and insulin insensitivity.[66] Numerous studies have shown that weight loss between 6 and 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.[2,9,67,68] Not all studies investigating the association between weight loss and insulin sensitivity have reported improvements in both insulin and glucose levels however. It has been reported that decreased fasting plasma insulin levels occur without concomitant improvements in OGTT insulin area.[5,6] Similarly, improvements in OGTT insulin area have been reported to have no effect on glucose tolerance.[67,69] The fact that pre-treatment glucose tolerance was normal in several studies may explain the lack of a response. More important however, a decrease in insulin area despite a corresponding decrease in glucose suggests that less insulin is required to dispose of a given amount of glucose into the cell, which signifies an increase in insulin sensitivity.

2.2.1 Mechanisms associating weight loss with improved insulin sensitivity

VAT

As described earlier, it is hypothesized that VAT leads to increased hepatic glucose output and decreased hepatic insulin clearance through increased FFA mobilization into the portal circulation.[38] Reductions in VAT are therefore believed to result in decreased VAT-mediated portal FFA release which would be likely to improve hepatic insulin sensitivity. Taken together, it is hypothesized that reductions in VAT, following weight loss, are associated with improvements in insulin sensitivity and reductions in both OGTT insulin and glucose levels.[2,9,67,68]

SAT

In addition to diet-induced reductions in VAT, the reduction of SAT, particularly abdominal SAT, may be associated with improved insulin sensitivity and glucose utilization since it is well established that diet-induced weight loss results in significant reductions in SAT.[22] Jensen et al[31] have reported that, in obese women matched for age and adiposity, FFA release is greater in upper- compared with lower body obese women. Accepting that plasma FFAs influence insulin sensitivity, these observations suggest that regional differences may exist with respect to the relationship between SAT distribution and insulin-glucose homeostasis. It can be hypothesized that a modest decrease in weight significantly reduces ASAT and accompanies an associated improvement in insulin sensitivity.

Skeletal muscle

In addition to the mechanisms associated with adipose tissue reduction, it is reported that an increase in skeletal muscle GLUT4 activity occurs with weight loss. After a 43kg weight reduction in 7 healthy obese and NIDDM individuals, Friedman et al[75] reported a significant increase in glucose disposal and a two-fold improvement in insulin-stimulated glucose transport. Although GLUT4 levels were unchanged, it was reported that the activity of these transporters increased.[75] Caro et al[76] have also reported that weight loss improves the tyrosine kinase activity of skeletal muscle insulin receptors in obese men and women with and without NIDDM. Whether this improvement is responsible for the upregulation of GLUT4 following weight loss is unknown.

2.3.0 Association between exercise, insulin sensitivity, and glucose tolerance

It has been suggested that exercise without weight loss may be important in the prevention of NIDDM as well as improving insulin sensitivity and glucose tolerance. Recent prospective studies tracking thousands of both men and women have investigated the relationship between the incidence of NIDDM and physical activity.[77,78] Manson et al[77] reported that 87,253 healthy women aged 34-59 who exercised vigorously at least once per week had a 33% decrease in their risk of developing NIDDM when compared to age-matched sedentary individuals who exercised less than once per week. The assessment of relative risk was calculated 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. However, after the researchers adjusted for both age and BMI, risk decreased only by 16%. Similarly, after adjusting for age and BMI, a five year follow up study which tracked 21,270 healthy men, who exercised once per week, reported a 22% decrease in the risk of developing NIDDM compared to sedentary controls.[78] Indeed, the age-adjusted relative risk showed a dose response relationship with increasing exercise frequency. A 23% reduction in age-adjusted relative risk of developing NIDDM was observed in those who exercised one session per week, a 38% reduction was observed in those who exercised 2-4 sessions per week, and a 42% reduction was observed for those individuals who exercised five or more sessions per week.[78] In addition, the highest responders to exercise were the obese men who had the highest incidence rate of NIDDM.[78] Taken together, these observations suggest that exercise may be important in the prevention of NIDDM as well as improving insulin sensitivity and glucose tolerance. The observations from cross-sectional studies have also confirmed that exercise-trained individuals have increased insulin sensitivity and glucose tolerance (Table 1).

Improving insulin sensitivity and glucose tolerance due to aerobic exercise training remains unclear however. Previous studies have shown that both aerobic[3,4,12,14,67] and resistance exercise training[8,13,15] are associated with improvements in insulin sensitivity and OGTT insulin responses (Table 2). In

Table 1. Cross-sectional studies examining enhanced insulin sensitivity in exercise-trained individuals

Reference	Comparison	Subject Characteristics	Percent Difference in Metabolic Variables (trained versus untrained)	Differences in Muscle Morphology
Bjorntorp et al. (1972)	15 trained vs 16 sedentary men	T-BMI= 10±1 T-$\dot{V}O_2$max= N/A U-BMI= 16±1 U-$\dot{V}O_2$max= N/A	fasting insulin T<U, 80% insulin area T<U, 66%** fasting glucose T=U glucose area T<U, 20%**	succinic oxidase T>U, 75% ****
Rodnick et al. (1987)	8 trained runners vs 8 sedentary men	T-BMI= 20. 5 T-$\dot{V}O_2$max= 62.0 U-BMI= 23.0 U-$\dot{V}O_2$max= 41.0	fasting insulin T<U, 45% insulin area T<U, 40% ** glucose disposal T>U, 42% * HGP T<U, 67%	N/A
King et al. (1988)	11 endurance trained vs 11 untrained men and women	T-body fat=14.6±1.3 T-$\dot{V}O_2$max= 58.4±2.9 U-body fat=17.0±2.1 U-$\dot{V}O_2$max=46.6±1.9	fasting glucose T<U, 9% fasting insulin T<U, 40% glucose disposal T>U, 28% * insulin response T<U, 50% ***	N/A
King et al. (1990)	8 endurance trained vs 9 sedentary men	T-BMI=21.2±0.7 T-$\dot{V}O_2$max=66.6±2.0 U-BMI=23.5±1.1 U-$\dot{V}O_2$max=49.1±1.9	insulin response T<U, 50% ***	N/A
Houmard et al. (1991)	11 trained vs 11 sedentary men	T-body fat= 14.1±1.1 T-$\dot{V}O_2$max=54.4±2.4 U-body fat= 27.7±2.9 U-$\dot{V}O_2$max=31.3±2.0	fasting insulin T<U, 60% insulin area T<U, 400% ** insulin sensitivity T>U, 450% **	GLUT4 T>U, 200% SO fibres T>U, 13% FG fibres T<U, 17%
Ebeling et al. (1993)	9 athletes vs 10 sedentary men	T-BMI=23.2±0.6 T-$\dot{V}O_2$max=57.6±1.0 U-BMI=23.9±0.9 U-$\dot{V}O_2$max=44.1±2.3	glucose disposal T>U, 32% * nonoxidative glucose disposal T>U, 62% *	glycogen T>U, 39% blood flow T>U, 64% GLUT4 T>U, 93% glycogen synthase activity T>U, 33%
Vestergaard et al. (1994)	7 athletes vs 8 sedentary men and women	T-BMI=N/A T-$\dot{V}O_2$max=74.0±3.9 U-BMI=N/A U-$\dot{V}O_2$max=42.9±5.1	fasting insulin T<U, 22% glucose disposal T>U, 27% * nonoxidative glucose disposal T>U, 20% * oxidative glucose disposal T>U, 33% *	glycogen synthase T>U, 34% phosphofructokinase T<U, 15%

*measured by euglycemic clamp; **measured by OGTT; ***measured by hyperglycemic clamp; ****marker of skeletal muscle oxidative metabolism; T= trained; U= untrained; < = less than; > = greater than; BMI = body mass index in kg/m^2; $\dot{V}O_2$max = maximal oxygen uptake in mlO_2/kg/min; OGTT = oral glucose tolerance test; HGP = hepatic glucose production; SO fibres = slow oxidative fibres; FG fibres = fast glycolytic fibres

Table 2. Studies examining the effects of exercise alone on insulin and glucose variables

Reference	Type of Exercise	Duration and Frequency	Subjects (sedentary)	Change in Insulin Sensitivity *	Relative Reduction in Fasting Values	Relative Reduction in OGTT areas
Lampman et al. (1985)	aerobic (walking)	9 weeks 3 x per wk (30- 40 min)	10 men middle aged	N/A	insulin - 20% glucose - none	insulin - 25% glucose - none
Segal et al. (1991)	aerobic (cycle ergometer)	12 weeks 4 x wk (60 min)	men 10 lean 10 obese 6 diabetic	none	insulin - none glucose - none	insulin - none glucose - none
Smutok et al. (1993)	aerobic (walking and jogging) or resistance (11 exercises)	20 weeks 3 x wk	aerobic - 8 obese men strength - 8 obese men	N/A	insulin(A) - none glucose(A) -none insulin(S) - 16% glucose(S) -none	insulin(A) - 21% glucose(A) - 16% insulin(S) - 22% glucose(S) - 12%
Miller et al. (1994)	resistance (14 exercises)	16 weeks 3 x wk 60 min	11 healthy men	24%	insulin - 28% glucose - none	insulin - unknown reduction glucose - none
Katzel et al. (1995)	cycling walking jogging	9 months 3 x wk 45 min	49 obese men	N/A	insulin - none glucose - none	insulin - 17% glucose - none
Ryan et al. (1996)	resistance (14 exercises)	16 weeks 3 x wk	13 obese women	none	insulin - none glucose - none	insulin - N/A glucose - N/A
Dengel et al. (1996)	cycling walking jogging	10 months 3 x wk 40 min	10 obese men	+ 22%	insulin - none glucose - none	insulin - 18% glucose - none
Torjesen et al. (1997)	endurance	1 year 3 x wk	54 obese men and women	none ***	insulin - none glucose - none	insulin - none glucose - none
Mourier et al. (1997)	cycling	2 months 2 x wk (45 min)	6 obese men	+ 46% **	N/A	N/A

* measured by hyperinsulinemic euglycemic clamp; ** measured by intravenous insulin tolerance test; *** measured by homeostasis model by Matthews et al; OGTT = oral glucose tolerance test; NIDDM = non-insulin dependent diabetes mellitus; IGT = impaired glucose tolerance; IIT - impaired insulin tolerance; N/A = not available

some of these same studies, glucose tolerance was improved. However, in many of these studies, no attempt was made to control for changes in body composition.[15,16,17] Therefore, it is unclear in these studies whether the improvements seen in insulin sensitivity and glucose tolerance were a result of chronic exercise training or reductions in adiposity. In addition, numerous studies failed to account for the acute effects of a single bout of exercise.[4,13,15,16,61] Under basal conditions, glucose transport in skeletal muscle is regulated primarily by insulin-stimulated GLUT4 translocation .[54] However, exercise-induced muscle contractions have been reported to stimulate glucose uptake, independently and in addition to insulin-mediated effects, through the translocation of GLUT4.[54] Evidence for two distinct pools of GLUT4 transporters suggests that muscle contractions and insulin cause stimulation of glucose uptake by two separate pathways (Figure 4).[54] Consequently, evidence exists that a single bout of exercise increases insulin sensitivity in healthy obese individuals and those with NIDDM for a significant period following the exercise session.[84,85] King et al[84] reported that a single bout of exercise improves insulin sensitivity for 3 but not 5 days. Unfortunately, many previous studies have reported upon the chronic effects of exercise before waiting at least 3 days for testing.[4,8,13,15,61] Therefore their measurements of insulin sensitivity and glucose tolerance did not accurately report upon the chronic effects of exercise training, as the acute exercise effects of the last exercise bout were still influencing glucose uptake.

