Metabolic Syndrome and Insulin Resistance: Underlying Causes and Modification by Exercise Training

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Abstract

Metabolic syndrome (MS) is a collection of cardiometabolic risk factors that includes obesity, insulin resistance, hypertension, and dyslipidemia. Although there has been significant debate regarding the criteria and concept of the syndrome, this clustering of risk factors is unequivocally linked to an increased risk of developing type 2 diabetes and cardiovascular disease. Regardless of the true definition, based on current population estimates, nearly 100 million have MS. It is often characterized by insulin resistance, which some have suggested is a major underpinning link between physical inactivity and MS. The purpose of this review is to: (i) provide an overview of the history, causes and clinical aspects of MS, (ii) review the molecular mechanisms of insulin action and the causes of insulin resistance, and (iii) discuss the epidemiological and intervention data on the effects of exercise on MS and insulin sensitivity.

Introduction

One earliest references to metabolic syndrome (MS) can be traced back to Camus in 1966 (97). However, in 1988 Gerald Reaven gave the Banting Lecture at the American Diabetes Association national meeting and introduced the concept of what he called "Syndrome X," an aggregation of independent, coronary heart disease (CHD) risk factors in the same individual. The risk factors included in the syndrome were insulin resistance, defined as the inability of insulin to optimally stimulate the transport of glucose into the body's cell (hyperinsulinemia or impared glucose tolerance) (*note*: for purposes of this review, we will use the terms insulin resistance and insulin sensitivity interchangeably), hypertension, hypertriglyceridemia, and low, high-density lipotrotein cholesterol (HDL) (522). The following year Kaplan (333) called it "the deadly quartet" and Foster (205) described it as "a secret killer." None of these acronyms described the point made by Reaven in his Banting

Lecture that insulin resistance/hyperinsulinemia might be the underlying cause of the syndrome. Reaven also suggested that insulin resistance/hyperinsulinemia was an underlying risk factor for T2D, which, at the time, was referred to as noninsulin-dependent diabetes mellitus. In 1991, Ferrannini et al. (194) published an article entitled "Hyperinsulinemia: the key feature of a cardiovascular and metabolic syndrome," terms that better reflected Reaven's point of view. Furthermore, use of the term MS acknowledges that this array of factors is associated with abnormal carbohydrate and lipid metabolism. These authors emphasized that insulin resistance was the underlying factor and, once acquired, those with a genetic predisposition would develop all the other aspects of the disorder. However, Ferrannini et al. pointed out that dietary intake and exercise could reduce insulin resistance, suggesting that the final phenotypic expression involves both genetic and acquired influences. Additionally, Haffner et al. (249) coined the term "insulin resistance syndrome" for the disorder to highlight the fact that insulin resistance preceded other aspects of the syndrome. Some individuals still use the term insulin resistance syndrome but now the term "metabolic syndrome" is more commonly used to describe the aggregation of multiple CHD and T2D risk factors. Insulin sensitivity/resistance is closely related to MS and the major manifestation of MS is coronary artery disease (CAD). In the Insulin Resistance Atherosclerosis Study (IRAS), a multi-ethnic cohort with variable glucose tolerance, the two lowest quintiles of insulin sensitivity, as estimated by frequently sampled intravenous glucose tolerance tests (FSIGT), had ORs of 2.4 and 4.7 for CAD compared with the highest quintile (535).

In addition to the factors mentioned by Reaven, Kaplan suggested that upper-body or visceral obesity needs to be considered as part of the syndrome and as a major risk factor for CHD and T2D, independent of overall obesity. Subsequently, many studies confirmed that visceral obesity (553) was correlated with the MS and its individual components, as reviewed by Despres and Lemieux (155, 156). As more studies were conducted, additional CHD risk factors were added to the syndrome. Landin et al. (380) suggested that elevated serum levels of fibrinogen and tissue plasminogen activator inhibitor were related to metabolic factors for CHD. Small dense particles of low-density lipoprotein (LDL) were found to have increased atherogenicity compared to large, less dense particles (604). Subsequently Barakat et al (46) and Reaven et al. (526) reported that small dense LDL particles were associated with insulin resistance, obesity, and T2D. Thus, small dense LDL was added to the list of factors associated with the MS. The combination of elevated serum triglycerides (TG), depressed HDL, and elevated small-dense LDL particles is commonly referred to as dyslipidemia.

Other aspects of atherosclerosis development and myocardial infarction that have been linked with the MS include endothelial dysfunction (663), inflammation (395, 718), and oxidative stress (661). In an animal model of diet-induced MS (50), Reil et al. (528) reported defective bradykinin and acetylcholine-induced relaxation with a normal response to nitroprusside in isolated artery strips. When the animals were switched from the high-fat, sucrose diet back to a low-fat, starch diet for 4 weeks, the endothelium-dependent defects were eliminated. In a recent study of 819 subjects, Suzuki et al. (621) reported that those

subjects with the MS (N = 377) had lower flow-mediated dilation, which is a measure of conduit artery endothelial function, compared to that of subjects without MS.

High-sensitivity C-reactive protein (CRP), a marker for systemic inflammation, is commonly used clinically to evaluate risk in primary and secondary prevention of vascular disease (648). Not surprisingly, CRP has been associated with the MS. Obesity is now recognized as a state of chronic, low-grade inflammation and is associated with increased serum markers of inflammation and oxidative stress (196, 345), and MS has been linked with inflammation and oxidative stress (196, 254). However, as pointed out by Despres and Lemieux (155) in their review, not all obese individuals have the MS. In a recent study, Van Guilder et al. (661) studied three groups of subjects: normal weight, obese without MS, and obese with MS. Plasma CRP was significantly elevated in both obese groups compared to the normal weight group but was significantly elevated in the obese with MS compared to obese without MS. Other markers of inflammation including tumor necrosis factor-alpha (TNFα), interleukin (IL)-6 and IL-18 were only elevated in the obese with MS. Ox-LDL was measured as a marker of oxidative stress and was found to be elevated in both obese groups; the obese with MS was significantly higher that the obese without MS. These results suggest that increased oxidative stress and inflammation might be involved in the development of the MS. In addition, inflamed adipose tissue, characterized by increased monocyte infiltration and cytokine production, (24, 300, 563) has recently been associated with MS.

What Causes the Metabolic Syndrome?

When Reaven introduced the concept in 1988, he suggested that insulin resistance/ hyperinsulinemia was the underlying cause. His suggestion was based on cross-sectional data showing associations between hyperinsulinemia and the other aspects of the syndrome in patients as well as experimental studies on rodents fed diets high in sucrose or fructose. Support for the role of hyperinsulinemia in the development of the syndrome came in 1992 when Haffner et al. (249) reported 8 years prospective data from 2217 subjects in the San Antonio Heart Study showing that fasting hyperinsulinemia preceded the development of other aspects of the syndrome including hypertension, hypertriglyceridemia, and depressed HDL-C, as well as the development of T2D. After adjusting for baseline obesity and fat distribution, as well as weight gain over the period of observation, significant relationships between insulin and the other factors remained present. Further support for the importance of hyperinsulinemia came from an animal study by Barnard et al. (50). Feeding rodents a high-fat sucrose diet resulted in skeletal muscle insulin resistance and hyperinsulinemia within a few weeks before any change in body fat or abdominal fat cell size. The animals subsequently developed hypertriglyceridemia, enhanced clotting and hypertension, that is, the MS.

Through his Banting Lecture, Reaven suggested some mechanisms to explain how insulin resistance/ hyperinsulinemia might cause the other aspects of the MS. He pointed out that hypertension was associated with elevated levels of plasma catecholamines and suggested enhanced sympathetic nervous system activity as a contributing mechanism. He also cited studies reporting that insulin caused the kidney to promote sodium reabsorption and increase

plasma volume. For the increase in TG associated with the syndrome, he cited a study reporting that in perfused rat livers insulin increased very low density lipoprotein (VLDL) TG production. The San Antonio group provided further support for these mechanisms in two subsequent papers (148, 248). They pointed out that although some data had shown that acutely, insulin could be a vasodilator [as reviewed by reference (54)], prolonged insulin resistance and hyperinsulinemia was associated with hypertension and could be due to several mechanisms including an overactive sympathetic nervous system, sodium retention, altered membrane ion transport, and proliferation of vascular smooth muscle cells. They also stated that hyperinsulinemia would increase liver production of VLDL to increase serum TG, while at the same time reduce high-density lipoprotein production and serum HDL-C. These data all support Reaven's suggestion that insulin resistance/hyperinsulinemia is the primary factor responsible for the MS. Using the insulin/glucose clamp technique, DeFronzo and Ferrannini (148) demonstrated that cellular resistance to insulin action subtends hyperinsulinemia. The important question, however, is what causes the insulin resistance. Reaven suggested that elevated plasma-free fatty acids were involved in the development of insulin resistance, as originally suggested by Randle et al. (518), and presented some experimental data to support his claim (522).

Based on the 1947 observation of Vague (657), women with upper body obesity were far more likely to get heart disease and T2D compared to women with lower body obesity. Kaplan (333), in 1989, suggested that obesity, especially abdominal obesity, was the primary factor that induced hyper-insulinemia and subsequently the MS. Today, a well-accepted theory on a cause of insulin resistance and the MS is excess abdominal fat. Many studies using waist-to-hip ratio, computed tomography, or similar measures have shown that abdominal fat, especially visceral fat, correlates best with the MS and CHD risk (155). In 1990, Bjorntrop (69) proposed that abdominal or "portal adipose tissue" would release excess free fatty acid that would go directly to the liver, increasing TG formation while also suppressing insulin clearance, resulting in hyperinsulinemia. He further stated that the lipid mobilizing capacity of portal adipose tissue is pronounced in men and abdominally obese women because of an abundance of β-adrenergic receptors with little α-adrenergic inhibition. In their review, Despres and Lemieux (155) discuss other factors associated with abdominal obesity that might be involved in the MS, including increased inflammatory cytokine production by fat cells along with reduced adiponectin release. However, they point out that while an abundance of data show that excess visceral fat is associated with both atherogenic and diabetogenic risk factors, an important question is whether visceral fat is a causal factor or simply a marker for the MS. The prospective studies discussed earlier suggest that it is a marker as opposed to being the true underlying cause.

In an editorial, Landsberg (381) stated, "the most important environmental cause of insulin resistance is central obesity, but a list would also include sedentary lifestyle and high-fat intake." We would reverse the order to state that the most important cause of insulin resistance is a high-fat, refined-carbohydrate diet and physical inactivity, which are exacerbated by genetic predispositions, such as the development of abdominal obesity, as was suggested in a review by Barnard and Wen published in 1994 (51). Two early studies from the Reaven group reported that feeding rodents diets high in sucrose or fructose resulted in insulin resistance and hyperinsulinemia in as little as two weeks while on the

diets (527, 722). A series of studies from the Barnard laboratory (49, 50, 52, 53, 237, 238, 543, 715) demonstrated that when rodents were placed on a high-fat and/or refined-carbohydrate diet compared to a low-fat, starch diet, skeletal muscle insulin resistance with elevated serum insulin developed in a few weeks, prior to differences in body weight or body fat. The high-fat, refined-carbohydrate diet eventually led to hypertension, hypertriglyceridemia, and enhanced clotting as well as obesity, which are characteristics of the MS (49, 50). The observation of diet-induced skeletal muscle insulin resistance is significant, as skeletal muscle is the most important target tissue for insulin action, is the primary site for glucose disposal following a meal (147), and shows a major defect in insulin-resistant T2D patients (147). The diet-induced insulin resistance in the rodent model was associated with a decrease in insulin receptor autophosphorylation and tyrosine kinase activity similar to the defects observed in muscle from type 2 diabetic patients (53, 575, 714). The mechanisms underlying these and other defects that lead to insulin resistance are discussed in detail later.