In a more stringent study which controlled for body composition and the acute effects of a single exercise bout, Segal et al[86] showed no improvement in insulin sensitivity due to aerobic exercise training, even though there was a 27% increase in $\dot{V}O_2$ max. The exercise protocol consisted of training on a cycle ergometer for 4 hours a week at 70% $\dot{V}O_2$ max. To explain these discrepant findings, the authors gave two possible explanations. Following exercise, the subjects were immediately refed calories to help maintain their weight. It has been reported that increased caloric intake is related to a diminished response in the glucose storage rate.[87,88] In addition, a sufficient amount of muscle mass may not have been utilized in the exercise protocol. Other studies used exercise which recruited a larger amount of muscle mass such as walking, jogging, or cycling to evoke a training response. Therefore the influence of exercise per se on insulin sensitivity remains unclear.

2.3.1 Exercise prescription

Although it appears that physical exercise beneficially affects insulin sensitivity and the incidence of NIDDM, the ideal intensity, duration, frequency, and modality of exercise that would provide the greatest benefits is unknown. A study by Young et al[89] examined whether cycling for 40min at different intensities on three subsequent days had a differential effect on insulin and glucose responses in untrained individuals following an oral glucose tolerance test. Although there was no improvement in glucose tolerance after either training intensity, it was found that whether the subjects expended the same amount of

energy at 40% or 80% of their $\dot{V}O_2$ max, the 40% and 45% respective decreases in insulin response were not different. Another study by Bonen et al[90] examined the effects of insulin binding to its skeletal muscle receptors at intensities below 60% of $\dot{V}O_2$ max and above 70% of $\dot{V}O_2$ max. A 30-50% decrease in insulin binding was found to occur in the latter condition while no change in insulin binding occurred in the lesser intensity condition. However, the reduction in insulin binding with heavy exercise does not necessarily correlate with a concomitant change in glucose uptake and metabolism. Although more information is needed on this topic, these studies indicate that, at least when total energy expenditure is held constant, low and high intensity exercise are equally effective in improving insulin sensitivity.

2.3.2 Exercise mechanisms associated with improved insulin sensitivity

The proposed mechanisms associated with improvements in insulin sensitivity as a result of chronic exercise include reductions in VAT and SAT, changes in GLUT-4 transport protein, skeletal muscle oxidative metabolism, and an increase in skeletal muscle mass.

Reductions in VAT and SAT

In the absence of weight loss, it is unclear whether exercise training will result in significant reductions in VAT or SAT. It is proposed that a reduction in FFAs mobilized from VAT would lead to decreased hepatic gluconeogenesis and increased hepatic insulin clearance.[38] In addition, the reduction of SAT, particularly ASAT, may improve peripheral insulin sensitivity, glucose tolerance

and decrease basal pancreatic insulin secretion via decreased levels of FFA in the systemic circulation.

A preferential reduction in VAT and ASAT has been found to result in a diminished insulin secretion by the pancreas and increased metabolic clearance of insulin by the liver in response to the same glucose concentration.[91] Wirth et al.[91] observed that about one third of the decrease in plasma insulin at rest was attributable to an increased metabolic clearance rate of insulin by the liver. The remaining decrease in plasma insulin concentration was due to a decrease in insulin secretion from the pancreas.

To date, only 2 studies have evaluated the effects of exercise by itself on VAT.[92,93] Despres et al[93] reported a 10% reduction in ASAT with no significant reductions in VAT after 14 months of endurance exercise in premenopausal women. In contrast, Schwartz et al[92] observed significant reductions in VAT in young (17%) and older (25%) men after six months of endurance training. Because of weaknesses in controlling for body composition characteristics, it is difficult to directly compare these two studies. The contribution of exercise per se could not be definitively determined as weight loss alone may have caused the observed changes in VAT. In addition, the women's initial VAT levels in Despres' study[93] were very low which may explain why a loss in VAT was not observed after the exercise treatment.

GLUT4 transporter proteins

The effect of insulin to acutely stimulate GLUT4 mediated glucose uptake

into muscle tissue is essential for normal glucose homeostasis. Glucose transport is the rate-limiting step in skeletal muscle glucose uptake.[54] Therefore, it is a probable site of improved insulin action. A study by Ferreras et al[9] reported that exercise training improves insulin sensitivity by translocating increased amounts of GLUT4 receptors to the sarcolemma from an intra-cellular compartment. Previous studies have reported normal levels of GLUT4 in skeletal muscle of physically trained subjects with NIDDM and obesity.[54] However, those studies did not differentiate between the total amount of GLUT4 protein with the amount which is translocated to the membrane. A study by Roshoolt et al[94] reported nearly a two-fold increase in the number and area of sites labelling for GLUT4 along the sarcolemma in lean healthy subjects when compared to moderately obese subjects. Therefore, the hypothesized increase in insulin sensitivity due to the GLUT4 transport system is due to increased translocation from the intra-cellular pool to the sarcolemma membrane rather than from increased phosphorylation of GLUT4 protein. Whether this insulin-mediated process is affected by systemic levels of FFA or insulin is unknown.

Skeletal muscle morphology

In addition to changes in glucose transport, many morphological changes may also occur in response to physical training. These changes include alterations in the biochemistry and hemodynamics of skeletal muscle as well as possible fibre type conversion. In addition, an increase in skeletal muscle mass may be associated with an enlarged glucose storage area and an increased

number of insulin receptors available for binding which could possibly lead to an increased glucose uptake via the stimulation of GLUT4 receptors.[15] However, current knowledge with respect to skeletal muscle mass and insulin-glucose variables remains unresolved.

The correlation between skeletal muscle citrate synthase (CS) activity, a marker for oxidative metabolism, and insulin sensitivity is consistent with the concept that muscle fibres with enhanced oxidative capacity manifest increased insulin sensitivity through an increase in insulin-mediated glucose uptake.[95] Houmard et al[10] have demonstrated that habitual exercise training over 14 weeks increased muscle fibre type conversion from (FG) to FOG which may explain the same relative increases seen in GLUT 4 (1.8-fold), CS activity (1.7-fold) and insulin sensitivity (2-fold).

Skeletal muscle blood flow also appears to be associated with glucose uptake. It has been shown that the most insulin sensitive subjects exhibit the greatest degree of vasodilation and that insulin resistant subjects show blunted vasodilatory responses.[96] Ebeling et al[11] observed that in trained athletes, blood flow was associated with forearm glucose disposal which was 3.3-fold greater in the basal state and 73% greater during insulin infusion as compared with sedentary controls. In the basal state and during insulin infusion, the trained athletes had an increased blood flow which may have contributed to the increased glucose disposal by increasing the supply of both insulin and glucose to the muscle.[11] It is hypothesized that increased blood flow occurs through

either increased capillarization, increased fibre area, or increased arteriolar function.

It has also been shown that the concentration of muscle glycogen is higher in exercise trained individuals than untrained.[11,97] Ebeling et al[11] reported a 62% increase in nonoxidative glucose disposal rates in athletes when matched with sedentary controls. This was explained by concomitant 33% and 39% increases in glycogen synthase activity and glycogen content, respectively. As a result, it is believed that the greater disposal rates in athletes was due to increased storage as glycogen.

Taken together, these results suggest that exercise training may have unique mechanisms by which insulin sensitivity may be improved. However, it is not known whether the skeletal muscle adaptations which are associated with exercise training are a direct result of muscle contractions per se or if they are secondary to a negative energy balance induced by an increased energy expenditure.

2.4.0 Influence of diet- and exercise-induced weight loss on insulin sensitivity

Although no studies have examined the separate effects of equivalent diet- and exercise-induced weight loss on insulin sensitivity, a few studies have investigated the combined effects of diet and exercise versus diet alone on insulin sensitivity.[4,8,15,17,98,99] It has generally been reported that the combination of diet with exercise is associated with greater reductions in insulin levels

compared to diet alone or exercise alone.

Recently, Torjesen et al[17] examined the combined effects of diet and aerobic exercise on insulin resistance. The protocol for the diet intervention included a decreased total fat intake and an increased fish intake, while the exercise intervention entailed supervised endurance exercise 3 times/week. After a one year treatment period, it was reported that the diet and combined diet with exercise interventions had significant reductions in insulin resistance, with the combined intervention exhibiting a greater improvement. Exercise alone did not significantly change insulin resistance. Unfortunately the results of this study are confounded because the diet plus exercise intervention had a greater reduction in BMI than the diet-only intervention. Therefore, it is uncertain whether the greater improvement in the combined intervention was due to the added benefits of exercise or the increased weight loss with a concomitant reduction in adiposity. In addition, the amount of weekly exercise which was performed within the exercise interventions is unclear.

Similarly, Dengel et al[5] examined the combined effects of diet and aerobic exercise compared to diet alone. The exercise training in that study involved walking, jogging, or stationary cycling at an intensity of 50-85% of heart rate reserve, 3 days per week, over a 10 month treatment period. Subjects initially exercised for 10 minutes per session and gradually progressed up to 40 min per session. Overall, exercise-induced weight loss had a 42% reduction in insulin response following an oral glucose tolerance test versus a 21% reduction in the

diet-induced weight loss. In addition, the exercise group exhibited a 22% improvement in glucose disposal during a glucose clamp, whereas, the diet group showed no change. The results from this study are confounded. The subjects were tested within two days of the last exercise session.

2.5.0 Summary

Weight loss is an effective treatment for improving insulin sensitivity and glucose tolerance in obese individuals. However, it remains unclear whether exercise, in the absence of weight loss, is beneficial. The literature is devoid of carefully controlled studies which report upon the specific improvements in insulin sensitivity by exercise per se. In addition, the exact mechanisms and the effects of equivalent diet- or exercise-induced weight loss on abdominal obesity, VAT, and insulin sensitivity in obese men and women has yet to be determined. Therefore researchers must pursue two courses of action before there are firm answers to explain the mechanisms of increased insulin sensitivity and glucose tolerance. First, carefully controlled studies which examine the separate effects of equivalent diet- and exercise-induced weight loss on skeletal muscle insulin sensitivity must be pursued. As well, the effects of exercise , in the absence of weight loss, must be carried out to differentiate between the effects of weight loss versus exercise.

3.0.0 MANUSCRIPT

The following chapter of this thesis is presented in a format required by the Journal of Applied Physiology. For simplicity the references for the manuscript are included in Chapter 5.0.0.

The Separate Effects of Diet- and Exercise-Induced Weight Loss On Insulin Sensitivity

INTRODUCTION

Obesity is associated with metabolic complications such as impaired insulin sensitivity and decreased glucose tolerance, both of which are putative markers for CVD and NIDDM.[18] Given that a recent U.S. National Health and Nutrition Examination Survey reports that 55% of men and women are overweight,[1] obesity poses a major public health challenge. While there is agreement concerning the health risks associated with obesity, there is less agreement regarding its management.

There is strong evidence that diet-induced weight loss is associated with improvements in insulin and glucose metabolism in both men and women.[67,68,100] However, it is unclear whether weight loss as a result of increased energy expenditure through exercise produces the same metabolic benefits compared to weight loss induced by caloric restriction. It has been reported previously that exercise, when combined with diet, induces a greater amount of fat loss than equivalent diet-induced weight loss.[7] If this increased fat loss resulted in a preferential reduction of abdominal fat, the region which conveys the greatest metabolic risk,[33] this would potentiate greater improvements in insulin sensitivity and glucose tolerance. In addition, exercise-induced changes in insulin sensitivity are highly correlated with exercise-induced changes in skeletal muscle morphology such as increased GLUT4 transporters,[15] glycogen content,[5,11] blood flow,[11,96,102] oxidative capacity,[95] and the percentage of fast twitch oxidative fibres.[9,103] Whether these changes in muscle morphology

augment the improvements in insulin sensitivity and glucose tolerance mediated by weight loss is not known. Therefore, given the independent effects of exercise, it is hypothesized that exercise-induced weight loss will have a greater effect on insulin sensitivity and glucose tolerance than equivalent diet-induced weight loss.