Clinical Aspects of the Metabolic Syndrome

Since Reaven introduced the concept in 1988, thousands of papers related to MS have been published. A search of PubMed in August 2010 resulted in over 31,000 responses demonstrating a high level of interest in the concept and in 2006 *The Journal of the CardioMetabolic Syndrome* appeared. The reason for such interest is not surprising as Ford et al. (201, 202) have estimated that using the revised National Cholesterol Education Program (NCEP)/Adult Treatment Panel (ATP) III criteria (182, 240, 241) showed that between 32% and 34% all US adults (31–34% of men and 33–35% of women) have MS. Based on International Diabetes Federation (IDF) criteria, estimates were 39%, with 40% of men and 38% of women (201); similar classification occurred 93% of the time for the two definitions. This equates to greater than 100 million in the US based on a population estimate of 310 million. A multiethnic representative US sample of 12,363 men and women 20 years and older from the third National Health and Nutrition Examination Survey (NHANES) were evaluated for MS as defined by the ATP III diagnostic criteria (abdominal obesity, hypertriglyceridemia, low HDL, hypertension, and fasting hyperglycemia) and the disorder was found to be present in 22.8% and 22.6% of the men and women, respectively. MS was present in 4.6%, 22.4%, and 59.6% of normal-weight, overweight, and obese men, respectively, and physical inactivity was associated with an increased risk of developing the syndrome (488). When Reaven published his paper in 1988 he stated,

> "[B]ased on available data, it is possible to suggest that there is a series of related
> variables – Syndrome X – that tend to occur in the same individual and may be of
> enormous importance in the genesis of coronary artery disease (CAD)" (522).

Many studies have investigated the syndrome as a possible independent risk factor for CHD. In a 2007 meta-analysis of longitudinal studies involving 172,573 individuals, Gami et al. (219) reported that the relative risk (RR) for individuals with the MS compared to those without the MS was 1.78 for cardiovascular events and death; for women the RR was 2.63. After adjusting for traditional cardiovascular risk factors those with the MS still had a RR of 1.54 for cardiovascular events and death. In 2006, results from another meta-analysis conducted by Galassi et al. (217) showed that the MS was associated with increased

incidence of cardiovascular disease (CVD) (RR 1.53), CHD (RR 1.52), and stroke (RR 1.76). Individuals with the MS had increased all-cause mortality (RR 1.35) and cardiovascular mortality (RR 1.74). Again, the risks were higher in women compared to men.

In his 1988 paper, Reaven pointed out that resistance to insulin-stimulated glucose uptake was present not only in patients with T2D but also in a majority of individuals with impaired glucose tolerance (IGT) as well as those with the MS. Thus, it was speculated that individuals with the MS and insulin resistance might be at high risk for the development of T2D; this turned out to be the case. In a meta-analysis of 16 cohort studies, Ford et al. (204) reported that the RR for T2D in individuals with the MS ranged from 4.42 to 5.17 depending on the criteria used to define the MS. The authors concluded that the MS, however defined, has a stronger association with T2D than previously demonstrated for CHD.

Although the MS appears to be a well-accepted syndrome associated with increased risk for both CHD and T2D, the use of the term MS has been questioned for a variety of reasons (326, 523, 525). These include, but are not limited to: (i) it occurs only in insulin-resistant persons, which the ATP III criteria does not directly evaluate and, currently, there is no simple clinical measure for insulin resistance; (ii) many individuals may not satisfy the arbitrary cutoffs for diagnosis, that is, might be sufficiently insulin resistant and have additional CAD risk factors to be at significant increased CVD risk; and (iii) it has low clinical utility since treating the individual factors may be a less effective approach than addressing the underlying problem, which is generally lifestyle-induced insulin resistance in genetically susceptible individuals. In fact, published data support this contention (398).

In 2005, a joint statement from the American Diabetes Association and the European Association for the Study of Diabetes questioned the existence of the MS (326). The groups undertook a review of the literature and concluded:

> "While there is no question that certain CVD risk factors are prone to cluster, we found that the MS has been imprecisely defined, there is a lack of certainty regarding its pathogenesis, and there is considerable doubt regarding its value as a CVD risk marker. Our analysis indicates that too much critically important information is missing to warrant its designation as a 'syndrome.'"

The fact that the MS is imprecisely defined stems from the different definitions adopted by different organizations to identify individuals with the syndrome. Due to the fact that insulin resistance is rarely measured clinically, other criteria have been adopted to identify individuals who might be insulin resistant and possess the MS. To date at least six different definitions from five different agencies have been proposed to define adults with the MS, with the criteria being dramatically varied among agencies. The problem is more pronounced in the pediatric arena where, according to Morrison et al. (453), as many as 40 different definitions have been used to identify youth with the MS. This is important as, not surprisingly, pediatric MS predicts adult MS, although in this cohort, body mass index (BMI) risk estimates were similar (415).

In 1998, a consultation group from the World Health Organization (WHO) published the first clinical criterion to define adults with MS (18). These criteria were proposed in part as simple tools to help health professionals identify individuals likely to have a clustering of metabolic abnormalities. Following Reaven's suggestion, this group emphasized the importance of insulin resistance and suggested several clinical measures that could be used to assess insulin resistance, that is, IGT, impaired fasting glucose (IFG), T2D mellitus, or impaired glucose disposal demonstrated with the insulin clamp test. In addition to a measure of insulin resistance to qualify for the MS, individuals must possess two of the following risk factors: obesity, hypertension, high TG, reduced HDL-C, or macroalbuminuria.

In 1999, the European Group for the Study of Insulin Resistance (EGIR) proposed a slight modification from what had been proposed by the WHO (41). This group used the term *insulin resistance syndrome* as opposed to the MS. In addition, they suggested also requiring evidence of insulin resistance, as measured by plasma insulin above the upper quartile for the population plus two other factors for the diagnosis, that is, abdominal obesity, hypertension, elevated TG, reduced HDL-C, or elevated plasma glucose. Interestingly, this group excluded T2D as a criterion.

In 2001, the NCEP/ATP III introduced alternative clinical criteria to Reaven's initially proposed definition to diagnose the syndrome and did not require any measure of insulin resistance, but did require three of the following five criteria, that is, elevated fasting glucose or a diagnosis of T2D, abdominal obesity, elevated blood pressure, elevated TG, or reduced HDL-C (1). Like the EGIR, the ATP III emphasized the importance of abdominal obesity and noted that some ethnic groups show signs of insulin resistance at lower levels of waist circumference than used as criteria for diagnosis of the syndrome.

In 2003, the American Association of Clinical Endocrinologists (AACE) also used the term *insulin resistance syndrome* and provided their criteria for the diagnosis including IGT or IFG with no specific number of other factors required but the left the decision to be based upon the judgment of the clinician. The major additional criteria to be considered included elevated TG, elevated blood pressure, reduced HDL-C and obesity (BMI). Other factors that could be used in the judgment included family history of atherosclerotic vascular disease or T2D, polycystic ovary syndrome, and hyperglycemia. The presence of T2D was excluded.

In 2005, the IDF (303) provided their criteria to define the MS. Although some of the members of the IDF writing group were also on the WHO consultation group, they replaced the requirement for a direct measure of insulin resistance with emphasis on abdominal obesity as it correlates well with insulin resistance. When abdominal obesity is present, two additional factors listed in the ATP III criteria were sufficient to define the syndrome. The definition of abdominal obesity involved waist circumference that was adjusted for different ethnic groups. For people of European origin (Europeans and Americans) thresholds were set at 94 cm or more for men and 80 cm or more for women. For Asian populations, excluding Japanese, the thresholds were set at 90 cm or more for men and 80 cm or more for women; while the thresholds for Japanese were set at 85 cm or more for men and 90 cm or more for women. The other difference from the ATP III criteria was a lower IFG value (100 mg/dL). This same value was also adopted by the ATP III group in 2005 (ATP III-R) (241).

In addition, the lower fasting glucose, ATP III-R added the presence of drug treatment for TG, reduced HDL-C, hypertension, or elevated glucose as additional criteria. The precise cut values for the various criteria used by the different agencies have been outlined in the article describing ATP III-R criteria by Grundy et al. (241).

Thus, one would have to agree with the statement from the two diabetes groups, " . . . the MS has been imprecisely defined . . ." (326). This lack of precision in defining the syndrome has led to different results in different studies depending on the criteria used to define the syndrome. Katzmarzyk et al. (339) conducted a longitudinal study of 20,789 US men aged 20 to 83 years who were followed for 11.4 years. They identified men with the MS using three different methods, the original ATP III, ATP III-R, and IDF. It was found that at baseline the percentage of men with the MS was 19.7, 27, and 30, according to the different criteria. The RR for cardiovascular mortality for men with the MS was 1.79, 1.67, and 1.67 according to ATP III, ATP III-R, and IDF, respectively; however, there were only 213 cardiovascular deaths total. In a similar study, Benetos et al. (59) followed 84,730 French men and women 40 years or more of age for 4.7 years. They also used three different methods to identify the MS, ATP III, IDF, and ATP III-R. The percent of individuals identified as having the MS were 9.6, 21.6, and 16.5. The RR for cardiovascular mortality was 2.05, 1.77, or 1.64 for the ATP III, ATP III-R, and IDF, respectively; again, the total number of cardiovascular deaths was small (104) over the 4.7 years. The results from these two studies on large populations clearly show that the different criteria used by the different agencies to define individuals with the MS varies dramatically, by as much as 50%. Regardless of the criteria used to identify the MS, both studies showed that the presence of the MS by any of three different definitions increased the risk for cardiovascular mortality but also with significant variability in risk.

Although the data clearly show that the presence of the MS increases the risk for CVD and cardiovascular mortality, some have questioned whether there is a need to identify such patients, especially since: (i) MS may not predict cardiovascular events better than the sum of its components and (ii) none of the definitions include traditional, well-established cardiovascular risk factors, such as smoking, total or LDL cholesterol and age factors that are standard clinical measures, along with blood pressure and HDL-C that are incorporated into the Framingham Risk Score (FRS). Wannamethee et al. (677) reported a prospective study of 5128 British men with no initial history of CHD or T2D, followed for 20 years. They compared the FRS with the MS identified by ATP III-R criteria as predictors for CHD, stroke, or T2D. Using ATP III-R criteria for MS the RR for CHD was 1.64, for stroke was 1.61 and for T2D was 3.57. When they compared the MS with the FRS, they found that the FRS was superior to the MS in predicting CHD and stroke but found it to be inferior in predicting T2D. de Zeeuw and Bakker (146) conducted a similar study of 8217 Dutch men and women followed for a median 6.5 years. The results showed that the FRS was superior to the MS in predicting cardiovascular mortality/morbidity. The FRS appears to be superior in identifying CHD risk not only because it contains the well-established CHD risk factors not included in the MS, but also because it is based on continuous data, as opposed to the discrete cutoff points used to identify the MS. Even Reaven (524) criticized the ATP III criteria, stating that the cut points are arbitrary and not based on sound scientific data, while insulin sensitivity is continuous in normal populations with at least a sixfold variation

between the most sensitive and the most insulin-resistant individuals. Thus, he states that there is no simple, objective way to classify an individual as being insulin resistant, which he claimed was the basis for his syndrome X.

Despite the criticisms, the MS has been strongly defended, especially since it is a powerful predictor for T2D [80% of those with T2D have MS (309)] and a major risk factor for CHD (233, 309). For example, in a cohort of 3323 middle-aged adults, the MS RR was 2.88 for CVD, 2.54 for CHD, and 6.92 for T2D in men and 2.25, 1.54, and 6.90 in women, respectively (695). Sattar et al. (571) noted that men with four or five features of the syndrome have been estimated to have a 3.7-fold increase in risk for CAD and a 24-fold increased risk for T2D compared with men with none, while Klein et al. (358) reported 2.5% and 1.1% incidence of CVD and T2D, respectively, in those with one component of the MS; meanwhile 15% and 18% developed these diseases in those with four or more components of the syndrome.

MS is also a predictor of mortality. For example Lakka et al. (377) reported that middle-aged men with the MS exhibited a 2.9- to 4.2-fold risk of CHD death over an 11-year follow-up compared to healthy men and after adjustment for conventional risk factors. In addition, all-cause mortality was increased 2.3-fold in those in the highest quartile for MS factors. In the Botnia study of 4483 subjects from Finland and Sweden, Isomaa et al. (309) estimated the risk for cardiovascular mortality over a 7-year follow-up was increased markedly in those with MS (12.0% vs. 2.2%). A meta-analysis noted increased risks of CVD [odds ratio (OR): 2.40] and all-cause (OR: 1.58) mortality in subjects with MS (454).