In an attempt to further clarify the separate effects of exercise, an exercise weight stable group was included within the study design. Although previous studies report that aerobic[3,4,12-14] and resistance exercise[8,13,15] without weight loss results in improvements in insulin sensitivity, there are limitations to these studies which have confounded the findings associated with exercise per se.

Thus, the purposes of this randomized and controlled study were twofold: to evaluate the effects of equivalent diet- or exercise-induced weight loss on insulin sensitivity in upper body obese men; and to determine whether exercise without weight loss is associated with improvements in insulin sensitivity and glucose tolerance.

METHODS

Experimental Approach

Forty subjects were recruited from the Kingston area. Inclusion criteria required that the men be upper body obese (BMI 30-35kg/m^2; WHR>0.95), weight stable (±2kg) for one year prior to the beginning of the study, consume on average <2 alcoholic beverages per day, be non-smokers, nonhyperlipidemic (total plasma cholesterol <7.0mmol/L and triglycerides <4.0mmol/L) and not taking medication. The study was conducted in accordance with the ethical guidelines of Queen's University.

To qualify for the study, all subjects underwent a pre-participation medical exam to ensure that they were free of disease such as diabetes, hypertension, or heart disease which would influence either their participation in the program or their biochemical assessment. Eligible men were randomly allocated into one of the following conditions: 1) isocaloric diet-weight stable (C), 2) hypocaloric diet-weight loss (DWL), 3) exercise only, isocaloric diet-weight loss (EWL) and 4) exercise only, weight stable (EWS). The duration of all treatments was 12 weeks. The descriptive characteristics for all groups are given in Table 1. The four groups were not different with respect to the anthropometric, MRI, or metabolic variables.

Pre-treatment baseline period

A weight maintenance diet, with less than 30% of the calories coming from fat, was followed for at least a 3 week baseline period by all groups to

monitor body weight and determine the accuracy of the isocaloric diets. This was aided by the collection of daily diet records throughout the baseline and treatment periods. A Registered Dietician met with each subject twice weekly to ensure weight maintenance and adherence to the dietary regimen. Each subject participated within his designated treatment group in a series of weekly educational seminars designed to teach proper food selection and preparation. Eight nutrition seminars, one per week, were given to each group for the first eight weeks of the treatment period. These sessions were consistent across all groups and led by a Registered Dietician. Both the maintenance and energy reduced diets prescribed suggested energy as follows: approximately 50-55% carbohydrate, 15-20% protein, and less than 30% fat. Subjects were required to keep daily food records for the duration of the study. These records were monitored individually twice weekly by trained undergraduate nutrition students., which were overseen by a Registered Dietician. The foods consumed were self-selected and store bought. No vitamins or other nutritional supplements were prescribed.

Dietary Regimen

The C and EWS groups were asked to maintain body weight for the duration of the study. The weight loss prescription for both DWL and EWL groups was designed to achieve a 0.6kg weight loss per week for a total weight loss of 7.5kg after the 12 week treatment period. The DWL group achieved this goal through a decreased energy intake of 700kcal/day and the EWL group

achieved this by increasing their energy expenditure by 700kcal/day via low to moderate intensity exercise. Adherence to the program was monitored by ensuring weights were on target. Subjects were instructed to eat more or less depending on whether their weight was too low or too high respectively. For the EWS group, the calories expended during daily exercise (700kcal) were refed. That is, the participants in this group were asked to maintain body weight. At the end of the 12 week treatment period, all groups were prescribed an isocaloric diet for two weeks during the post-treatment period measurements.

Exercise Regimen

The subjects within both the EWL and EWS groups performed daily aerobic exercise at ~60-75% VO_2 max through brisk walking or light jogging on a motorized treadmill for the duration of the 12 week treatment period. Using the heart rate and oxygen consumption data obtained from the pre-treatment (baseline) graded exercise test, the heart rate associated with a $\dot{V}O_2$ of 60-75% was determined and prescribed for the duration required to expend 700kcal daily. A second and third graded exercise test were performed on all exercise subjects at the end of weeks 4 and 8 to verify the relationship between heart rate and oxygen consumption. All exercise sessions were by appointment, monitored by a graduate or undergraduate student, and performed in the laboratory.

Magnetic Resonance Imaging

The MRI images were obtained within the Magnetic Resonance Unit at Kingston General Hospital. The MRI data were obtained with a General Electric,

1.5-tesla scanner using software version 5.4.2. (Wisconsin). A T-1 weighted spin-echo sequence with a 210-ms repetition time and 17-ms echo time was used to acquire the MRI data. The MRI protocol is described in detail elsewhere.[73] Briefly, the body was divided into upper, lower, and truncal regions using L4-L5, and the femoral and humeral heads as landmarks. Thirteen data sets (7 images per set) were obtained while the subject lay in a prone position, with arms straight above the head. Transverse images (10-mm thickness) were obtained every 40mm over the whole body. For all subjects a total of ~46 images were acquired. The total time required to obtain all MR data for each subject was 45min. All MRI data were transferred to a stand-alone work station (Indigo2, Silicon Graphics Inc., Mountain View, CA) for analysis using specially designed software (Tomovision Inc., Montreal, PQ).

Calculation of tissue areas and volumes. 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 skeletal muscle and subcutaneous AT were calculated using all 46 images. Because it is proposed that abdominal adiposity is associated with metabolic complications, this region

was subdivided into visceral AT and abdominal subcutaneous AT depots. Visceral AT and abdominal subcutaneous AT volumes were derived using 5 abdominal images extending from one below to four above the L4-L5 intervertebral space. Femoral SAT was determined using 18 images extending from the femoral head to the foot.

Laboratory Measurements

Duplicate fasting blood samples for the measurement of plasma lipid, lipoprotein, glucose and insulin levels were obtained pre- and post-treatment in the morning after abstaining for 12 to 16 hours from all foods and vigorous activity. Blood was drawn and collected in tubes containing 0.15% EDTA and plasma was separated by centrifugation at 1,000g for 20 minutes at 4°C.

Anthropometric Measurements

To assure that all possible combinations of anthropometric measures were compared to body composition data obtained by MRI, a complete set of skinfolds, body diameters and circumferences was acquired using the procedures described within the Anthropometric Standardization Reference Manual (1988).

Maximal Oxygen Uptake ($\dot{V}O_2$ max)

Maximal oxygen uptake ($\dot{V}O_2$max) was measured using a treadmill exercise protocol and standard open spirometry techniques using a metabolic cart (TEEM 100, Aerosport Inc, Ann Arbor, MI). All subjects were familiarized with the equipment and testing protocol prior to the actual day of testing. It was

assumed that $\dot{V}O_2$ max was attained when two of the following three criteria had been reached: a plateau in $\dot{V}O_2$ persisted despite further increases in treadmill grade, maximum age predicted heart rate was reached, and a respiratory quotient of greater than 1.00 was achieved. Repeat tests were performed on separate days if the above criteria were not met upon completion of the test.

Hyperinsulinemic Euglycemic Clamp

For the three days preceding the clamp, all subjects ingested >250g/day of carbohydrate to help ensure that normal muscle glycogen levels were attained. In addition, the subjects did not perform exercise for the three days immediately preceding the clamp procedure, both pre- and post-treatment. The subjects were admitted to Kingston General Hospital for an overnight stay in the Fraser Armstrong Patient Clinic the night preceding the clamp. Subjects were awakened at 6am for basal metabolic rate, resting blood pressure, and bioelectrical impedance measurements. Following the completion of these measurements, subjects underwent a hyperinsulinemic euglycemic clamp procedure as described by DeFronzo et al.[106]

Two catheters were inserted for the clamp procedure: one in an antecubital vein for the infusion of insulin (Novolin, Toronto, Canada), glucose, and potassium, and the second into a heated hand vein for the sampling of arterialized blood. The plasma concentration of insulin was raised to approximately 100uU/ml above basal and maintained by a constant infusion of 40mU/m^2 surface area per minute for ~110min. Plasma insulin concentrations

were verified by taking samples every 30 minutes. The glucose infusion was initially set at 30ml/hr and administered at the onset of insulin infusion. Based on plasma glucose values determined from arterialized blood samples obtained at 5min intervals, plasma glucose was infused at a variable rate to maintain the fasting level. The rate of glucose disposal (M) was expressed per kilogram skeletal muscle.

Indirect calorimetric methods (TEEM cart) were used to estimate substrate utilization for the final 30 minutes of the clamp procedure. The oxidation rates of carbohydrate and lipid were estimated based on a 0.707 NPRQ for 100% fat oxidation and a 1.00 for 100% carbohydrate oxidation. Non-oxidative rates of carbohydrate utilization were also calculated by subtracting the carbohydrate oxidation rate from M.

OGTT

In addition to obtaining fasting levels for glucose and insulin, both variables were measured during a 75-g 2 hour oral glucose tolerance test (OGTT). The test was performed in the morning after an overnight fast with blood samples obtained in the fasting state and at 0, 15, 30, 60, 90, and 120 minutes following glucose ingestion. Blood was collected through an intravenous catheter placed in a forearm vein. Blood glucose values were determined by the glucose oxidase method using a Beckman Glucose Analyser II (Beckman Instruments). Plasma insulin was determined using a radioimmunoassay method with anti-beef insulin serum (Wright), human

standard and ^{125}I-labelled insulin (Novolin, Toronto, Canada) and precipitated with Dextran (Pharmacia Fine Chemicals, Sweden) coated charcoal. The second OGTT was performed at least 7 days post-exercise.

Statistical Analysis

The sample size required to observe a significant difference in MRI and clamp measurements was determined using a t-test (one-tailed).[104] The algorithm used to determine the associated power for small sample size designs was adapted from Kvanli.[105] For MRI VAT volume, the precision (standard deviation) in our laboratory is 10% (0.4 litres) and the expected difference is 35% or 1.7 litres.[22] Based on these data and an alpha of 0.05, the sample size required to obtain a meaningful difference in VAT is >5. A sample size of 21 would provide a power of 90% to detect a difference of 0.2 litres. For clamp measurements, assuming a standard deviation of 7% (0.57 mg/kg·min^{-1})[106] and an expected difference of 20%, based on a 8.5 kg weight loss,[4] a sample size of 12 subjects would provide a power of 90% to detect a difference of 8.6%.

The data are presented as mean $\pm$ standard deviation. A 2-way analysis of variance, group (C, DWL, EWL,EWS) by time (pre,post) was employed to evaluate main treatment effects and interactions for all dependent variables. Significant differences between groups were analysed using a Scheffé post hoc comparison technique. Paired and unpaired t-tests were used to assess within group changes respectively for all dependent variables. Bonferroni adjustments ($p<0.01$) were used for all t-tests. Data were analysed using SYSTAT.

RESULTS

Descriptive characteristics. The groups were not different ($p>0.05$) for all pre-treatment anthropometric, MRI-measured, and metabolic variables (Table 1). Subjects were characterized as being upper body obese (BMI 28-35kg/m^2, WHR >0.95) and middle aged (45 $\pm$ 9yrs).

Adherence to the exercise program. For the EWS group, attendance at the exercise sessions averaged 97% (range 94%-100%) which was not different from the 97.8% attendance rate of the EWL group (range 96.4%-97.8%).