Grundy (239) stated that the intended definition of the MS was not a tool to estimate absolute risk, but rather a tool to be used by clinicians to improve obesity counseling. In an attempt to clear up some of the controversy and unify the clinical definitions of the MS, a meeting was convened with representatives from the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. In 2009, a "joint interim statement" was published in Circulation (17), attempting to establish criteria to identify patients with the MS as shown in Table 1. It was agreed that there should not be an obligatory component, although there was agreement regarding the importance of central obesity, and thus waist measurement would continue to be a useful preliminary screening tool. Three abnormal findings out of five would qualify a person for MS. A single set of cut points would be used for all components except waist circumference, for which further work is required, and, at present, would be based upon population/country-specific definitions. The statement reiterated that patients with MS have two and five times the risk of developing CVD and T2D, respectively, over the next 5 to 10 years, as compared to individuals without MS.

As the debate continues more and more data are published relating insulin resistance and/or the MS to other common health problems found in the industrialized nations. In 2006, the Harvard School of Nutrition hosted a conference, *Metabolic Syndrome and the Onset of Cancer,* where several papers were presented showing that hyperinsulinemia was related to breast, prostate, and colon cancers. The proceedings were published in September 2007 in a

supplement to the American Journal of Clinical Nutrition. Barnard (48) suggested that the MS was linked to prostate cancer risk as a result of hyperinsulinemia acting on the liver to increase production of insulin-like growth factor-I (IGF-I), a factor known to stimulate tumor growth and block apoptosis. Kalmijn et al. (327) reported that men diagnosed with the MS in their early 50s were more likely to develop dementia, especially vascular-related dementia, later in life. In a recent review, Galluzzo et al. (218) pointed out that several recent studies recommend that women with polycystic ovary syndrome should be evaluated for MS and that lifestyle modification should be the first-line therapy. Kawamoto et al. (343) tested over 3000 men and women and reported that those with the MS had a risk ratio of 1.53 for chronic kidney disease. Tsochatzis et al. (649) reported that insulin resistance was associated with chronic liver disease, especially hepatitis C and nonalcoholic fatty liver disease (449), and MS predicts hepatic steatosis (252). Additionally, accumulating evidence supports that sleep apnea is a manifestation associated with MS (665). D'Aiuto et al. (139) analyzed data from 13,994 men and women from the Third National Health and Nutrition Examination Survey (NHANES) and found that individuals with severe periodontitis were 2.31 times more likely to have the MS compared to individuals without periodontitis. D'Aiuto et al. (139) even suggested that the chronic low-grade inflammation characteristic of periodontitis might contribute to the development of the MS. The mechanisms linking the MS to CHD and T2D are well understood; however, the links to these other health problems are not well understood and require further study.

It is obvious that much more research is needed before we understand how all of these factors are related from a mechanistic point of view. It is also likely that the true underlying factors are inappropriate diet and physical inactivity, characteristic of industrialized nations. In an analysis of the 1999–2004 NHANES data, Wildman et al. (693), showed support for the value of physical activity in preventing the MS. They found that 23.5% of normal weight (BMI < 25) were metabolically abnormal while 51.3% and 31.7% of overweight or obese (BMI > 30) were metabolically healthy. Low physical activity was an independent correlate of clustering of cardiometabolic factors in the normal-weight individuals while high physical activity correlated with zero or only one cardiometabolic abnormality in the overweight or obese individuals. The importance of exercise, and to some extent diet, will be discussed in the later sections.

Insulin Action

Section "Overview" will focus on an overview of the molecular aspects of insulin resistance. Insulin resistance (i.e., low insulin sensitivity) has been suggested as the major underpinning link between physical inactivity and MS. Many tissues, including skeletal muscle, liver, and adipose tissue may exhibit insulin resistance. Given the clinical benefit of treating those with insulin resistance, techniques have been developed to assess insulin sensitivity *in vivo*. The euglycemic-hyperinsulinemic glucose clamp (EHC) involves injecting a fixed dose of insulin to increase insulin to postprandial or to supraphysiological levels with normal glucose concentrations being maintained by infusing glucose. The glucose infusion rate (often referred to as M-value) reflects insulin sensitivity and is generally considered an inverse measure of insulin resistance; glucose disposal is often also determined. The FSIGT can estimate insulin sensitivity and acute insulin response using the Bergman minimal

model (65), yielding a hyperbolic relationship between insulin secretion and insulin sensitivity (9). The product of these two indices is referred to as the disposition index (DI), a marker of β-cell function. As depicted in Figure 1, exercise training/physically activity status modify insulin sensitivity and insulin secretion in accordance with this relationship, and failure of insulin secretion to compensate for a fall in insulin sensitivity leads to elevated fasting glucose and prediabetes (impaired glucose tolerance), and depending on genetic predisposition a continued progressive decline in both insulin secretion and insulin sensitivity to T2D. Generally, use of the EHC and FSIGT are the gold standard methods for estimation of insulin sensitivity and/or β-cell function. However, these methods are expensive, not simple to perform and generally not applicable in standard clinical practice. The oral glucose tolerance test (OGTT) is less expensive and its simplicity allows for more widespread use. Other techniques used include insulin suppression testing, insulin tolerance testing (ITT) and continuous glucose monitoring systems (CGMSs).

Overview

Insulin is a polypeptide hormone that was first discovered in 1921 by Frederick G. Banting and Charles H. Best while working in the laboratory of J.R. Macleod at the University of Toronto. The hormone was later purified in 1923 by James B. Collip and is now used in clinical practice to treat insulin deficiency diseases, including type 1 and T2D. Insulin is secreted from the β-cells of the pancreatic islets of Langerhans in response to glucose and amino acids consumed during a meal. Insulin is a central regulatory hormone in the maintenance of glucose homeostasis and is also involved in anabolic processes including tissue growth and development. In a healthy person, glucose is controlled within very narrow limits in the blood. This is achieved by the regulation of glucose production by the liver, and to a lesser extent the kidney, as well as uptake by peripheral tissues, primarily skeletal muscle, liver, and adipose tissue. In addition to the control of blood glucose, insulin also exerts strong control over lipid metabolism by stimulating lipid synthesis in liver and fat cells and by attenuating lipolysis, that is, TG breakdown to fatty acids.

Glucose is utilized by cells to produce potential energy in the form of adenosine triphosphate (ATP). The entry of glucose into the cell is achieved primarily via a carrier-mediated process, which includes a family of transporters known as GLUT proteins. GLUT, proteins encoded by *SLC2A* family members, are membrane proteins found in most mammalian cells and contain 12 membrane-spanning helices with both the amino and carboxy terminal regions exposed on the cytoplasmic side of the plasma membrane. To date, over 14 GLUT family members have been identified (317). Each transporter isoform performs a specific role in hexose metabolism as dictated by expression patterns within tissues, protein transport kinetics, substrate specificity and the physiological conditions controlling gene expression. The GLUT family is divided into three subclasses based upon sequence similarities; however for the purposes of this review, we will focus on the well-characterized class I glucose transporters, GLUT1–GLUT4, as these are primarily expressed in glucoregulatory tissues. Insulin-stimulated transport of glucose into cells is achieved by insulin binding to its cell surface receptor and the initiation of a cascade of signaling events culminating in the redistribution of GLUT4 (the insulin responsive glucose transporter) to the plasma membrane. Glucose is then transported across the plasma membrane where it is

immediately phosphorylated and either stored as glycogen or metabolized to produce ATP. In the subsequent sections we will provide an overview of the insulin signal transduction pathway and glucose transport system as well as discuss the mechanisms contributing to impaired insulin action, insulin resistance. We will explore both myocyte-related mechanisms contributing to skeletal muscle insulin resistance as well as describe insulin resistance producing factors secreted from adipose tissue and liver. We will close this section discussing the impact of muscle-secreted factors on metabolism and propose that myokines may in part mediate aspects of exercise-induced effects. Much of the focus of this section will be centered on muscle insulin action as exercise-induced improvements in insulin sensitivity appear related to gains in muscle rather than hepatic insulin action (356, 696).

Insulin Signal Transduction

Insulin and the insulin receptor

Insulin is a peptide hormone, consisting of 51 amino acids with a molecular weight of 5808 Da, secreted by the pancreas as either the full length proprotein or as the fully biologically active form in which the c-peptide is cleaved. Because insulin release into the portal circulation is susceptible to first pass degradation by the liver, c-peptide escapes this fate and is therefore a more accurate marker of insulin secretion. Insulin binds to its receptor (IR) in target tissues including skeletal muscle, liver, and adipose tissue. The *IR* gene is located on chromosome 19 and is comprised of 22 exons and 21 introns, spanning 150 kb (580). IR is synthesized as a preproreceptor. Following cleavage of a 30-aa signal peptide, the proreceptor undergoes glycosylation, folding, and dimerization. The final IR product consists of a heterotetrameric complex of two α-subunits and two β-subunits linked by disulphide bonds (Fig. 2). In glucoregulatory tissues, including adipose and muscle, the IR is thought to be more highly localized to caveolae located in the plasma membrane (247).

The basal form of the insulin receptor has very low kinase activity, as the activation loop, which traverses the N-and C-terminal lobes in the unliganded state, blocks ATP, and substrate binding (295). Insulin, following binding to the extracellular α-subunits, yields a conformational change in the receptor and transmits a signal across the plasma membrane, which activates the intrinsic tyrosine kinase domain of the intracellular β-subunit. This results in a series of intermolecular autophosphorylation reactions on tyrosine residues that are now known to serve distinct functional roles (138, 391).

Comprehensive studies using selective mutations in the IR as well as computational models from crystal structure analyses have yielded specific details regarding these molecular events (296, 727). Specifically, insulin binding causes the phosphorylation of three key tyrosine residues (Y1158, Y1162, and Y1163), allowing for movement in the A-loop and exposure of the ATP and substrate binding sites (178, 296, 551). Additionally, auto-phosphorylation of tyrosine residues 965 and 972 in the juxtamembrane region, 1158, 1162, and 1163 in the regulatory region (also known as the activation loop of the kinase domain), and 1328 and 1334 in the C-terminus of the cytoplasmic domain of the IR are essential for full kinase activity (687). Moreover it was shown that pTyr 960 is critical for appropriate IR substrate recognition (392), and pTyr972 serves as a binding site for the phospotyrosine

binding domains (PTB) of IRS-1, Shc, and STAT5 (110, 246, 321, 573) (Fig. 2). Considered an important feature of hormone signaling, the autophosphorylated IR is rapidly internalized following ligand binding. Endocytosis of the IR leads to proteolytic degradation of the ligand receptor complex, thus terminating ligand action. Recent work by Fagerhom et al. (184) shows that this process is caveolae-mediated and involves the tyrosine phosphorylation of caveolin-1.

Proximal insulin signaling

The IR, upon phosphorylation, recruits various substrates and scaffolding proteins to exert downstream effects. These include the four well-described insulin receptor substrate (IRS) proteins, or IRS1–4, as well as Gab1, SIRPs, Cbl, Shc, and APS (Fig. 3) (500, 632). Upon phosphorylation, these substrates serve as docking or scaffolding platforms for distinct cellular kinases or effectors that mediate the divergent biological actions of insulin. In addition, each of these substrates may be compartmentalized to distinct cellular locations also owning to the specificity to which interactions with other proteins or lipids occur and to which unique downstream effects are achieved. For example, IRS and Shc are recruited to the juxtamembrane region in IR containing a critical arginine-proline-any amino acid-tyrosine (NPXY)-binding motif (342, 468), while APS binds directly to the activation loop.

Insulin receptor substrate-1, 2

IRSs are the major substrates of the insulin receptor and the IGF)-I receptor tyrosine kinases. Of the several IRS proteins described, IRS-1, 2 are shown to have biological relevance in peripheral tissues for glucose transport. Briefly, tyrosine phosphorylation of IRSs creates recognition sites for additional effector molecules containing Src homology 2 (SH2) domains, including the adaptor proteins Grb2 and Nck, the SHP2 protein phosphatases and the 85-kDa, p85 regulatory subunit of phosphatidylinositol 3-kinase (PI3K) (686). The pleckstrin homology (PH) domain of the substrate protein is obligatory to elicit the full signal response, as insulin-stimulated tyrosine phosphorylation is significantly reduced in by PH deletion (460). Both IRS-1 and IRS-2 contain multiple YXXM motifs that are phosphorylated by the activated IR (687). *In vitro*, IRS-1 and IRS-2 display similar capacities to bind p85 of PI3Ks. With respect to insulin action and substrate metabolism, critical roles for IRS-1 and IRS-2 are well established (627, 697). Furthermore, human genetic inactivating mutations in either *Isr1* or *Irs2* are associated with insulin resistance and T2D (47, 427). While the IRS family shares a high degree of homology, studies in genetically engineered rodents delineate specific roles for these protein isoforms (637, 697). Genetic ablation of either *Irs1* or *Irs2* in rodents or cells leads to dire physiological consequences, including impaired insulin signal transduction and growth retardation (25, 627).

IRS-1

IRS-1 was first identified by Sun et al. in 1991 and was found to be expressed in a wide variety of tissues (619, 620). *Irs-1* null mice are growth restricted and display marked skeletal muscle insulin resistance, but the development of frank T2D in this model is prevented by pancreatic *Irs2*-induced hyper-insulinemic compensation (25, 627).

Furthermore, short-term inhibition of *Irs-1* by anti-sense oligonucleotide administration in rats recapitulated much of the insulin resistance phenotype observed in *Irs-1* knockout mice (26). In the context of findings for *Irs-1* deletion relating to insulin action, recent evidence obtained from *Irs-1* transgenic mice suggests that increased expression of IRS-1 is not associated with improved insulin sensitivity (455). In fact, transgenic mice displayed glucose intolerance, increased visceral adipose mass, and increased levels of circulating inflammatory cytokines (455). Interestingly, while *Irs-1* mRNA was significantly elevated in all tissues, IRS-1 protein levels were preferentially elevated by 50% and 200% in skeletal muscle and adipose tissue, respectively. The IGT seen in the transgenic mice is explained by reduced tyrosine phosphorylation of IR and YXXM motif of IRS-1 in liver, which may be caused by indirect action given that IRS-1 protein levels were unchanged in liver (455). Taken together these data indicate a relatively narrow window in which IRS-1 levels must be maintained to preserve glucose homeostasis and healthy tissue morphology.

IRS-2

IRS-2 is expressed in all of the primary glucoregulatory tissues including pancreas, liver, adipose, and skeletal muscle. Mice with an *Irs2* homozygous null mutation display metabolic defects in liver, muscle, adipose, and pancreas but develop frank diabetes as a result of defects in signal transduction in pancreatic β-cells (511, 697). Furthermore, the importance of IRS-2 in regulating β-cells mass and in the prevention of type 1 diabetes was recently shown by Norquay et al. (467) in nonobese diabetic (NOD) mice overexpressing IRS-2 in β-cells. Remarkably, glucose tolerance was markedly improved and the risk of diabetes decreased 50% in NOD *Irs2* Tg mice due to a tenfold greater β-cell mass. In contrast to pancreas, IRS-2 is not necessary for insulin or exercise-stimulated glucose transport in skeletal muscle (268). In liver, insulin-stimulated regulation of sterol regulatory element-binding protein (SREBP)-1c and fatty acid homeostasis is previously thought to depend almost exclusively on the IRS-2 arm for activation of PI3K, PDK1, and atypical protein kinase C isoforms (aPKCs) (187, 561, 602). Again, recent work from the laboratory of Morris White using Lox Cre approach to generate mice with hepatic specific deletions of IRS-1 and or IRS-2 calls into question the established role of IRS-2 in the liver. Findings suggest that IRS-1, not IRS-2, plays a dominant role in regulating hepatic nutrient homeostasis (243). Whether these findings in rodents can extend to isoform specific roles in regulating insulin action in human tissues requires further investigation.

Insulin Receptor Downstream Effectors

Phosphoinositide 3,4,5 (PI3)-kinases

It is well accepted that class IA PI3K is required for insulin-dependent GLUT4-mediated glucose transport in muscle and adipose. In mammals, this class of kinase comprises a p110 catalytic subunit (p110 α, β, or δ) bound to one of five "p85" regulatory subunits (p85α, p85β, p55α, p55γ, or p50α). In the relative absence of insulin, p85 is bound tightly and stabilizes basal p110 protein, inhibiting its catalytic lipid kinase activity. In contrast, during insulin stimulation, the p85–p110 complex is recruited to phosphotyrosine residues in activated receptor or adaptor molecules containing SH2 domains. Recruitment of the p-85/p110 heterodimer to a location proximal to the plasma membrane brings p110 into close

proximity with its lipid substrates, thus reducing the inhibitory actions of p85 on p110. Class IA wortmannin sensitive PI3K generates phosphatidylinositol 3,4,5 triphosphate, from PIP_3 PtdIns $(4,5)P_2$ at the cell surface and this is thought to interact with specific lipid binding domains present in Ser/Thr protein kinases, including PDK1 and protein kinase B (PKB/Akt). Subsequently, these kinases then act upon GTPases and other scaffolding proteins to promote further propagation of the insulin signal. Early studies using wortmannin to inhibit PI3K showed the insulin-mediated glucose transport into cells is nearly abolished; therefore, PI3K is considered a central and essential signaling regulator for a variety of biological cell responses, notably growth, proliferation, and metabolism (222).

Mammals express seven PI species, two of which are described above and the function of five of which remains poorly understood. While PtdIns$(3,4,5)P_3$ is shown to rise transiently in response to acute insulin treatment and is thought to be the primary PI species regulating metabolic processes, overexpression of PtdIns$(3,4,5)P_3$ alone is not sufficient to fully stimulate transport-mediated uptake of glucose into cells (590). Furthermore, a role for class II wortmannin-insensitive PI3K C2α and the other five PI species has recently been proposed for fine tuning the overall metabolic response of a cell to insulin (185, 590). The importance of this adjunct-signaling pathway in glucose disposal and insulin sensitivity requires further investigation.

Akt

Protein kinase B, also known as Akt, is a Ser/Thr kinase involved in a large and diverse set of cellular processes including glycolysis, glycogen synthesis, lipogenesis, suppression of gluconeogenesis, and cell survival. One of Akt's many important functions is mediating the metabolic actions of insulin to stimulate glucose transport (688). Akt is a PI 3-K effector molecule and its isoform expression dictates cell specific actions *in vivo*. RNA silencing studies conducted by the Czech laboratory (728) and gene deletion strategies in mice conducted by the Birnbaum laboratory (38) show that Akt2/PKBβ is critical for insulin-mediated glucose disposal. While it is well accepted and evident that it serves as an essential role for Akt2 in glucose transport, studies where Akt inhibition did not cause impaired glucose uptake have been reported. While Akt is thought to be a central effector driving glucose transport, other signaling cascades are thought to participate in parallel including the aPKCλ/ζ (187, 188, 363), p-38 mitogen-activated protein kinase (622), and the CAP/c-Cbl/TC10 cascade (57, 500).

Atypical protein kinase C isoforms, PKCλ, ζ

aPKCs are also downstream effectors of PI 3-K; however these signaling molecules may serve different functions in regulating substrate metabolism in the various glucoregulatory tissues (187). In muscle IRS-1 knockout has a marked effect on aPKCs whereas IRS-1 knockout in liver has little effect on aPKC activation (561). While a role for aPKCs in regulating glucose uptake and metabolism is shown in muscles and in the liver, aPKCs are thought to exert insulin-mediated effects preferentially on hepatic lipid synthesis via regulation of SREBP-1c (SREBP-1c) (422). While previously considered an independent and parallel effector signaling system, recent evidence supports that aPKCs and the TC10 pathways may interact at the plasma membrane (111, 331). Atypical PKCs belong to the

AGC subfamily of protein kinases [reviewed by Pearce et al. (491)] and, thus, while phosphorylated by PDK1 downstream of PI3K, can be recruited to lipid rafts in a TC10-dependent manner by Par3 (partitioning-defective) and Par6 proteins (331). Thus, atypical PKCs may represent a point of convergence between PI3K signaling and the TC10 pathways (111). Furthermore, evidence from the Klip laboratory shows that PKCε translocates to the plasma membrane of C2C12 myotubes in culture in response to contraction and that GLUT4 translocation proceeds in a PKCε-dependent manner (464). Whether PKCε is critical for glucose transport into muscle during physical exercise remains to be demonstrated.

AS160

The Rab-GTPase activating protein known as AS160 (or TBC1D4) is a 160 kDa putative substrate of Akt (330) and is widely expressed in a variety of tissues including brain, testes, kidney, pancreas, liver, heart quadriceps, and white and brown adipocytes. AS160 undergoes phosphorylation in response to insulin and contains multiple Akt phosphorylation sites: Ser^{318}, Ser^{341}, Ser^{570}, Ser^{588}, Thr^{642}, and Ser^{751} (330, 565). In addition to insulin, AS160 is phosphorylated in response to PDGF, activation of nPKCs and adenosine monophosphate kinase (AMPK), and following skeletal muscle contraction (216, 639). AS160 is thought to regulate GLUT4 trafficking as well as serve as a convergence point for insulin and contraction-mediated GLUT4 translocation to the plasma membrane (334, 366). Briefly, GLUT4 vesicles migrate and recycle along the cellular framework of cytoskeletal elements and are acted upon by molecular chaperone and GTP-bound Rab proteins. Insulin stimulation causes a rapid phosphorylation of AS160 and its dissociation from GLUT4 vesicles. Removal of AS160 from the vesicle causes an accelerated rate of GLUT4 exocytosis, leading to greater accumulation at the plasma membrane culminating in elevated cellular glucose uptake (723). Phosphorylation incapable AS160 abolished insulin, PDGF, K + depolarization, and AICAR-induced GLUT4 translocation (639). Furthermore, Karlsson et al. (334) have shown that insulin-stimulated phosporylation of AS160 is significantly impaired in type 2 diabetic muscle. More recently, TBC1D1, an AS160 paralog was identified by immunoprecipitation and mass spectral analyses (635), and its expression is several-fold higher in skeletal muscle versus other insulin responsive, glucoregulatory tissues. Similar to TBC1D4 (AS160), TBC1D1 is phsophorylated in response to insulin, exercise, and AMPK activation by AICAR; however, many novel AMPK binding sites have been identified and activation studies reveal AMPK as a more robust regulator of this signaling molecule (635, 643). Furthermore, genome wide association across multiple strains of mice identified TBC1D1 as an important obesity and diabetes candidate gene (109), similar linkage was established in human subjects as well (616). Mice harboring a truncated TBC1D1 protein lacking the Rab-GTPase-activating protein domain conferred a lean phenotype despite consumption of a high-fat diet (109). These engineered mice showed impaired glucose metabolism and thus relied more heavily on fatty acids as a primary fuel source as reflected by the reduced respiratory quotient and increased rates of whole body fatty acid oxidation, a finding recapitulated in C2C12 myotubes.

Insulin signaling via PI3-kinase independent pathway: CAP, c-Cbl, and TC10

Given the evidence that PI 3-K activation alone is not fully sufficient to achieve insulin-mediated glucose transport, activation of one or more class I PI3K-independent pathways is

thought to be requisite (564, 681). This alternative signaling hypothesis is also supported by the fact that glucose transport is stimulated by exercise and hypoxia, independent of any detectable alteration in PI3K. TC10, identified by Chiang et al. (115), along with the canonical PI3K pathway are thought to be required to achieve the full effects of insulin to stimulate GLUT4 translocation. TC10 is a Rho-like GTPase that is highly expressed in adipocytes and skeletal muscle (115). Activation of PI3K-C2α (wortmannin insensitive) is also proposed to occur via TC-10 (111,185). TC-10 dependent actions were found to rely on localization to caveolin-enriched lipid raft microdomains (564, 681).

Within these lipid domains resides the Cbl protooncogene and its adaptor proteins, CAP (Cbl-associated protein) and APS (Cbl-binding protein). Insulin acting through its receptor stimulates the phosphorylation of APS and then Cbl on tyrosine residues (403, 564). Phosphorylated Cbl binds to CAP and migrates to the caveolin-enriched lipid rafts where the CAP complex is anchored by the lipid raft-associated protein flotillin (403, 564). Subsequently, the Crk/C3G (a guanyl nucleotide exchange factor) complex is recruited to this microdomain, leading to the activation of TC10. In that much of this work was performed in adipocytes, findings from JeBailey et al. (314) suggest that TC10-dependent signaling may function differently within other cell types. Additional studies are required to parse out the tissue specific function of the CAP/c-Cbl/TC10 pathway in the regulation of glucose disposal *in vivo*.