Functional Capacity. The duration (61.7 vs. 59.9 min) and intensity (77.6% vs. 77.0% maximum heart rate) of daily exercise was not different ($p>0.10$) between exercise groups. The improvements in $\dot{V}O_2$ max within the EWS (+20.8%) and the EWL (+14.5%) groups were not different ($p>0.05$) from each other but were both different from the DWL group. The improvement in the EWS group was different from the C group.

Change in anthropometric variables. Total weight loss (7.3 $\pm$ 0.9kg vs. 7.5 $\pm$ 0.6 kg) within the DWL and EWL groups were not different ($p>0.05$) from each other but were different from the C and DWL groups (Figure 1). The changes in selected anthropometric variables are given in Table 2. Significant ($p<0.001$) and non different ($p>0.10$) within group reductions were observed for both the diet- and exercise-induced weight loss groups for BMI and waist circumference (last rib) compared to the C and DWL groups. Waist-to-hip ratio was also significantly reduced within the DWL group only ($p<0.005$) .

Table 1
Descriptive characteristics[1]

Variable	C (n=7)	DWL (n=10)	EWS (n=11)	EWL (n=12)
Anthropometry				
Age (y)	43.1 ± 11.2	44.5 ± 10.9	44.5 ± 8.5	44.5 ±10.9
Weight (kg)	96.6 ± 9.0	95.5 ± 9.9	95.5 ± 9.9	97.6 ± 7.9
BMI (kg/m^2)	30.6 ± 1.7	30.7 ± 2.0	30.7 ± 2.0	31.2 ± 2.6
WHR[2]	0.97 ± 0.07	0.97 ± 0.04	0.97 ± .04	0.99±0.05
Waist circumference (cm)[3]	107.7 ± 5.1	109.2 ± 6.6	109.2 ± 6.6	109.0 ± 6.6
MRI-measured variables				
Total AT (L)	32.7 ± 5.1	30.7 ± 5.9	31.9 ± 6.7	35.9 ± 6.7
Subcutaneous AT (L)	24.1 ± 4.2	23.1 ± 5.9	24.1 ± 5.0	33.5 ± 2.8
ASAT (L)	4.4 ± 1.0	4.3 ± 1.6	4.6 ± 1.0	5.2 ± 1.5
LSAT (L)	9.9 ± 2.0	9.2 ± 2.1	9.4 ± 2.0	10.6 ± 3.2
Visceral AT (L)	4.3 ± 2.0	3.8 ± 1.1	3.8 ± 1.1	4.2 ± 0.9
Skeletal Muscle (L)	33.2 ± 3.7	33.4 ± 5.0	33.7 ± 3.4	33.5 ± 2.8
Metabolic				
Fasting Insulin (uU/ml)	4.8 ± 3.5	5.8 ± 4.4	8.1 ± 5.1	7.9 ± 4.4
Fasting Glucose (uU/ml)	4.5 ± 0.6	4.8 ± 0.5	4.8 ± 0.6	4.9 ± 0.4
OGTT insulin area	216.0 ± 185.4	223.2 ± 196.9	221.4 ± 132.5	311.1±144.3
OGTT glucose area	26.9 ± 7.1	27.9 ± 5.2	27.3 ± 7.1	29.9 ± 5.1
IGAR	8.5 ± 5.5	8.4 ± 7.6	8.1 ± 4.6	10.4 ± 4.6
Glucose disposal (M)[4]	14.7 ± 6.0	12.1 ± 6.6	11.9 ± 5.5	12.0 ± 5.5
Oxidative[4]	3.1 ± 1.0	2.9 ± 1.7	2.4 ± 2.1	3.7 ± 2.8
Nonoxidative[4]	11.4 ± 6.3	11.5 ± 7.2	9.3 ± 5.3	8.3 ± 5.4

[1] Mean ± standard deviation. No between group differences ($p<0.05$) for the variables presented. C, control; DWL, diet-induced weight loss; EWS, exercise weight stable; EWL, exercise weight loss; BMI, body mass index; WHR, waist-to-hip circumference ratio; MRI, magnetic resonance imaging; AT, adipose tissue; ASAT, abdominal subcutaneous adipose tissue; LSAT, leg adipose tissue; IGAR, insulin-glucose area ratio.
[2] Calculated by using last rib circumference.
[3] Waist circumference at the umbilicus.
[4] Units: mg-min^{-1}-kg skeletal muscle

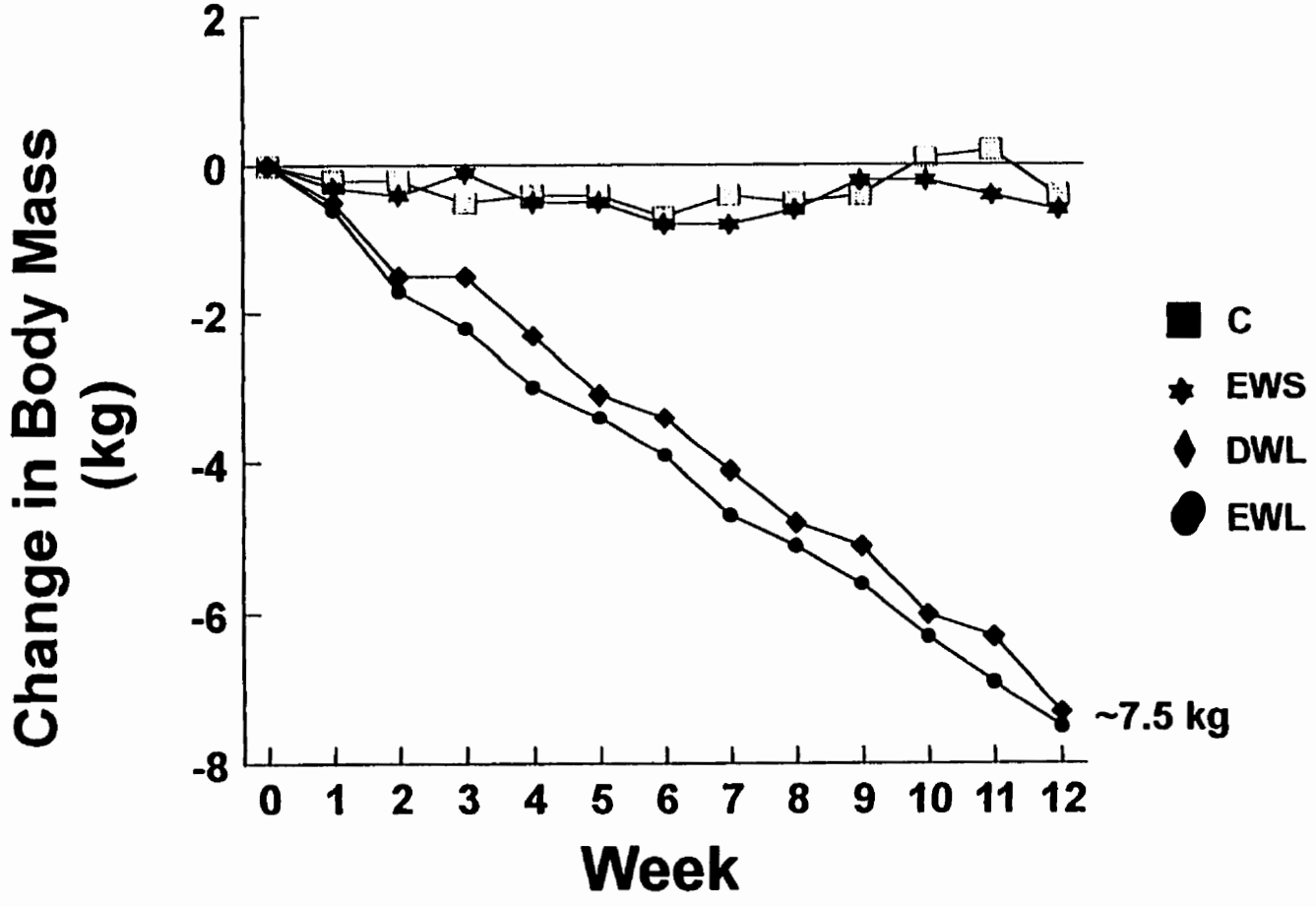

Figure 1. Rate of Exercise- or Diet-induced weight loss

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

Variable	C (n=7)		DWL (n=10)		EWS (n=11)		EWL (n=12)	
	Change		Change		Change		Change	
	Abs	%	Abs	%	Abs	%	Abs	%
Anthropometry								
Weight (kg)	-0.01	-0.4	-7.3[4,5]	-7.7	-0.7	-0.8	-7.5[4,5]	-7.5
WHR[2]	0.00	0.2	-0.04[4,7]	-4.3	-0.02	-2.7	-0.02	-2.4
Waist circumference[3]	0.2	0.2	-7.7[4,5]	-7.3	-2.8	-2.9	-6.4[4,5]	-5.9
MRI-measured variables (L)								
Total AT	-0.5	-1.8	-6.2[4,5]	-20.4	-1.7[4]	-5.6	-6.7[4,5]	-19.2
Subcutaneous AT	-0.3	-1.3	-3.9[4,5]	-17.0	-1.1[4]	-4.6	-4.8[4,5]	-17.9
ASAT	-0.1	-3.8	-0.8[4,5]	-18.9	-0.3[4]	-6.2	-0.9[4,5]	-18.6
LSAT	-0.1	-1.3	-1.4[4,5]	-15.8	-0.5[4]	-5.2	-1.5[4,5]	-14.1
Visceral AT	0.02	-1.3	-1.0[4,5,6]	-26.5	-0.5[4,6]	-14.2	-1.1[4,5,6]	-26.2
Skeletal Muscle	0.01	0.2	-1.6[4,7]	-4.7	0.5	1.5	-1.1	-3.4

[1] Mean ± standard deviation. C, control; DWL, diet-induced weight loss; EWS, exercise weight stable; EWL, exercise weight loss; BMI, body mass index; WHR, waist-to-hip circumference ratio; MRI, magnetic resonance imaging; AT, adipose tissue; ASAT, abdominal subcutaneous adipose tissue; FSAT, leg adipose tissue.
[2] Calculated by using last rib circumference.
[3] Waist circumference at the last rib (cm).
[4] Significant within-group differences $p<0.05$ (paired t-test with Bonferroni adjustment)
[5] Significant between-group differences; DWL, EWL > C, EWS; $p<0.05$
[6] Significant between-group differences DWL, EWL, EWS > C; $p<0.05$
[7] Significant between-group differences DWL > C; $p<0.05$

Dietary intake. The DWL (1918 kcal) and EWS (3406 kcal) groups were different ($p<0.05$) from each other and the EWL (2610 kcal) and C (2749 kcal) groups for daily caloric intake. As well, the DWL (40.9 g) group was different ($p<0.05$) from all other groups for total daily fat intake. The EWS (83.9 g) group was different ($p<0.05$) only from the DWL (40.9 g) and EWL (62.6 g) groups for total daily fat intake. No differences ($p>0.05$) were oberved for daily percent fat intake between any groups.

Change in MRI-measured variables. The changes observed in adipose tissue and skeletal muscle variables are given in Table 2.

VAT. The relative reductions in VAT (~26%) were not different ($p>0.10$) between the DWL and EWL groups but were different ($p<0.05$) compared to the EWS and C groups. The relative reduction in VAT in the two weight loss groups was significantly greater ($p<0.05$) than reductions in whole body SAT. Within the EWS group, a significant reduction ($p<0.05$) in VAT (~14%) was observed which was also different ($p>0.05$) from the control group.

SAT. The relative reductions in whole body SAT (~17.5%) and abdominal SAT (~19%) were not different between the DWL and EWL groups but were different compared to the EWS and C groups. Within the EWL group alone, the relative decrease observed for abdominal SAT (~19%) was greater ($p<0.01$) than that for gluteal-femoral SAT (~14%). Reductions in whole body (~4.6%) and ASAT (~4%) were also seen within the EWS group which were not different from the control group.

SM. Whereas SM was preserved within the control and both exercise groups ($p>0.05$), a significant 4.7% reduction ($p<0.01$) in SM was observed within the DWL group.

Change in metabolic variables.

OGTT. No changes in fasting glucose were observed within any group. Within the EWL group only, a significant improvement ($p<0.05$) in fasting insulin was observed which was not different from the other groups (Figure 2). A significant reduction ($p<0.05$) in insulin area was observed within the EWL group which was different from the EWS group only ($p<0.05$). Improvements ($p<0.05$) in glucose area were observed in the EWL and DWL groups which were not different ($p>0.05$) from each other but were different from the EWS group ($p<0.05$). Accordingly, a significant decrease ($p<0.05$) in insulin-glucose area ratio was observed in the EWL group only which was not different from any other group ($p>0.05$).

Hyperinsulinemic euglycemic clamp. During the last 30 minutes of the 4-h euglycemic clamp, pre- and post-clamp plasma insulin (52.4 $\pm$ 17.8 vs 50.0 $\pm$ 18.3 uU/ml) and whole blood glucose values (5.0 $\pm$ 0.2 vs 5.0 $\pm$ 0.2 uU/ml) were not different ($p>0.10$) for all subjects combined. Improvements ($p<0.05$) in rates of total (5.9 $\pm$ 3.5 vs. 5.7 $\pm$ 4.0 mg-min^{-1}-kg SM) and nonoxidative (5.9 $\pm$ 4.7 vs. 5.1 $\pm$ 5.4 mg-min^{-1}-kg SM) glucose disposal were not different ($p>0.10$) within the DWL and EWL groups (Figures 3 & 4) but were different from the C and EWS groups. Within the EWS group, a significant

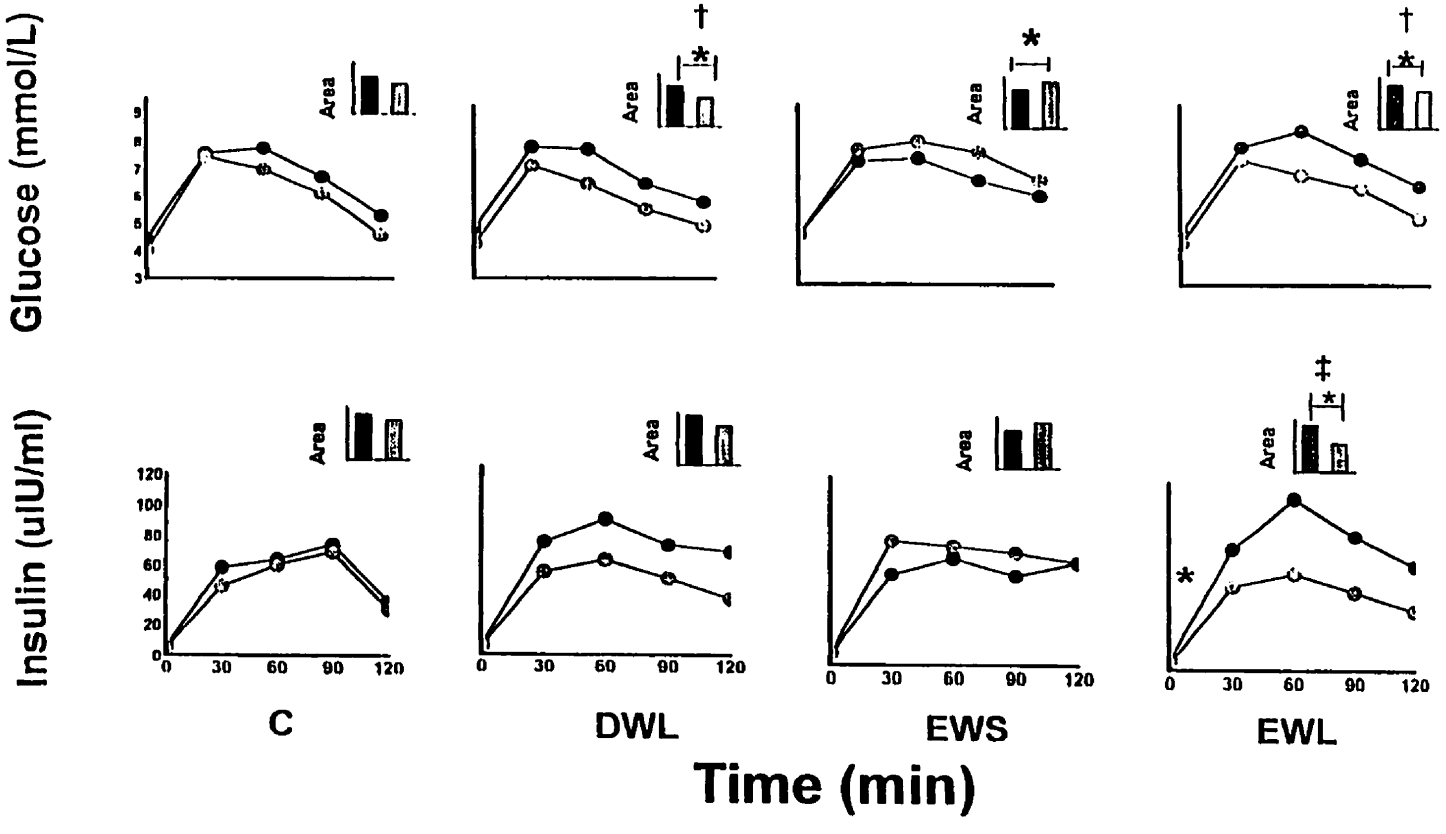

Figure 2. Effects of Exercise- or Diet-induced Weight Loss On OGTT Insulin and Glucose Values

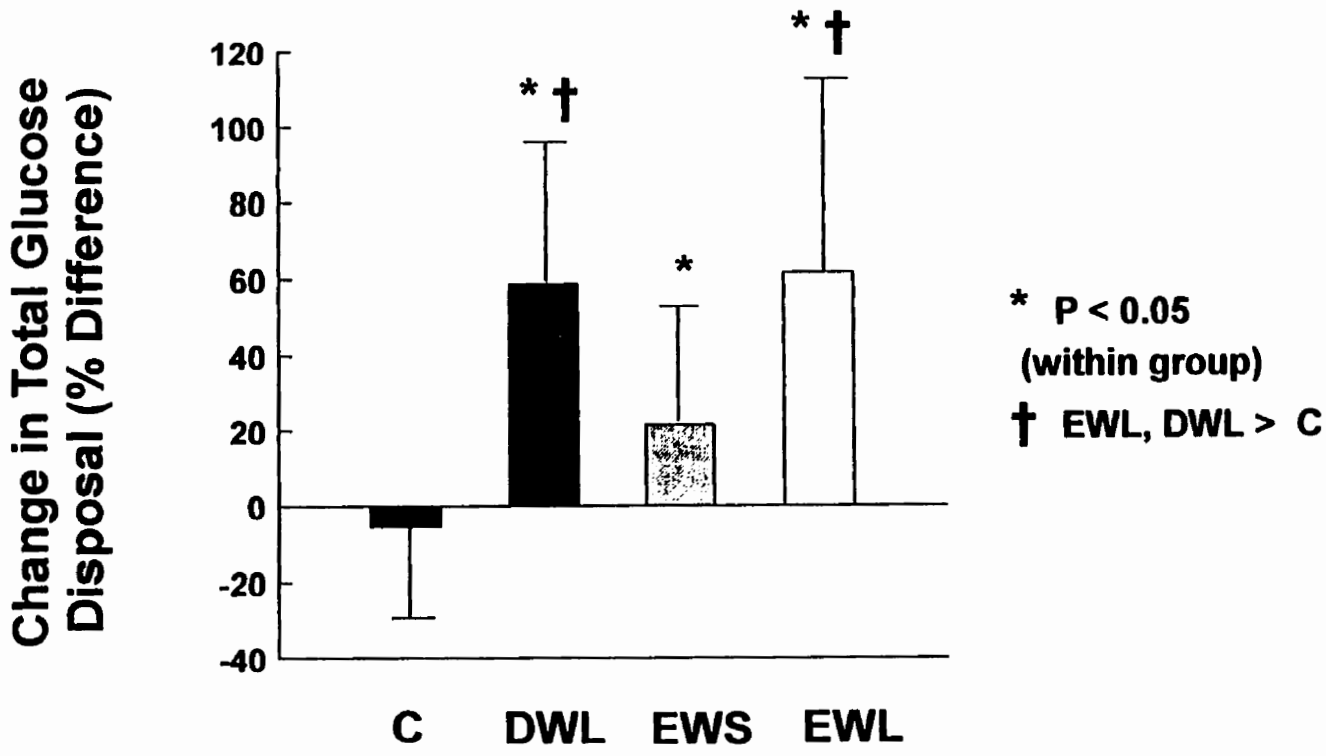

Figure 3. Effect of Exercise- or Diet-induced Weight Loss On Glucose Disposal

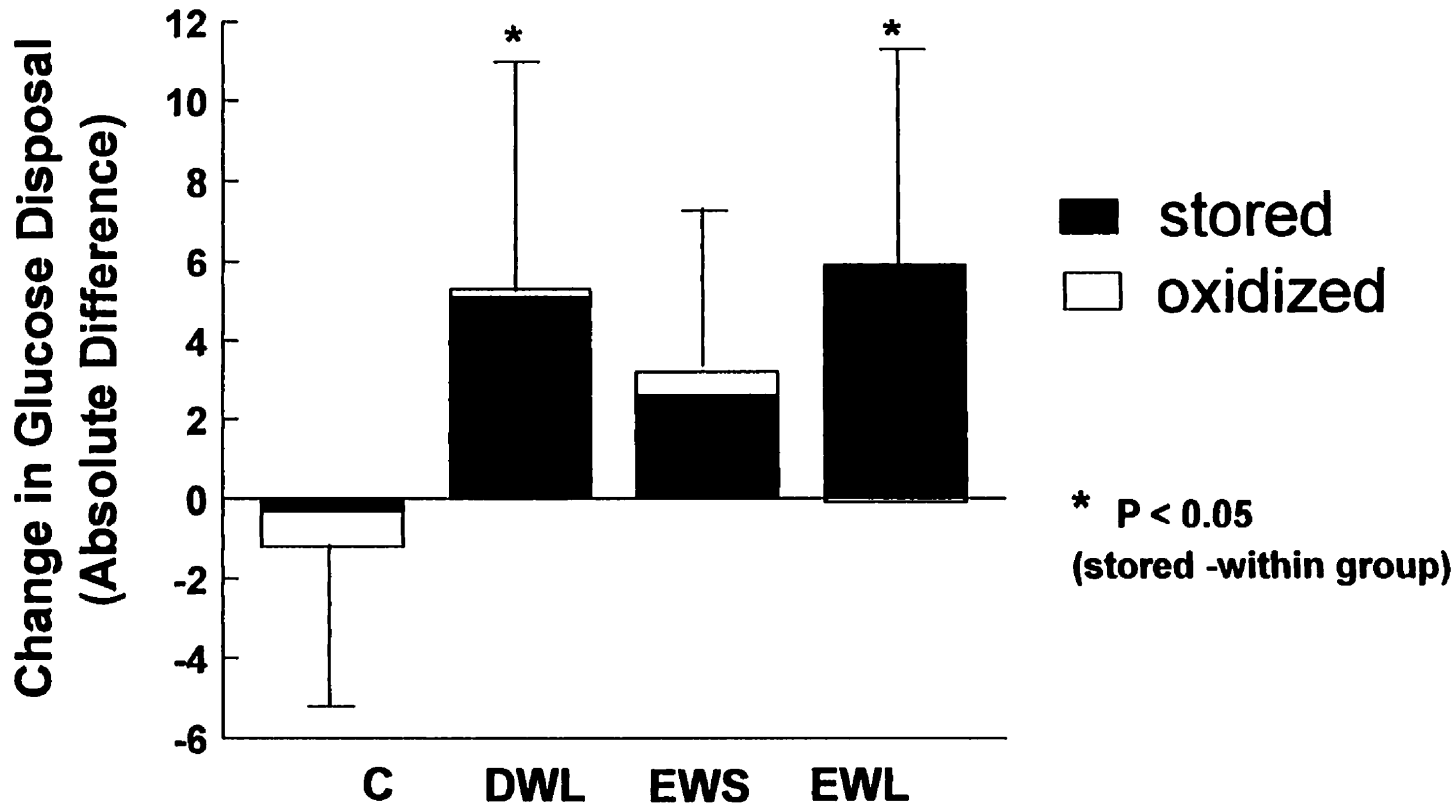

Figure 4. Effect of Exercise- and Diet-induced Weight Loss on Oxidative and Nonoxidative (Stored) Glucose Disposal