GLUT4 expression

Adipose tissue and skeletal muscle are primary sites of postprandial glucose uptake, and GLUT4, the primary insulin responsive glucose transporter, is highly expressed in these tissues. Under fasting conditions, when circulating insulin levels are low, GLUT4 is minimally present at the plasma membrane and is instead sequestered to intracellular membrane compartments (680). Consumption of a meal stimulates insulin secretion from the pancreatic β-cells and activates a cascade of events as mentioned above that culminate in the movement of the GLUT4 vesicle to the plasma membrane thus increasing transport of glucose from the blood into the cell to participate in metabolism or storage as glycogen. The mechanisms and cellular machinery involved in GLUT4 packaging and trafficking are reviewed in detail elsewhere (89, 167, 332, 348, 383, 402, 443, 444, 501, 680). Suffice to say, an essential role for GLUT4 in insulin-mediated glucose transport is well established.

GLUT4 null mice show many severe developmental defects and a shortened life span (84, 336). Mice heterozygous for the null mutation were insulin resistant and predisposed to diabetes (336, 609). Ablation of GLUT4 specifically in skeletal muscle led to glucose intolerance and severe impairments in insulin-mediated glucose disposal into muscle in mice as young as 8 weeks of age (730). Ablation of GLUT4, specifically in adipose tissue, led to secondary phenotypes of insulin resistance in skeletal muscle and liver, suggesting that an impairment in glucose transport in adipose causes the release of a secretory factor that impairs insulin action in other glucoregulatory tissues (5). Clearly, expression of GLUT4 in skeletal muscle and adipose tissue is essential for the maintenance of glucose homeostasis; however, defects in GLUT4 expression cannot explain the insulin resistance associated with obesity and T2D in rodents or humans (45, 83, 220, 221). Despite this, genetic

overexpression or exercise-induced elevation in GLUT4 expression can ameliorate insulin resistance observed in diabetic and obese rodents and humans (84, 255, 531).

Mechanisms of Insulin Resistance

Resistance to the biological effects of insulin is a hallmark feature of the MS and an important contributing factor in the pathogenesis of T2D. In the early stages of insulin resistance, the pancreas compensates by increasing the secretion of insulin into the bloodstream in an attempt to overcome defects in peripheral insulin action. In response to this increased demand for insulin production, the β-cells hypertrophy. Under fasting conditions, basal compensation is sufficient to maintain blood glucose in the normal range. Following a meal though, when glucose is rapidly absorbed from the gut, a relative lack of insulin due to inadequate compensation is detected as the glucose excursion over time is exaggerated. This inability to take up and dispose of glucose appropriately following a meal or glucose challenge is known as glucose intolerance.

It is important to note that genetic mutations or defects in the participants of the insulin-signaling cascade only in rare occasions underlie the insulin resistance and T2D. It is now well supported that lipid oversupply and alterations in substrate metabolism due to inactivity are central underpinnings of chronic tissue inflammation and contribute to the manifestation of peripheral insulin resistance. Tissue accumulation of bioactive lipid species in peripheral tissues activate proinflammatory signaling pathways and novel PKCs; and as reviewed in references (576, 651), which are shown to impair insulin signal transduction by altering key phosphorylation events and key protein-protein interactions. Postreceptor defects are thought to account for much, if not all, of the impairment in muscle insulin action observed in T2D. Many agree that impaired insulin action at the level of IRS-1 occurs as a result of stress kinase activation [e.g., c-Jun N-terminal kinase (JNK) and nuclear factor-κB (IκB) kinase (IKK)β] and impaired phosphorylation of IRS-1 (10, 11, 555). Reduced IRS-1 phosphorylation on critical tyrosine residues and prevents binding with p85 of PI3K and downstream signal transduction. Furthermore, alteration in phosphorylation status, specifically phosphorylation of serine residues, is shown to target IRS-1 for proteasomal degradation and this is a plausible explanation for reduced IRS-1 protein levels in glucoregulatory tissues harvested from obese and/or diabetic rodent (13, 495, 510, 674). Recent work from Shulman, Copps et al. calls into question this paradigm, as *in vivo* evidence in mice suggests that phosphorylation of IRS-1 at Serine 307 (human Ser312) may promote insulin sensitivity (130). Given conflicting findings to previous studies from the same investigators, further studies will be necessary to test whether selective phosphorylation of IRS-1 on specific serine/threonine residues can modulate insulin action in glucoregulatory tissues in human subjects.

Downstream of IRS-1, PI3K exists in a heterodimer composed of a p110 catalytic subunit and a p85 regulatory subunit as described above. Transcription of the *Pik3r1* gene leads to expression of three splice variants p85α, p50α, and p55α (213) and when under normal conditions are in excess compared to the expression of the p110 catalytic subunit. All three variants can bind p110. Interestingly, all three variants are elevated in total in skeletal muscle samples from obese and type 2 diabetic subjects; this increase in expression is

associated with reduced insulin resistance and diminished insulin-stimulated PI3K activity (43). Findings in mice with a heterozygous deletion of p85 splice variants as well as in mice with a homozygous deletion of p85α or p85β support the notion that while p85 is critical in recruiting the catalytic subunit of PI3K to IRS proteins, excess levels of monomeric p85 play a role in the inhibition of insulin signaling (425,655).

Lipid phosphatases—SHIP and PTEN

PI3-kinase activity is attenuated by dephosphorylation via 3′ and 5′ lipid phosphatases. SH2 domain containing inositol 5′phosphatase 2 (SHIP2) and skeletal muscle and kidney-enriched inositol phosphatase (SKIP) hydrolyze $PI(3,4,5)P_3$ to $PI(3,4)P_2$, while the phosphatase and tensin homolog deleted on chromosome ten (PTEN) hydrolyzes $PI(3,4,5)P_3$ to $PI(4,54)P_2$. SHIP2, as opposed to SHIP1, is broadly expressed and abundant in glucoregulatory tissues. SHIP2 is phosphorylated in response to insulin and IGF1 stimulation, which leads to its translocation to sites near PI3K. In humans, polymorphisms in the SHIP2 genes are associated with the MS and T2D. These findings are supported in rodents, as SHIP2 expression levels are elevated in skeletal muscle and adipose tissue from obese and type 2 diabetic mice (279). Consistent with these findings, transgenic overexpression of SHIP2 led to IGT and insulin resistance in mice fed a normal chow diet (325) while targeted disruption of SHIP2 improved insulin sensitivity and protected mice from high-fat diet-induced obesity. PTEN was originally identified as a candidate tumor suppressor and was later found to share homology with protein tyrosine phosphatases (397). Overexpression of PTEN and SKIP are also shown to inhibit insulin action in cultured cells, although homozygous deletion of PTEN results in embryonic lethality due to tumor formation. Tissue selective deletion of PTEN in liver, skeletal muscle, fat, and pancreas appears to offer protection against insulin resistance and reductions in β-cell mass in the face of high-fat feeding and streptozotocin treatment, respectively (373,614,615,691). Interestingly, glucose tolerance and insulin sensitivity are reported in human subjects who possess germline mutations in the *PTEN* gene. Several population-screening studies have failed to identify a relationship between PTEN polymorphisms and T2D susceptibility; however, three variants were identified in Japanese diabetic patients (307), but the differences between the ethnic groups studied to date have yet to be explained. Great care should be taken when considering the role of PTEN as a target for therapeutic intervention as mutations in this gene are associated with tumorgenesis and neurological defects and neurodegenerative diseases. Clearly, PTEN is a critical regulator of many signaling systems throughout the body. Lipid phosphatases acting as therapeutic targets to combat insulin resistance and complications associated with T2D have been reviewed in detail previously (386, 568).

Downstream of PI3K, defective activation of aPKCs has also been observed in muscle from type 2 diabetic rats, monkeys, and humans [as reviewed in reference (187)]. This defect in aPKC signaling is at least in part due to impaired upstream signaling at IRS-1 and PI3K. Furthermore, insulin-stimulated AS160 phosphorylation is reduced in patients with T2D, although the GAP activity of AS160 appears to be specific for Rabs 2A, 8A, and 14 (334).

Protein tyrosine phosphatase 1B (PTP1B)

Protein tyrosine phosphatase is a negative regulator of insulin signal transduction as it dephosphorylates phosphotyrosine residues of the IR and IRS-1. In general, PTPases are redox sensitive enzymes and all share a common catalytic motif (21). Insulin induced ROS-mediated oxidation of critical AA residues in the catalytic domain of the enzyme leads to inactivation, and thus enhanced signal transduction downstream of the IR (225, 417). Indeed, low-level ROS production during insulin stimulation is critical for certain aspects of insulin signal transduction (404, 416).

In insulin-resistant states including obesity-associated insulin resistance, PTP1B expression and activity are elevated in muscle and adipose tissue from humans and rodents (13,701). Furthermore, polymorphisms in the *PTPN1* gene confer increased phosphatase express in muscle; this is associated with insulin resistance and T2D (62, 159). Overexpression of PTP1B in mouse muscle or myocytes led to impaired insulin signal transduction of reduced glucose uptake and glycogen deposition (173, 720). Conversely, high-fat fed mice with genetic deletion of PTP1B (176, 357) and diabetic or obese animals treated with PTP1B antisense oligonucleotide (242,729) showed improved insulin sensitivity. In addition, mice lacking PTP1B are also protected from TNFα-induced insulin resistance (462). Thiazolidinedione (TZD)-induced insulin sensitization as well as exercise and caloric restriction interventions that improve whole body insulin sensitivity are associated with reduced PTP1B in skeletal muscle (14, 702). PTP1B as a therapeutic target to ameliorate insulin resistance associated with T2D has received greater attention and is reviewed in reference (362).

Inflammation and insulin signaling

Nuclear factor (NF)-κB and activating protein (AP)-1 are two central proinflammatory pathways activated in glucoregulatory tissues during overnutrition and in type 2 diabetic patients (Fig.). Studies in rodents with inactivating mutations in the upstream kinases associated with these signaling pathways, IKKβ and JNK, have shown remarkable efficacy in preventing diet-induced insulin resistance, restraining obesity, and ameliorating T2D (28, 269). Interestingly, for over a century now it has been observed that aspirin (acetylsalicylic acid) exerts glucose lowering effects and can ameliorate certain complications associated with T2D, and work by Yuan and colleagues (717) has identified NF-κβ as the pharmacologic target of this antidiabetic agent. Recently, a favorable safety profile and a remarkable efficacy in reducing glycemia, insulin resistance, and diabetic complications, such as CVD, have been observed in clinical trials where salsalate, a prodrug form of salicylate, was administered to type 2 diabetic patients (198, 224).

In addition to the effects of these stress kinases, namely, IKKβ and JNK, to activate transcriptional inflammation programs leading to increased expression of cytokines and chemokines (e.g., TNFα, IL-6, IL-1, and MCP-1), both are thought to directly alter tyrosine kinase activity of proximal insulin signaling (10,11,269). It is currently thought that these stress kinases are activated by the intracellular accumulation of proinflammatory lipid intermediates including diacylglycerol (DAG) and ceramide although activation via cell surface toll-like receptors (TLRs) has also been implicated.

Toll-like receptors and cellular inflammation

TLRs are transmembrane protein receptors that are expressed in a variety of cell types and are critical for innate immune responses. TLRs are now viewed as an important molecular link between lipid oversupply and activation of proinflammatory signaling (207). While eleven members of the TLR family have been identified in humans and 13 in mice (508), of interest, TLR2 and TLR4 are expressed in glucoregulatory tissues including adipocytes, hepatocytes, and myocytes (382, 399). Furthermore in skeletal muscle cells and adipocytes, *in vitro* and *in vivo* evidence show that lipid oversupply causes TLR2/TLR4 upregulation, and this is associated with activation of stress-linked kinases (including p38, JNK, and PKC), as well as NF-κB nuclear translocation and subsequent transcription of downstream targets (Fig. 4) (583). Moreover, *Tlr4*-deficient rodents are protected against the obesigenic effects of a high-fat diet and, in addition, exhibit reduced cellular NF-κB activity including diminished circulating levels of MCP-1 (144). However, recent work shows that when accumulation of intracellular lipid intermediates including ceramide is prevented pharmacologically or genetically, long chain fatty acid-induced inflammatory signaling is also prevented; however, critically, TLR2/4 signaling by their specific ligands including lipoteichoic acid and lipopolysaccharide is maintained. Whether TLR2/4 are important and/or essential in the induction of the tissue inflammatory response in obese humans remains unknown. Clearly, critical work must be undertaken to identify the central mechanism(s) linking cellular uptake of saturated fatty acids with the activation of inflammatory signaling.