increase ($p<0.05$) in total glucose disposal (2.8 $\pm$ 3.7 mg-min^{-1}-kg SM) was observed, as well as, a trend ($p=0.06$) towards significance for nonoxidative glucose disposal (2.6 $\pm$ 4.2 mg-min^{-1}-kg SM). No change in any variable was observed in the C group ($p>0.05$).

DISCUSSION

The findings of this study clearly indicate that equivalent diet- or exercise-induced weight loss are associated with similar improvements in insulin sensitivity in obese men. In addition, aerobic exercise without weight loss is also associated with a smaller but still significant improvement in insulin sensitivity.

The mechanisms by which weight loss improves insulin sensitivity are not firmly established. It is generally proposed that reductions in adiposity are associated with concomitant reductions in systemic FFA flux which would beneficially affect skeletal muscle insulin sensitivity[66,107] and/or pancreatic secretion.[68,108] In addition, hepatic sensitivity to insulin is likely to be improved through a reduction in VAT-mediated portal FFA flux.[16] Plasma FFA flux was not measured in the present study. It is reasonable to assume, however, that the equivalent reductions observed for VAT (~27%) and SAT (~17%) in both weight loss groups are associated with corresponding decreases in both portal and systemic FFA concentrations respectively. Although the association between VAT and portal FFA concentrations has not been measured in vivo, a 32% reduction in systemic FFA levels has been reported in insulin resistant women in response to a 12kg weight loss which was associated with a corresponding improvement in insulin sensitivity.[31] This suggests that weight loss, regardless of modality, elicits common changes in body composition which may partially explain the equivalent 60% improvement in insulin sensitivity.

The finding that exercise-induced weight loss did not enhance insulin

sensitivity by comparison to diet-induced weight loss was unanticipated. It was expected that the adaptations in skeletal muscle morphology such as increases in GLUT4 transporters, oxidative enzymes, the percentage of FOG fibres, and blood flow known to occur in response to chronic exercise, would have potentiated the effects of weight loss on insulin sensitivity. However, after controlling for the reductions in VAT and SAT in the EWL group, the observed improvement in insulin sensitivity was no longer significant.

To further clarify whether exercise has effects on insulin sensitivity independent of weight loss, an exercise weight stable group was incorporated into the study design. The findings observed in the EWS group are consistent with the results in the EWL group. Within this group, a smaller but still significant improvement (~20%) in insulin sensitivity was observed. However, significant reductions were observed in VAT and ASAT. That abdominal fat was reduced without weight loss suggests that the EWS group was in a negative energy balance because the energy associated with the fat loss was greater than the energy gained from the small increase in lean tissue.[7] After controlling for the reductions in VAT and ASAT, the improvement in insulin sensitivity within the EWS group was no longer significant. These observations are consistent with the findings in both weight loss groups and thus, it would appear that the influence of exercise on insulin stimulated glucose disposal is subtle and that the beneficial effects are mediated in large measure by concomitant reductions in abdominal adiposity.

Consistent with the improvements in insulin sensitivity measured by the glucose clamp technique, improvements in OGTT-measured glucose tolerance were also observed in both weight loss groups which were not different. However, significant decreases in fasting insulin and OGTT insulin area were observed in the EWL group alone. Thus, the insulin required to dispose of a given quantity of glucose (insulinogenic index) demonstrates an improvement in insulin sensitivity in the EWL group which was not observed in the DWL group and is consistent with previous studies.[4,17] Although plasma C-peptide measurements were not taken, Torjesen et al[17] reported that significantly greater reductions in C-peptide occur after exercise combined with weight loss compared to diet-induced weight loss alone. Thus, the improvement in insulin sensitivity observed in the EWL group may reflect a decrease in pancreatic β-cell insulin secretion as a consequence of exercise.

Contrary to the improvements in OGTT variables in the EWL group, the subjects in the exercise weight stable group exhibited a deterioration of glucose tolerance. This is consistent with others who report similar observations in response to exercise training without weight loss.[3,86] Two arguments may partially explain these findings. First, the consumption of a hypercaloric diet (~700-1000kcal per day) has been shown to increase fasting insulin,[7] OGTT insulin[87] and glucose areas,[3] and decrease insulin-mediated glucose disposal.[87] Evidence suggests that increased caloric intake can lead to increased pancreatic β-cell stimulation, leading to islet cell hypertrophy and/or hyperplasia

and chronic hyperinsulinemia.[108] A deterioration of glucose tolerance could then result as an adaptive response to chronic hyperinsulinemia through the downregulation of peripheral insulin receptors.[108]

Although counterintuitive, this is not inconsistent with improvements in insulin sensitivity as measured by the euglycemic clamp technique. Unlike the OGTT which stimulates hepatic and pancreatic responses to a large, acute dose of glucose, inherent to the clamp is the maintenance of a constant euglycemic state via intravenous administration of glucose. Thus, the clamp technique effectively isolates insulin stimulated skeletal muscle glucose disposal by suppressing the integrative hepatic and pancreatic responses.[106] Therefore, a decreased ability to efficiently manage glucose immediately following an oral glucose challenge is not necessarily related to skeletal muscle glucose disposal measured in a fasted state.

A second argument which may help to explain the deterioration of glucose tolerance in the EWS group is the composition of carbohydrate consumed. In order to facilitate weight maintenance throughout the 12 week treatment period, the subjects within the EWS group consumed a large amount of fast absorbing carbohydrate which effectively trained the gut to absorb this type of carbohydrate more quickly.[109-111] Thus, a given 75 gram glucose drink will effectively increase absorption post-treatment.[109,110] Taken together, the quantity and composition of carbohydrate intake in the EWS group may have masked the effects of exercise per se on insulin sensitivity and OGTT insulin and glucose

variables.

The increased amount of glucose disposed into the muscle cell must either be oxidized or stored. It is reported that the body's capacity to increase carbohydrate storage in response to insulin is greater than its capacity to increase carbohydrate oxidation rates.[112] Therefore, an increase in glucose storage is a primary mechanism of increasing glucose disposal rates. This is consistent with the improvements observed in nonoxidative glucose disposal which accounted for ~90% of the increases in total glucose disposal across the three treatment groups respectively. It is also consistent with other studies which report similar findings in obese men and women.[98,113]

Apart from the reductions in adiposity, it has recently been suggested that skeletal muscle lipid content, measured by CT, is a strong, independent, positive correlate of insulin resistance in obese men and women.[44] Based on these initial reports, we measured SMIAT to test the hypothesis that SMIAT might be related to improvements in insulin sensitivity. However, despite increases in insulin sensitivity, no change in SMIAT was observed. It is possible that either subtle changes in SMIAT are not detected using MRI[114] or that MRI-measured SMIAT does not adequately represent CT-measured skeletal muscle lipid content.[44]

To our knowledge, this is the first study to examine the separate effects of diet- and exercise-induced weight loss on insulin sensitivity. Although these are preliminary findings, the similar beneficial increases in total and nonoxidative glucose disposal observed in both the diet- and exercise-induced weight loss groups suggests that improvements in insulin sensitivity are not mediated

through independent mechanisms. However, a larger subject pool might have decreased the standard deviation within each treatment group and enabled the separate influence of exercise to be teased out. Thus, reductions in adiposity, namely SAT and VAT, appear to be primarily responsible for these improvements. To a lesser extent, evidence suggests that exercise, in the absence of weight loss, also reduces abdominal adiposity and results in increases in total and nonoxidative glucose disposal. However, the separate and potential benefits of exercise on other cardiovascular risk factors such as hypertension and blood lipids remain to be determined.

In summary, these findings strongly support the hypthesis that both exercise- and diet-induced weight loss alone lead to significant improvements in insulin sensitivity and glucose tolerance. Exercise, in the absence of weight loss, appears to have significant beneficial effects on ameliorating metabolic complications of insulin resistance. In addition, because the exercise training program increased functional capacity and was well tolerated, it is prudent to recommend that routine exercise be included within a therapeutic strategy designed to improve insulin sensitivity and maintain weight loss.

4.0.0 CONCLUSIONS

The U.S. National Institute of Health (NIH) recently released clinical guidelines on the identification, evaluation, and treatment of obesity in adults.[1] At a prevalence rate of 55%, obesity is the second leading cause of preventable death and consequently poses a major public health challenge.[1] As a result, the principal recommendation from the NIH is weight loss in the order of a 10% reduction in body weight to decrease the risk of cardiovascular disease and all cause mortality. The findings of the present study, that weight loss in obese individuals improves insulin and glucose tolerance, confirms the appropriateness of this recommendation. In addition, it was shown that aerobic exercise alone increases insulin sensitivity with concomitant decreases in abdominal adiposity. Taken together, this suggests that both weight loss and exercise are successful strategies for the reduction of insulin resistance and obesity, both of which are cardiovascular risk factors and putative markers for non-insulin dependent diabetes mellitus.

Whether the improvements in insulin sensitivity and glucose tolerance are proportionate to the degree of weight loss is unknown. That is, would a greater magnitude of weight loss induce greater benefits? In addition, what minimum amount of weight loss is needed to induce significant clinical benefits? Whether age, race or sex differentially affect insulin sensitivity and glucose tolerance also remains to be determined. In particular, the testing of women using this study's protocol would present a unique opportunity to delineate sex differences.

Because women between the ages of 50 and 75 are at equal risk for developing CVD as men[115]and previous observations suggest that sex may influence the effects of weight loss on adipose tissue distribution,[42,116,117] it needs to be established whether women respond to both weight loss and exercise similar to men.

It also needs to be established whether exercise training which would induce the same total energy expenditure over a longer period of time elicits the same effects. In addition, the optimal intensity of exercise required to improve insulin sensitivity and glucose tolerance needs to be resolved. Furthermore, whether a training induced increase in $\dot{V}O_2$ max is necessary to improve these same variables remains unclear. Absent from this study are findings which report upon changes in other cardiovascular risk factors such as blood lipids, lipoproteins, and blood pressure. Whether exercise has independent effects separate from weight loss on these variables is unknown.

Once identified, this information would enable clinicians to appropriately prescribe both optimal weight loss and exercise of optimal quantity, intensity, duration and frequency to those who are obese and at increased risk for cardiovascular disease.

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Appendix A: Informed Consent

SCHOOL OF PHYSICAL AND HEALTH EDUCATION

Queen's University
Kingston, Canada
K7L 3N6

CONSENT TO ACT AS A SUBJECT IN A CLINICAL STUDY

TITLE: **Reduction in Cardiovascular Risk Factors and Visceral Adipose Tissue In Men: Separate Effects of Diet- and Exercise-Induced Weight Loss**

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SOURCE OF SUPPORT: MEDICAL RESEARCH COUNCIL

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.

BACKGROUND INFORMATION

Obesity is a major risk factor for cardiovascular disease and a public health problem. Recent information suggests that body fat located in the upper body region, in particular visceral or intra-abdominal body fat, conveys the greatest health risk. This is particularly true for men as they generally deposit more adipose tissue in the intra-abdominal region. Indeed, intra-abdominal fat is strongly associated with numerous risk factors that are predictors of cardiovascular disease. These findings suggest that if body fat reduction is to control the health risks associated with obesity, upper body obesity, in particular intra-abdominal body fat should be reduced. At the present time there are no known strategies that selectively reduce intra-abdominal body fat in men. Nor is it known whether reductions in intra-abdominal fat are related to concurrent reductions in cardiovascular risk factors.

Therefore, you are being asked to participate in a weight loss study, the principal objective of which will be to access the separate effects of diet and exercise on upper-body obesity, in particular intra-abdominal fat, and cardiovascular risk factors. The study will provide important information which will help to answer the following questions for upper-body obese men: 1) Is equivalent diet- and exercise-induced weight loss associated with a reduction in abdominal obesity and intra-abdominal fat, and if so, are there treatment differences? 2) Are there treatment differences with respect to improvements in cardiovascular risk factors? 3) Is the reduction in intra-abdominal fat related to concurrent improvements in cardiovascular risk factors independent of reductions in total fat, and if so, are there treatment differences? 4) Is exercise associated with significant improvements in cardiovascular risk factors in the absence of weight loss? Answers to these questions are of significance to the many Canadians, clinicians and practitioners who seek information regarding the benefits of diet and exercise as a means of reducing central obesity and improving cardiovascular risk factor profile.

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 your physician, or a medical doctor at the Kingston General Hospital. In addition to your medical examination, you will be required to have a fasting blood test that will be used to measure your glucose (sugar) and lipid (fat) levels. This procedure is explained in further detail on the last page of this form.

Study Protocol

The study will be 18 weeks in duration. The diet and exercise part of the study will last 12 weeks. The 12 week treatment period will be prefaced and followed by a 3 week weight maintenance 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 four groups: (1) diet - no weight loss, (2) diet - weight loss, (3) exercise - no weight loss, (4) exercise - weight loss.

Diet Procedure

All participants in each group will eat the same type of foods. The difference between groups will be how much food is eaten. The diet will consist of regular foods that you will buy and prepare yourself. All aspects of the diet plan will be explained to you by a dietician. 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 12 week study. All of your meetings with the dietitian will be at the Fitness Center in the Physical Education building at Queen's.

Group 1: For the entire study participants in this group will consume a diet that will maintain bodyweight. Thus there will be no weight loss.

Group 2: During a 3 week weight maintenance period we will determine the calories you need to maintain your weight. For the 12 weeks following you will be asked to reduce your caloric intake by the appropriate amount (usually 700 calories per day) to loose 1.5 lbs/week. After the 12 week period, you will be given a diet that will increase your total caloric intake to a level that will maintain your new weight.

Group 3: The participants in this group will exercise daily, however will maintain their weight for the entire study. Calories expended through exercise will be refed by increasing dietary caloric intake appropriately.

Group 4: For the entire study, participants in this group will consume a diet that maintains bodyweight for the baseline (first three weeks) period. The weight loss will be induced through exercise only.

Exercise Procedure

Groups 3 and 4: The participants in groups 3 and 4 will be required to perform aerobic exercise (walk/run type exercise) daily for 12 consecutive weeks. The aerobic exercise program will be designed to meet your abilities. The duration of the sessions will vary according to the time it takes for you to burn 700 kilocalories per exercise session. Most men would burn approximately 700 kilocalories by walking about 6 miles. Each exercise session will be supervised by a trained physical educator and will be performed within the Physical Education building at Queen's.

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 to 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 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 examination. 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 about 35 minutes. All MR images will be obtained at Kingston General Hospital.

Energy Expenditure

The amount of energy (calories) you need to maintain body weight at rest will be determined by measuring how much oxygen you use while resting. After an overnight fast, while resting a supine (on your back) position, we will measure the amount of oxygen you use while you breath normally into a mouthpiece attached to a specially designed oxygen meter. This is a routine procedure that takes about 45 minutes to complete.

A second proceedure used to determine how much energy you expend (use) in a day is described in Appendix A. Briefly, at the beginning of week 5, you will be asked to come to the Physical Education Center at about 8 am at which time you will be given a glass of water to drink that contains two stable isotopes (D_2O and ^{18}O). After a two week period, in the morning, we will collect a urine sample for the purpose of measuring the amount of these two isotopes that remain in your body. The information from this test will permit determination of energy intake (calories) and expenditure that occurred for each participant during the previous two week period. The two isotopes that you will be given are naturally occuring and are harmless at the dose provided.

Anthropometry/Summation of skinfolds

Many circumference and diameter measurements will be taken at numerous sites on the body. These measures 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.

Bioelectrical Impedance

This is a very simple and safe procedure requiring no more than 10 minutes to complete. Laying on your back, 7 electrodes will be placed on the surface of your right hand, shoulder, lower neck, leg and foot. One set of electrodes will introduce an alternating current that you can't feel into the body, while the other set record the resistance. The results are used to determine your body composition.

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 knealing 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 underwater weighing, the anthropometric measurements (bioelectrical impedence, skinfolds and MRI) will be obtained at the Kingston General Hospital.

Assessment of Cardiovascular Fitness

In addition to body composition measurements we will measure your cardiovascular fitness by using either a treadmill procedure. The test 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 want because of personal feelings of fatigue or discomfort.

The treadmill or bicycle test will involve risks comparable to any strenuous exercise situation. The 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. Your fitness test will be supervised by a trained graduate assistant and, when necessary, a medical doctor.

The 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.

Laboratory measurements (blood glucose (sugar) and lipid (fat) tests)

The measurement of how much sugar and lipids you have in your blood will be done at the Kingston General Hospital. Before and after the competion of the 12 week study, you will have a fasting blood test in order to measure blood sugar, blood fats and 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, you will be given a glucose tolerance test to determine your body's response to sugar. 81

For the glucose tolerance test, you will be asked to drink a fluid that contains 75 grams of sugar (like an orange drink). At 30 minute intervals for 2 hours after you drink the sugar solution, a small amount of blood will be taken from your arm for the purpose of measuring the amount of sugar in your blood. If your blood sugar levels are normal, you will participate in a second test on a separate day.

For the second test you will be admitted to the hospital the evening before, fasting after the evening meal and having not exercised on the prior day. The next morning catheters (needles) will be placed in a vein on the top of one hand and in a vein in the opposite arm. The catheter in your arm vein will be used to infuse glucose and insulin at a rate designed to keep your blood glucose (sugar) level normal for three hours. In addition, a small dose of radioactive glucose will be infused throughout the procedure to ensure that your liver is not releasing glucose during the study. The dose of radioactive glucose is very small and should not cause any health problems. Every 5 minutes during this procedure a small amount of blood will be taken from the vein in your hand to measure your blood sugar level to ensure that it remains normal.

The purpose of these tests is to determine your bodies sensitivity to insulin. Reduced sensitivity to insulin is a complication of obesity and may be associated with diabetes mellitus, high blood pressure, and other health problems. This test should not have any lasting side effects.

CONFIDENTIALITY

All information obtained during the course of this study is strictly confidential and your anonymity will be protected at all times. All subject information will be kept in locked files and will be available only to Dr. Robert Ross. Your identity will not be revealed in any description or publication.

VOLUNTARY CONSENT

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, Dr. Robert Hudson, 545-2973, or the head of the Department of Medicine, Dr. Peter Munt, 545-6327, should I have any questions about the study and, that I may keep a copy of this consent form for my records. My signature below means that I freely agreed to participate in this experimental study.

_____
Subject's Name (Please PRINT)

_____ _____
Date: **Subject's Signature**

_____
Witness' Signature

STATEMENT OF INVESTIGATOR

I, or one of my colleagues, have carefully explained to the subject the nature of the above research study. I certify that, to the best of my knowledge, the subject understands clearly the nature of the study and demands, benefits, and risks involved to participants in this study.

_____ _____
Principal Investigators Signature **Date**

Appendix A

Doubly Labelled Water (DLW) Testing Procedures

Day 1 of the DLW test:

- Arrive at the Fitness Centre in the morning before breakfast.
- You must **fast the night before** (no eating after 8pm the night before)
- You will be asked to give a saliva sample and a urine sample as soon as you arrive (this must be the second void of the day).
- Next you will be given a drink of doubly labelled water
- This entire process should take no more than 30 minutes
- You will be given 2 containers to take home and collect saliva samples both 3 and 4 hours after your DLW drink (ie: if you drink the water at 8:30 am you will take saliva samples at 11:30 and 12:30). We will provide you with a muffin and juice to eat after your DLW drink. You will be asked not to eat or drink anything else until after your last saliva sample.
- The saliva samples must be dropped off at the Fitness Centre the same day. We will ask you to give the second saliva sample at the Fitness Centre. (ie: your 11:30 sample can be done at work and you can return for 12:30 to give your last sample)

Day 2 of the test

- 24 hours after your Day 1 DLW dose, you will be asked to return and give a urine sample (second void of the day). ie: If you had the drink at 8:30 on Monday you would give a urine sample at 8:30 Tuesday.
- This sample should be done at the Fitness Centre

Day 7 of the test

- You will provide a urine sample (second void of the day) taken at the same time as your Day 2 sample
- This sample should be done at the Fitness Centre

Day 14 of the test

- This is a complete repeat of the Day 1 procedure
- You will be asked to fast from 8pm the night before, come in at the same time as Day 1, give a urine and saliva sample, drink the DLW water and give a 3 and 4 hour saliva sample. Once again, until the second saliva sample is completed, you will be asked not to eat or drink anything except the muffin and juice provided by us at the fitness centre.

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:

_____

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?

_____

_____

Volunteer Name: _____
Date of Birth: _____
Weight: _____

MRI RESEARCH SCREENING FORM

To ensure patient safety, this form MUST BE completed.

I have been informed how the MR examination is performed. I have answered the following questions.