Fatty acid-binding proteins as lipid sensors

In 1981, Abumrad et al. (7) showed that cellular uptake of long chain fatty acids is saturable and involves a plasma membrane transport system. In 1991, cloning of the cDNA encoding human skeletal muscle fatty acid-binding protein (FABP), its peptide sequences and chromosomal localization was achieved by Peeters et al. (496). Two years later Abumrad et al. (6) cloned a rat adipocyte membrane protein homologous with human CD36 so named FAT/CD36, and in 1994, Schaffer et al. (574) cloned and characterized a novel adipocyte LCFA transport protein, FATP (*Slc27a1*). All of these are highly expressed in muscle and regulate LCFA uptake.

Fatty acid-binding proteins are abundantly expressed cytosolic (c) or membrane bound (pm) and coordinate cellular lipid metabolism, binding with high affinity, long-chain fatty acids and eicosanoids (127). FABPs are involved in FA import, storage, and export as well as cholesterol and phospholipids metabolism (258). Additionally, it is thought that FABPs are an adaptive lipid-sensing system, as their levels are altered during elevated fatty acid exposure, chronic endurance exercise (350, 653), genetic obesity, and pathology-associated nutrient changes (406, 641, 652, 654). Interestingly, recent work suggests that in addition to regulating the transport of fatty acids into the cell, FABPs may serve as coregulators of transcription factors known to modulate lipid metabolism and inflammation via a nucleocytoplasmic shuttling mechanism (266, 322, 699). The most actively studied interaction is between FABPs and the family of peroxisome proliferator-activated receptors (PPARs) including α, δ, and γ. Thus, it was hypothesized that selective modulation of FABPs may serve as a potential therapeutic mechanism to treat lipid- and inflammatory-

associated diseases. Specifically, adipocyte and macrophage FABPs play a powerful role in regulating tissue inflammation and whole body glucose metabolism. Small molecule inhibitors of aP2 (FABP4) in macrophages blunt FABP activity and reduce cellular inflammation in a time- and dose-dependent fashion. aP2 inhibition is also shown to reduce lesion area in the proximal aorta of atherosclerosis prone $Apoe^{-/-}$ mice fed a Western diet (215). Similar findings were observed in mice with a genetic deletion of aP2 (FABP4) and mal1 (FABP5) in adipocytes and macrophages (411). Collectively, these studies provide substantial evidence that aP2 is an important regulator of cellular fatty acid handling, inflammation, and whole body glucose tolerance and insulin sensitivity. This work implicates lipid chaperones, FABPs, as potential clinically relevant therapeutic targets in the treatment of T2D and CVD; however, studies in human subjects are still required. It is also important to note that these binding proteins are upregulated with physical exercise (350,653) and fasting (652), from which a coordinated increase in fatty acid oxidation, repression of inflammation, and improved insulin sensitivity are achieved.

Protein fatty acid transporter FAT/CD36 expression is also elevated in response exercise training and the 88 kDa protein translocates rapidly to the plasma membrane during muscle contraction. Increased expression and activity of this transport protein contributes in large part to the fivefold to 15-fold increase in fatty acid uptake by contracting skeletal muscle (73,91,544). The protein is shown to colocalize with caveolin-3 and most highly abundant in type 1 oxidative muscle fibers (666). Interestingly, similar to GLUT4, FAT/CD36 is skeletal muscle is maintained under basal conditions in an intracellular pool and translocates to the plasma membrane primarily in response to contraction or insulin stimulation (74, 407). Over the past decade, it has been disputed whether FAT/CD and FATP-1 may be involved in deciding the metabolic fate of LCFA, specifically partitioning FAs to oxidation. Bezaire and colleagues put forth the notion that fatty acid transporters FAT/CD and FATP1 are involved in the transfer of FAs into the mitochondria possibly by direct binding to the mitochondrial membrane (66, 96). This work is recently disputed by Jeppesen et al. (315). Regardless of whether these proteins bind directly to mitochondria, at least in the case of FATP, skeletal muscle-specific overexpression in mice promoted increased skeletal muscle fatty acid uptake and oxidation specifically, but did not predispose animals to diet-induced insulin resistance (274). In aggregate, despite over two decades of intense research since their identification, it would seem that our understanding of the involvement of fatty acid binding proteins in regulating substrate metabolism, tissue inflammation, and insulin action requires further investigation.

Fatty acid handling

High-fat feeding or elevation of circulating fatty acid levels achieved by TG and heparin infusion are well known to cause skeletal muscle insulin resistance; however, the precise signaling events that underlie fatty acid-induced insulin resistance remain incompletely defined. It is currently held that excessive fatty acid uptake into the myocyte and reduced fat oxidation lead to the accumulation of proinflammatory lipid metabolites, such as fatty acyl CoAs, DAG, and ceramide, which, as stated above, activate serine/threonine "stress" kinases (Fig. 4). These kinases include JNK, IKKβ, and PKCθ, all of which promote inflammatory signaling and antagonize insulin action. Reduced expression of the rate limiting enzyme for

LCFA entry into the mitochondria, carnitine palmitoyltransferase-1 (CPT1), and impaired mitochondrial function (decreased mitochondrial number, lower levels of oxidative enzymes, and lower ATP synthetic rates) are found in insulin-resistant skeletal muscle and coincide with muscle lipid accumulation (58, 351, 503, 541, 694). Furthermore, genes of oxidative metabolism were shown to be coordinately reduced in muscle from human patients with insulin resistance and T2D (450, 490). It is important to note that in human subjects these are merely observational and coincident changes in multiple signaling pathways; causal relationships between impairments in oxidative metabolism and mitochondrial function with insulin resistance is not established (253), and indeed there is evidence that in the condition of primary congenital insulin resistance, mitochondrial dysfunction follows (597). Additional longitudinal studies are necessary to delineate the pathogenesis and molecular underpinnings of this often-heterogeneous mix of metabolic disorders that characterize MS.

Despite this controversy and lack of mechanistic insight into the human pathology, several studies have shown that TG accumulation in skeletal muscle correlates most highly with insulin resistance, even when compared to other factors including BMI, percent body fat, and waist-to-hip ratio (313, 371, 499). TG accumulation is regulated directly and indirectly by several important enzymes located in the cytoplasm and mitochondria. For example, CPT1 is a key metabolic regulator of fatty acid oxidation, located in the outer mitochondrial membrane and in close proximity with acetyl-CoA carboxylase (ACC), a cytosolic enzyme that catalyzes the carboxylation of cytosolic acetyl CoA to form malonyl CoA, a potent inhibitor of CPT1. Malonyl-CoA levels are controlled by the relative activities of ACC and malonyl-CoA decarboxylase, the principal enzyme involved in malonyl CoA degradation. When malonyl CoA levels rise, mitochondrial fatty acid import, and oxidation are suppressed, thus favoring fatty acid storage in the form of TG. ACC inhibition, CPT1 activation, and enhanced fatty acid oxidation are previously shown to associate with insulin sensitivity and protection against diet-induced insulin resistance (118, 161). Importantly, in skeletal muscle from obese individuals, the activity of CPT1 is reduced (351) and may account for at least some of the decrement in skeletal muscle fatty acid oxidation observed in obesity and insulin resistance. This notion is consistent with recent work showing that CPT1 overexpression in myotubes (579) and murine skeletal muscle (87), or enhanced β-oxidation in mice harboring a null ACC2 mutation (118) is protective against diet-induced insulin resistance. Given that endurance exercise in rodents and humans is associated with elevated CPT1 activity levels and greater fatty acid oxidative capacity, therapies targeted at improving fatty acid flux through the tricarboxylic pathway to ameliorate insulin resistance are warranted. It is also important to note that while elevated TG levels correlate well with insulin resistance in type 2 diabetic and sedentary individuals, TG levels are also elevated in insulin sensitive highly trained athletes (556). The notion of the lipid paradox is well supported and suggests that other factors independent of TG, such as accumulation of more bioactive lipid species, including DAG or ceramide, and peroxidation of lipid bilayers promote inflammation and are the true culprits of insulin resistance (165, 226, 556). Stored muscle triacylglycerol is thought to be a biologically inert pool of stored fat in certain instances activation of TG synthesis may be advantageous in reducing the inflammatory consequences of nutrient excess. Identification of the precise causal factors underlying

proinflammatory signaling and insulin resistance associated with increased muscle lipid storage in sedentary individuals compared with those engaging in daily exercise, is of biological and clinical interest.

Accumulation of bioactive lipid intermediates and insulin resistance

Indeed, there are mechanistic links between the development of insulin resistance and the accumulation of DAG and ceramide in muscle (8, 271, 272, 310), although, as put forward by Goodpaster and colleagues previously for triacyclyglycerol, a paradox for DAG in muscle of endurance-trained athletes is now also suggested (19). Dissecting the athlete's paradox further, in sedentary individuals, a major contributor to increased lipid deposition is an impaired ability to oxidize fat as a fuel source (108, 593, 594). Elevated intracellular fatty acids are shown to induce enzymes that promote tissue sphin-golipid synthesis. Despite being a relatively small component of the total lipid pool, sphingolipids, such as ceramide and glucosylceramide, are considered the most pathogenic (618) and are elevated almost twofold in insulin-resistant obese compared with lean, sedentary or exercise-trained subjects (19). Four serial reactions promote the synthesis of ceramide from fatty acids and serine. Two of these enzymes, serine palmitoyl-transferase (SPT)-1 and dihydroceramide desaturase (Des-1), have received attention regarding their therapeutic potential to reverse insulin resistance and ameliorate complications associated with T2D. SPT-1 catalyzes the first reaction that condenses serine with palmitoyl-coenzyme A (CoA) to produce 3-ketosphinganine. This first reaction is the rate-limiting step in the synthesis of ceramide. SPT-1 is highly selective for saturated fatty acyl-CoA and the rate of this reaction is influenced largely by the availability of fatty acid substrate. Experimental elevation of fatty acids in rodents increases ceramide accumulation in skeletal muscle and liver and is associated with insulin resistance. However, coinfusion of an SPT-1 inhibitor, such as myriocin or cycloserine, prevents both lipid-induced ceramide accumulation and impaired insulin action (272). Similarly, myriosin administered to Zucker diabetic fatty rats reduces tissue ceramide levels, improves glycemia and circulating TG, and ameliorates glucose and insulin intolerance (271, 272). Des-1 oxidizes inactive dihydroceramide into active ceramide. In line with findings for myriosin-treated rodents, tissues harvested from Des-1$^{+/−}$ mice accumulate less ceramide and these animals are refractory to insulin resistance (271). Overall, these findings in rodents warrant further investigation in humans so as to discern whether SPT-1 and Des-1 are viable therapeutic targets to reverse insulin resistance and restrain T2D progression. Additionally, exhaustive exercise diminishes total content and saturation of ceramide and sphingomyelin-FA as well as activity of sphingomyelinase in oxidative muscles from rats (162) and vastus lateralis from humans (265).

Collectively, these findings in rodents warrant further investigation in humans to discern whether SPT-1 and Des-1 are viable therapeutic targets to reverse insulin resistance and restrain T2D progression by diminution of cellular bioactive lipids, including ceramides. Furthermore, it will be important to unravel mechanistic underpinnings of the athlete's paradox to determine the site of uncoupling related to lipid accumulation for proinflammatory signaling. It is likely that mitochondrial content, lipid droplet localization, the precise molecular species of the lipid and the relative abundance and activity of potent transcriptional regulators of key pathways in metabolism, insulin action, and inflammation

converge to explain the discrepancies in human populations and experimental mouse models.

Protective chaperones - heat shock protein response

Heat shock proteins (HSPs) are shown in murine models to block inflammation and protect against obesity-induced insulin resistance (120). HSPs are adaptive proteins that protect against cellular stress including alterations in temperature, pH, misfolded proteins, and inflammation (465). In humans, exercise training is also shown to cause increased tissue HSP levels; this adaptation is thought to be associated with disease prevention (85, 705). Thus, it is hypothesized that loss of heat shock response may underlie susceptibility to chronic disease while activation of the heat shock response may have broad therapeutic benefit in the treatment of such diseases including CVD and T2D. This notion is supported by work from Chung et al. (120), showing that upregulation of the inducible HSP, HSP72, either by heat stress, pharmacological or genetic means leads to protection against diet- and obesity-induced inflammation, glucose intolerance and insulin resistance. HSP72-mediated protection was associated with suppressed inflammatory signaling as well as improved oxidative metabolism (100); however, the precise mechanisms underlying the cellular and tissue-specific therapeutic actions of HSP72 require further elucidation. Indeed, follow-up studies by Gupte et al. (244) in heat-treated rats confirmed findings by Chung et al., showing that induction of Hsp72 protected against high fat diet-induced glucose intolerance and insulin resistance. Furthermore, reduction in activity of citrate synthase and mitochondrial cytochrome oxidase induced by high-fat feeding was prevented by one bout of thermal stress (244). Similarly, Geiger and colleagues also noted that one bout of thermal stress improves skeletal muscle insulin action in aged Fischer 344 rats, and this was associated with reduction in proinflammatory signaling (245). In addition muscle,

Given that muscle HSP72 expression is diminished in obese and type 2 diabetic patients (85, 120), studies are currently underway to investigate whether a novel investigational compound, which causes induction of HSP72, leads to improved insulin sensitivity and reversal of complications associated with T2D.

In addition to pharmaceutical intervention, endurance exercise also elevates Hsp72 mRNA and protein levels in skeletal muscle of humans and rodents (190, 191, 601) and the degree of Hsp72 induction is thought mediated by a variety of factors including muscle glycogen content (191), tissue hypoxia (636), the severity of exercise thermal stress, and or the degree of protein oxidation (601). In addition, activation of HSP72 by thermal stress conditioning is also shown to improve antioxidant capacity and this was associated with reduced muscle injury in rats following downhill running (589). The precise stimuli and mechanisms required for the induction of HSP72 during exercise requires further investigation as well as the molecular underpinnings mediating the therapeutic benefit of HSP72 elevation.

Endoplasmic reticulum stress

Evidence implicating inflammation, specifically endoplasmic reticulum (ER) stress in the etiology of β-cell apoptosis as well as liver and adipose tissue dysfunction is now well supported (281). It is clear that the capacity of the ER to adapt to stress is paramount for the

maintenance of cellular health. The ER is the organelle responsible for protein folding, maturation, quality control, and trafficking. This organelle becomes "stressed" when newly synthesized unfolded proteins accumulate excessively in the lumen and, as a consequence, the unfolded protein response (UPR) is initiated to resolve the cellular stress. Importantly, the branches of the canonical UPR intersect with two main inflammatory pathways including NF-κB and JNK-AP1. In addition to the accumulation of unfolded nascent proteins, ER stress can also be induced by imbalances in calcium, glucose and energy deprivation, hypoxia, pathogen, toxins and certain lipids (281). Thus, cells specifically involved in handling and secreting large quantities of proteins, lipid, and lipid mediators are highly susceptible to ER stress and the cellular consequences of the UPR.

In the pancreas, lipotoxicity directly affects ER stress-mediated β-cell death (93). ER stress initiates a cascade of signaling events culminating in the attenuation of *de novo* protein synthesis and transcriptional activation of genes encoding ER chaperones to further assist in protein refolding or removal by the ubiquitin-proteosome pathway. An impaired or defective UPR leads to apoptosis. Markers of ER stress include PKR-like ER kinase (PERK), activating transcription factor (ATF), and inositol requiring (IRE)1. During cellular stress PERK becomes phosphorylated, leading to subsequent phosphorylation of eukaryotic initiation factor (EIF)2α, causing induction of ATF4. Additionally, ATF can also activate apoptotic pathways including C/EBP homologous protein (CHOP), JNK, and caspases. A strong link between ER stress signaling and β-cell function is evidenced by ER stress gene expression increased in islets from humans with T2D as well as d*b/* d*b* mice (294, 385). Within the lumen of the ER, protein chaperones, such as BiP or GPR78, GPR94, calnexinm, and calrecticulin assist in the execution of proper protein folding and the elimination of misfolded or unfolded proteins. Phenylbutyrate (PBA) or BiP overexpression in INS-1 cells causes inactivation of IRE1, reduced ER stress, and prevention of palmitate-induced cell death (93). This work suggests that selective targeting of the UPR response in β-cells could prevent cellular apoptosis, preserve β-cell mass, and prevent T2D; however, evidence for this in humans is lacking.

In liver and adipose tissue samples from genetically obese or high-fat fed mice, markers of ER stress (increased PERK, EIF2α, and c-Jun phosphorylation) were elevated when compared to lean and normal chow fed controls (235, 486). This inflammatory stress response leads to suppression of insulin receptor signaling through hyperactivation of JNK and subsequent serine phosphorylation of IRS-1. X-box-binding protein (XBP)-1 is a bZIP protein that is spliced during ER stress and becomes a key transcriptional regulator of an array of genes that are important for ER stress resolution including the induction of molecular protein chaperones. In cells, the degree of ER stress induced by the chemical compound and JNK activator tunicamycin was directly impacted by XBP-1 expression; that is, cells overexpressing XBP-1 were refractory to ER stress. *In vivo* studies in rodents support cell-based studies as mice deficient (heterozygous null) in XBP-1 develop glucose intolerance and insulin resistance that is associated with tissue inflammation and impaired insulin signaling (486).

In follow-up studies by the same research group, 4-phenyl butyric acid and taurine-conjugated ursodeoxycholic acid were shown to alleviate ER stress in cells and rodents.

Chemical or pharmaceutical chaperones, such as 4-phenyl butyric acid (PBA), trimethylamine *N*-oxide dihydrate (TMAO), and dimethyl sulfoxide, are a group of low molecular weight compounds known to stabilize protein conformation, improve ER folding capacity, and facilitate the trafficking of mutant proteins. Similarly, endogenous bile acids and derivatives including ursodeoxycholic acid and its taurine-conjugated derivative (TUDCA) are also shown to modulate ER function. Specifically, treatment of obese and diabetic mice with PBA and TUDCA resulted in normalization of hyperglycemia, restoration of systemic insulin sensitivity, resolution of fatty liver disease, and enhancement of insulin action in liver, muscle, and adipose tissue (487), suggesting that chemical chaperones enhance the adaptive capacity of the ER and exhibit potent antidiabetic effects in rodents.

In humans, weight loss following gastric bypass (GBP) was associated with reduced ER stress in adipose and liver and a marked improvement in hepatic, skeletal muscle, and adipose tissue insulin sensitivity (236). Markers of ER stress in adipose tissue significantly decreased with weight loss including expression of Grp78 and spliced sXBP-1, as were phosphorylated EIF2α and JNK1. Liver sections from a subset of subjects showed intense staining for Grp78 and phosphorylated EIF2α before surgery, which was reduced in post-GBP sections. Similarly, 8 weeks of daily endurance exercise reduced proinflammatory signaling and as well as PERK and EIF2α phosphorylation in adipose and liver from high-fat-fed rats (141). Interestingly, recent work from the Spiegelman laboratory shows that the UPR is initiated in skeletal muscle following an acute bout of treadmill exercise and is involved in mediating muscle adaptations when exercise is performed repetitively (700).

Collectively, these findings demonstrate that chronic ER stress is a central feature of peripheral insulin resistance and T2D and that pharmacologic manipulation of this pathway coupled with weight loss may offer a novel therapeutic strategy for treating these common chronic diseases. Whether endurance exercise provides a therapeutic benefit in ameliorating chronic ER stress associated with obesity and T2D requires further study. The role that muscle-specific ER stress plays in tissue remodeling and metabolic function is an emerging area of investigation also requiring greater delineation and mechanistic insight.

Adipose tissue as an endocrine organ

It is known for over a decade now that adipose tissue dysfunction is a central underpinning link to obesity in the pathogenesis of the MS and T2D (Fig. 5). Over the past decade adipose tissue has been redefined as a dynamic metabolic, endocrine organ secreting various cytokines, chemokines and adipokines in a paracrine, autocrine, and endocrine fashion. Much of this work is reviewed in references (71, 229, 515, 521, 669, 732). Adipose tissue is no longer simply considered a passive energy storage depot, but instead is now recognized as the largest endocrine organ in the body secreting more than a hundred factors including fatty acids, cytokines, chemokines, prostaglandins, and steroids. These factors can exert local paracrine effects or are released into the circulation yielding systemic effects on brain, liver, and skeletal muscle. These adipose-secreted factors regulate such processes such as glucose metabolism, appetite, inflammatory signaling, immune function, angiogenesis, blood pressure, and reproductive function. Given that adipose tissue comprises a

heterogeneous mix of cell types, including macrophages and other immune cells, endothelial cells, vascular smooth muscle cells, fibroblasts/preadipocytes, and mature adipocytes, the interplay among these cell types and specific roles of each of these cells in adipose tissue development, substrate metabolism, and production of secretory factors are extremely complex and still not well understood.

Dysfunction within adipocytes specifically is an important contributor to the pathogenesis of obesity and T2D. Recent evidence suggests that enlarged adipocytes, relative impairment in tissue blood flow, cellular hypoxia, local inflammation, and adipose tissue infiltration of proinflammatory immune cells are interrelated processes thought to modulate adipocytes function including adipokine production and secretion; these important factors are reviewed in more detail elsewhere (229). Enlargement of adipocytes, frequently seen in obesity and consumption of a diet rich in saturated fatty acids, is associated with increased expression of proinflammatory adipocytokines whereas small adipocytes or therapies used to promote adipogenesis are associated with insulin sensitization (420, 445). While adipocyte size correlates well with insulin action and a favorable adipokine secretion profile, whether adipocytes size is a primary and central factor in determining adipose health remains to be determined, so herein we have focused on describing the effects of adipose-secreted demonstrating a regulatory role in modulating insulin sensitivity *in vivo* in both humans and rodents.

Leptin

The identification of leptin (726), a 16-kDa cytokine-like peptide, and its receptor (114, 389, 634) initiated the burgeoning field of study into the role of adipose tissue as an endocrine organ. Leptin gained increasing attention in the late 1990s and this work fashioned leptin into a central regulator of feeding and energy homeostasis (209). Mice with mutations in the leptin gene or its receptor are remarkably obese (114, 208, 389). Likewise, human leptin mutations recapitulate an obese phenotype. A primary effect of leptin is exerted in the brain where the receptor is highly expressed in the hypothalamus. Leptin is shown to repress orexigenic pathways including neuropeptide Y and agouti-related peptide and activate anorexigenic pathways, pro-opiomelanocortin, and cocaine and amphetamine-regulated transcript (CART) (177, 179). The leptin receptor belongs to the IL-6 receptor family of class I cytokine receptors and exerts its central and peripheral effects on metabolism via the Janus kinase (JAK)-signal transducers and activators of transcription (STAT) and PI3K (512). Leptin administration by intracerebral catheter directly into the brain decreases food intake and increases energy expenditure, and prolonged exposure leads to a reduction in total body weight (12).

Despite the known anorexic actions of leptin, administration of recombinant leptin as an obesity therapeutic proved futile given central leptin resistance that occurs with increasing adiposity. This is consistent with the many observations that leptin levels are markedly elevated in obese humans and rodents and correlate well with adiposity. Several regulators of leptin signaling have been proposed including SH2 containing SHP2 and protein tyrosine phosphatase 1B (PTP1B) and SOCS proteins. Early work by the Flier laboratory showed that leptin administration causes a rapid induction of hypothalamic Socs3 mRNA in mice

and mediates feedback inhibition of the leptin receptor (67,68). Hypothalamic deletion of *Socs3* (451) or whole body *Socs3* haploinsufficiency (292) confers enhanced central leptin sensitivity and protection against diet-induced obesity. Furthermore, work by Levin et al. (396) showed that leptin-induced STAT3-phosphorylation, a surrogate marker for leptin receptor activation, was markedly reduced in the hypothalamic arcuate, ventromedial, and dorsomedial nuclei of high-fat fed rats even prior to obesity, while impaired leptin transport across the blood brain barrier was only observed after animals became obese. Collectively, these findings suggest that leptin resistance occurs early in the pathogenesis of obesity and that impaired receptor function is mediated by reduced receptor activation and expression mediated by *Socs3* feedback inhibition.

In addition to the effects of leptin on the brain in the regulation of feeding, leptin also exerts direct effects in the periphery to improve insulin action independent of weight loss. Similar to the leptin resistance that develops in the brain, high-fat feeding can reduce leptin mediated effects in skeletal muscle (605, 607) and liver (672). Leptin resistance in muscle during high-fat feeding is thought to occur as a result of reduced leptin receptor expression (452) and elevated *Socs3* mRNA (606, 608). A similar increase in *Socs3* mRNA is also observed in skeletal muscle from obese subjects (606). Furthermore, *Socs3* overexpression in human myotubes can prevent leptin-induced activation of AMPK (606).