I have:	Yes	No
surgical aneurysm clips	___	___
a cardiac Pacemaker	___	___
a cochlear implant	___	___
a prosthetic heart valve replacement	___	___
a neurostimulator device	___	___
metal fragments (in or around eyes in particular?)	___	___
a hearing aid	___	___
an implanted insulin/chemotherapy pump	___	___
an IUD	___	___
shrapnel	___	___
dentures	___	___
metal rods, plates, screws, or nails	___	___
claustrophobia/vertigo	___	___
removed my eye makeup	___	___
I am pregnant	___	___
had previous surgery	___	___

If yes, explain: _____

Volunteer Signature: _____ Date: _____

Witnessed by: _____ Date: _____

Body Part: _____ Research Physician: _____

Appendix C: Anthropometric Data Collection Forms

Anthropometric Data Collection Form

Subject Name: _____ **Test#** Pre / Post

Tester: _____ **Dates:** **BIA** _____ **Time:** _____

Anthro. _____ **Time:** _____

Gender: M / F

Age(years): _____ **Blood Pressure (mmHg):** _____

BIA Weight(kg): _____

Impedance (OHMS)

R: Leg _____ Torso _____ Arm _____ Whole R_____ L_____

Xc: Leg _____ Torso _____ Arm _____ Whole R_____ L_____

Stand. Height (cm): _____ **Arm Length(cm):** _____

Sitting Height(cm): _____ **Acromion Height(cm):** _____

Anthro Wt.(kg): _____

Skinfolds (mm)	**1**	**2**	**3**	**mean**
Subscapular				
Tricep				
Bicep				
Mid-Axillary				
Iliac Crest				
Abdomen				
Thigh				
Calf				

Circumference Measures (cm):

	1	2	mean
Chest:	_____	_____	_____
Hip:	_____	_____	_____

		1	2	mean
Waist (standing)	Last Rib:	_____	_____	_____
	Umb.:	_____	_____	_____
Waist (supine)	Last Rib:	_____	_____	_____
	Umb.:	_____	_____	_____

			1	2	mean		1	2	mean
Bicep:		Right:	_____	_____	_____	Left:	_____	_____	_____
Forearm:		Right:	_____	_____	_____	Left:	_____	_____	_____
Thigh:	Proximal	Right:	_____	_____	_____	Left:	_____	_____	_____
	Medial	Right:	_____	_____	_____	Left:	_____	_____	_____
	Distal	Right:	_____	_____	_____	Left:	_____	_____	_____
Calf:		Right:	_____	_____	_____	Left:	_____	_____	_____

Saggital Diameters (cm):		**1**	**2**	**mean**
Supine	Last rib	_____	_____	_____
	Umb	_____	_____	_____
	IC	_____	_____	_____
Standing	Last rib	_____	_____	_____
	Umb	_____	_____	_____
	IC	_____	_____	_____

Appendix D: Diet Record

Name: _____

Date: _____

Target kcal	Max. fat(g)

	Source (SEE BELOW)	Amount	Food	Calories	Fat (g)
Breakfast					
Breakfast Subtotals:					
Lunch					
Lunch Subtotals:					
Dinner					
Dinner Subtotals:					
Snacks					
Snacks Subtotals:					
Totals:				**A**	**B**

Please include source book and page or reference number (eg. T-5 = T-factor, page 5)

T = T-factor

P = Photocopied book

*= Food label

? = Best guess

Fat calories: **(B) x 9 kcal/g fat** _____ **C**

% kcal from fa **'(C / A) X 100 =** _____ **%**

Appendix E: Aerobic Exercise Recording Form

Name: _____ Week # _____

Date:																				
kcal:																				
Time	HR	Sp.	Elev.	HR	Sp.	Elev.	HR	Sp.	Elev.	HR	Sp.	Elev.	HR	Sp.	Elev.	HR	Sp.	Elev.	HR	Sp.	Elev.
0																				
5																				
10																				
15																				
20																				
25																				
30																				
35																				
40																				
45																				
50																				
55																				
60																				
65																				
70																				
75																				
80																				
85																				

Comments:

Appendix F: Diet Meetings Summary Form

Queens Diet and Exercise Study: Summary of Diet Sessions

Canada's Food Guide

A Variety of Foods = A Balance of Vitamins/Minerals

Recommended Servings (for 2000-2500 kcal diets)

8-10 Grain products(ie:1 slice bread, ½ bagel, ½ c rice)
6-8 Veg's and Fruits (ie:½c juice, ½c veg,1 med banana)
2-4 Milk products (ie: 1c milk, 3/4c yogurt, 50g cheese...)
2-3 Meat and alternat.(ie:3oz meat,½c beans,½ can tuna)

Make low fat, high fibre choices

A Matter of Fat

Fat is an essential part of our diet
Fat should be limited to < 30% of total calories

Much of the fat we eat is not "Visible", therefore watch for the hidden fats in: processed foods, meats(even lean), milk products, chocolate, cookies, spaghetti sauce, muffins, crackers, olives, eggs ....

Understanding the Fat Issue

There are 3 main dietary factors affecting the amount of build up you get in your arteries.
1. The amount of fat you eat (eat <30% calories from fat)
2. The amount of cholesterol you eat (animal FATS)
3. The type of fat you eat

Choose	**Avoid**
polyunsaturated and monounsaturated fats ie: canola oil, olive oil, corn oil, sunflower oil, non-hydrog. margarine.	Saturated and Trans fats ie: butter, hydrogenated margarines, coconut oil, palm oil, lard.

Food Labels

Don't be fooled by Nutrition Claims:

Fat free
In the US means <0.5g fat/serving (check svg. size)
In Canada means <0.1g fat/100g
Cholesterol free - is not fat free! Just no animal oil
Lite/Light - can mean light in flavour, colour, taste. Not necessarily light in calories or fat.

Lean meat - still has 17% calories from fat

Eating on the go

Plan ahead when you are busy:
- make big meals and pack leftovers for lunch
- pack healthy snacks to avoid buying quick fixes like muffins

Lowest fat fast food choices at:
Subway, Mr. Sub, Wendys, Swiss Chalet
Restaurant choices:
Steamed, poached, baked, broiled **are better than** fried, cream sauces, au gratin, buttery, basted. **Get a doggie bag**: they make good lunches and you don't feel so stuffed!

Beyond Beef

Red meat is an excellent source of IRON but, also is high in saturated fat. Reduce servings to lean 2-3 oz in size.

Meat alternatives are usually lower in fat and higher in fibre. Try replacing some of your meat with:
chick peas (hummus or chili)
kidney beans (chili or 3 bean salad)
black beans (tasty dips and burritos)
tofu (stirfrys and baking)
veggie: hot dogs, pepperoni, burgers

Fibre Facts

Fibre benefits: reduced risk of colon cancer, lower cholesterol in the blood, feel full longer, slow release of sugars into the blood.
High fibre foods: whole grain products, vegetables and fruit with the skin (where appropriate), legumes (beans)

Gradually build up to **25-30 grams** of fibre per day
Drink lots of fluids (6-8 glasses per day)

Low fat Cooking and Baking

Modifying recipes:
Reduce fat in your recipe by 2-3 tablespoons at a time. You may be able to omit ½ or even all the fat.
Replace 1 egg: with 2 egg whites to lower fat and cholesterol
Quick breads and Muffins: use grated fruit or vegetable to add moisture and then reduce the fat

Appendix G: Weight Record Form

Name _____ Group_____

Start weight_____kg_____lb Finish weight_____kg_____lb

Date	Time	Week	Goal Weight LBS	Weight KG	Weight LBS	Diff. from Goal (lbs)	Intake(kcal)	gfat	%fat	target kcal

Start Date_____ Finish Date _____

Appendix H: Formulae

Anthropometric Formulae

a) Body Mass Index:

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

b) Waist-to-Hip Circumference Ratio:

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

Metabolic Formulae

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

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

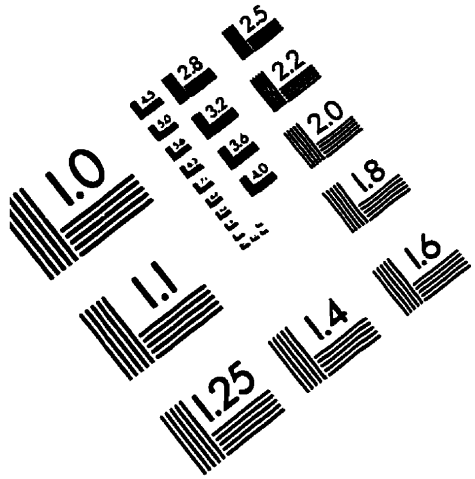
Where, t = time
[x] = glucose or insulin concentration at hours 0 to 2

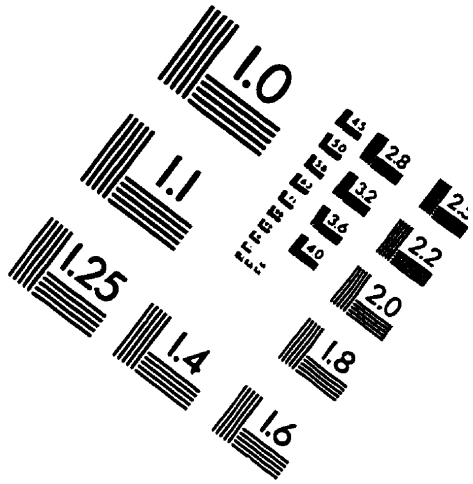
Units: Glucose Area (mmol/L · 2hr)
Insulin Area (mmol/L ·2hr)

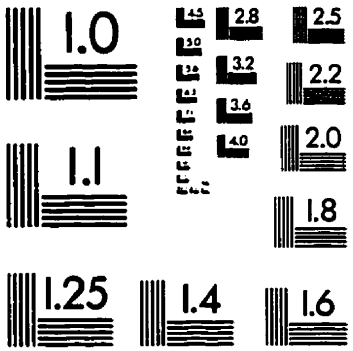
b) Insulin-to-Glucose Area Ratio:

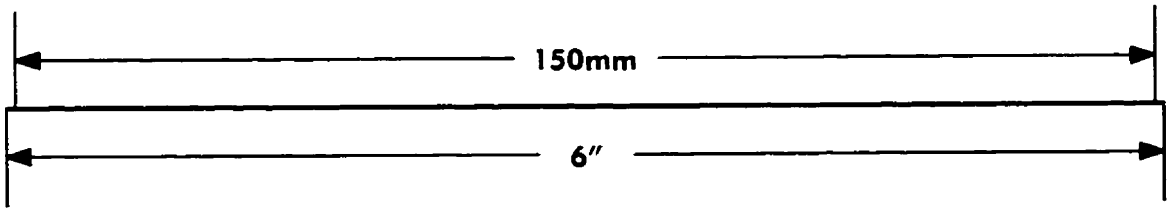
$$IGAR = \frac{\text{insulin area (pmol/L} \cdot \text{2hr)}}{\text{glucose area (pmol/L} \cdot \text{2hr)}}$$

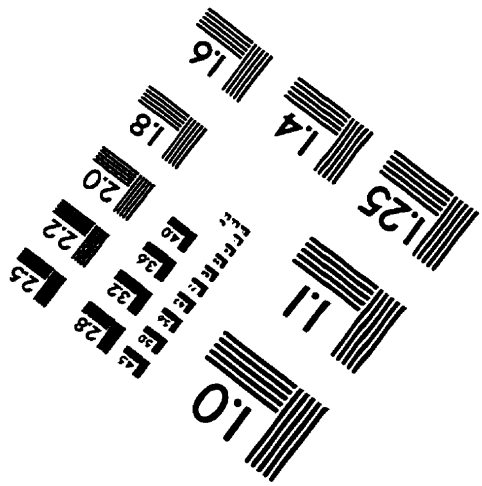
IMAGE EVALUATION TEST TARGET (QA-3)

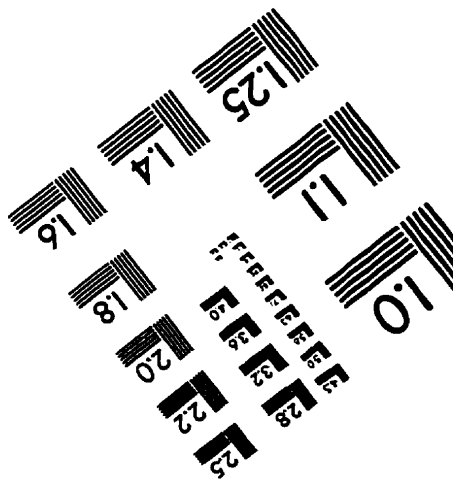












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