Interestingly, swimming exercise improves hypothalamic leptin sensitivity and reduce food intake. Findings show that this exercise-induced effect is mediated by IL-6 (548, 549). While the dual roles of IL-6 in insulin action remain to be clarified, the collaborative work of Pedersen and Febbraio, clearly show that skeletal muscle IL-6 mRNA is rapidly induced at the onset of exercise and is secreted in abundance into the circulation. Furthermore, homozygous IL-6 deletion promotes hepatosteatosis and systemic insulin resistance (423). In addition to the effects of IL-6 on peripheral tissue metabolism, it is likely that IL-6 secreted from muscle during contraction is requisite for exercise-mediated effects in the brain given that IL-6 neutralization prevents exercise-mediated improvements in hypothalamic leptin signaling (199). Indeed, Steinberg et al. (608) also showed that endurance exercise can protect against high-fat diet-induced leptin resistance. Additional, studies are required to dissect apart the leptin-induced effects on metabolism mediated by the brain versus peripheral tissues in response to endurance exercise.

Adiponectin

Adiponectin represents the most abundant protein secreted by adipose tissue (212) and adipose transcript as well as circulating levels of this protein are reduced in humans and in rodent models of obesity and T2D, as reviewed in references (27, 293, 323, 497, 645). A diabetes-susceptibility locus to human chromosome *3q27*, where the adiponectin gene is located, and a quantitative-trait locus strongly linked to the MS in individuals of European and Asian descent have previously been identified (129, 256, 664). In rodents, administration of recombinant adiponectin or genetic overexpression lead to improved insulin sensitivity and enhanced fatty acid oxidation in liver and skeletal muscle (63, 212); while in contrast, genetic deletion is associated with glucose intolerance and insulin resistance (372, 412).

Adiponectin circulates in plasma as a low-molecular weight trimer, a mid-molecular weight hexamer, and a high-molecular weight 12- to 18-mer, and all forms are shown to exert differing biological function (670). The high molecular weight of adiponectin is thought to provide the greatest biological activity of all of the forms; however, additional work to substantiate this notion is required. However, Waki et al. (670) showed that impaired multimerization of human adiponectin is associated with T2D. Two distinct receptors, AdipoR1, which is expressed ubiquitously, and AdipoR2, which is expressed most abundantly in the liver, mediate the biological actions of adiponectin (707). Adiponectin binds and stimulates interaction of the N-terminal cytoplasmic domain of its receptor with and intracellular adaptor protein to activate intracellular pathways (418) including p38 MAPK, AMPK, and PPARα.

Accordant with reductions in circulating adiponectin levels observed in mouse models of insulin resistance and obesity, expression of both receptors was also shown to be diminished (706, 708). Experimental disruption of AdipoR1 or R2 causes blunted adiponectin-induced AMPK and PPARα responses, respectively, both leading to increased hepatic glucose production and hepatic insulin resistance (708). Conversely, adenoviral restoration of AdipoR1 or R2 in liver of diabetic mice improves adiponectin action leading to a partial restoration of insulin sensitivity (708). Interestingly, polymorphisms in both adiponectin receptors are associated with insulin resistance and T2D (135, 324, 429). An important aspect of adiponectin action includes anti-inflammatory effects to inhibit NF-κB and toll-like receptor signaling and these effects on immune cells and endothelium coupled with improved metabolism in peripheral tissues is thought to provide protection against atherosclerosis. In fact, when stratified for levels of serum adiponectin, the risk of myocardial infarction was dramatically reduced in men in the highest adiponectin quintile (504).

Thus taken together, improvement in adiponectin secretion or receptor function may serve as a therapeutic strategy to ameliorate the complications associated with insulin resistance and T2D. Consistent with this notion, it is thought that elevations in adiponectin and adiponectin receptors cause in large part TZD-induced insulin sensitization in type 2 diabetic subjects. Furthermore, recent evidence from reference (346) showed that 7 days of aerobic training (AT) increased circulating HMW adiponectin by 21%, and this alteration was associated with improved basal fat oxidation, glucose tolerance, and insulin sensitivity in middle-age obese individuals. The exercise-induced mechanisms and time course underlying enhanced adiponectin production by adipose tissue and whether corresponding changes in receptor function also occur requires further characterization.

RBP4

In 2005, DNA arrays performed in adipose tissue from mice with an adipose specific deletion or overexpression of GLUT4 to identify adipose secreted factors that may be associated with insulin resistance; retinol binding protein (RBP)4 was identified (710). RBP4 is a circulating transport protein specific for retinol, vitamin A. RBP4 is elevated in tissue and in the circulation of insulin-resistant humans and rodents (234, 710). Furthermore, mice injected with recombinant RBP4 became insulin resistant while mice with a

heterozygous or homozygous deletion of RBP4 were more insulin sensitive and protected from diet-induced insulin resistance. TZD and fenretinide, a synthetic retinoid, both lower circulating RBP4 levels in rodents, and this is associated with improved insulin action in rodent models of obesity and insulin resistance (710). There still remains some controversy with RBP4 and its relationship with obesity and its *in vivo* effects on the pathogenesis of insulin resistance in humans.

Lipocalin

Lipocalin 2 (*Lcn2*), also known as neutrophil gelatinase-associated lipocalin, 24p3, and siderocalin, is a member of a large family of secreted proteins, including RBP4 that are associated with insulin resistance (106, 673, 709, 725). *Lcn2* is an iron transport protein and its expression is induced in 3T3L1 adipocytes by TNFα and dexamethasone (709). In addition to being expressed in adipocytes, *Lcn2* is also expressed in neutrophils, liver, kidney, and macrophages (673). Importantly, *Lcn2* expression is elevated in visceral fat from obese human subjects (106), as well as adipose and serum from multiple rodent models of obesity and insulin resistance (709, 725). In addition, the *circulating Lcn2* concentration is positively correlated with human adiposity, hypertriglyceridemia, CRP, and hyperglycemia but negatively correlated with HDL (673). Retroviral delivery of short hairpin RNA into 3T3L1 adipocytes yielding reduced *Lcn2* expression was associated with improved insulin action while exogenous *Lcn2* promoted insulin resistance in cultured hepatocytes (709). In addition, thiazolidindione-induced insulin sensitization in rodent models of obesity also causes reduced adipose tissue *Lcn2* expression. Therefore, taken together, it is thought that lipocalin 2 is an adipokine that may be involved in potentiating obesity-induced insulin resistance.

PEDF

The serine protease inhibitor pigment epithelium-derived factor (PEDF) is predominantly released from adipocytes and recently was shown to play a causal role in metabolic dysfunction and insulin resistance. PEDF is elevated in obese, insulin-resistant mice, and reduced upon insulin sensitization. Lean mice injected with recombinant PEDF exhibit insulin resistance during hyperinsulinemic-euglycemic clamps, while neutralizing PEDF in obese mice enhances insulin sensitivity (136). PEDF is also shown to alter whole body fatty acid metabolism by increasing adipose tissue lipolysis and decreasing fatty acid oxidation in skeletal muscle, resulting in ectopic lipid deposition in muscle and liver. Together, these results support a causal role for PEDF in obesity-induced metabolic dysfunction and insulin resistance (136, 186).

Resistin

Resistin, first described by Steppan et al. (610), is a cytokine expressed exclusively in adipocytes in mice but is expressed predominantly in macrophages in human subjects (489). Resistin was identified as a TZD-downregulated gene in mouse adipocytes (610) and TZD therapy is also shown to reduce macrophage expression and levels of circulating resistin in humans (489). Furthermore, circulating resistin levels are elevated with obesity (516); experimental resistin elevation in rodents using acute administration (516), adenoviral-

mediated delivery (570), and transgenic overexpression (519) is shown to induce insulin resistance. Consistent with these observations, loss-of-function mutations, achieved by antibody neutralization (610), genetic deletion (44), and anti-sense oligonucleotide administration (459) leads to improved insulin sensitivity and glucose homeostasis.

The receptor for resistin remains unknown and the details regarding resistin action to induce insulin resistance in glucoregulatory tissues is not completely understood; however, downstream of its putative receptor, resistin appears to inhibit hepatic and skeletal muscle AMPK (44, 459, 570). AMPK is known as the master energy regulator and controls substrate production and utilization in liver and muscle, respectively. In addition, findings in adipocytes suggest that resistin is also capable of activating *Socs3* that was previously shown to cause impaired insulin action (612). While a clear relationship between circulating resistin levels and obesity/T2D in humans remains ill defined, differences in assay type and the existence of multiple higher molecular weight oligomers may contribute to the discrepant observations. Resistin levels do, however, correlate well with other inflammatory factors, including CRP peptide and the presence of atherosclerosis (318,472,529,588,611). In humans, this observation is particularly relevant given that resistin is predominantly produced by macrophages, a cell type central in the pathogenesis of arterial lesion development. Lastly, there is genetic support that resistin may play a role in T2D susceptibility given that a single nucleotide polymorphism in the promoter region is linked with obesity and insulin resistance in several populations in the United States, Japan, and Europe (117, 121, 479, 598).

Visfatin, omentin, chemerin, adipsin, ASP

Visfatin is a 52 kDA protein that is highly expressed in visceral but not adipose tissue from obese type 2 diabetic rodents (214). In humans, visfatin is correlated with visceral adipose mass and is upregulated during adipogenic differentiation; thus, plasma levels track well in some studies with human obesity. Interestingly, visfatin binds to the insulin receptor with the same affinity as insulin and promotes adipogenesis, an observation consistent with increased visfatin secretion rates from adipocytes following treatment with the PPARγ agonist rosiglitazone (250). Many unanswered questions remain as to the mechanistic role that visfatin may play in the pathogenesis of obesity and insulin resistance.

Omentin is a 38 kDa protein primarily expressed in omental fat and is thought to be secreted primarily from stromal vascular cells, not adipocytes, within the tissue compartment (711). Little is known about the physiological role of this protein, however, some studies suggest it is regulated by glucose and insulin and is associated with obesity cardiovascular syndromes (630).

Chemerin, also known as tazarotene-induced gene 2 or retinoic acid receptor responder 2 is an 18-kDa novel adipokine expressed predominantly in mature 3T3L1 adipocytes and is elevated in adipose tissue collected from obese animals. Chemerin is secreted as an inactive proprotein and is converted to its biologically active form following C-terminal proteolytic cleavage. While two studies published in 2007 (230, 546) suggest that chemerin modulates adipogenesis and that receptors for the adipokine are present in immune cells, little is known regarding the functional role of this adipokine or its true relationship to disease pathology.

Recent work by Ernst et al. (181) show that chemerin and its receptors chemokine-like receptor 1, C-C motif receptor-like 2, and G protein-coupled receptor 1 (341) are altered in white adipose, liver, and skeletal muscle of obese type 2 diabetic mice. Administration of chemerin exacerbates glucose intolerance in these animals, thus, suggesting a role for chemerin in glucose homeostasis (181). Two independent studies by Bozaoglu et al. (79,80) found that circulating chemerin levels associate with obesity and the MS in Caucasian and Mexican-American populations. Furthermore, experimental hyperinsu-linemia caused a rapid induction of chemerin expression in adipose tissue explants and led to increased chemerin cellular protein level and secretion of chemerin into the conditioned media. Insulin-induced adipose tissue chemerin production was markedly reduced by the addition of metformin, a clinically utilized antidiabetic drug, to the media (631). In addition, a recent report by Ress et al. (533) showed that weight loss achieved by bariatric surgery resulted in significantly reduced circulating chemerin. These findings are consistent with at least a permissive if not a regulatory role for chemerin in glucose metabolism.

In vitro findings from Sell et al. (582) suggest the latter as chemerin release from *in vitro* differentiated human adipocytes and adipose tissue explants were elevated in the obese versus lean subjects. Additionally, chemerin release is correlated with BMI, waist-to-hip ratio, and adipocyte volume. Higher chemerin release also associated with insulin resistance. *Ex vivo* chemerin treatment induced insulin resistance in human skeletal muscle cells at the level of IRS 1, Akt and glycogen synthase (GS) kinase 3 phosphorylation, and glucose uptake (582). Chemerin also activated p38 mitogen-activated protein kinase, NF-κB, and extracellular signal-regulated kinase (ERK)-1/2. Given these recent findings and the known chemoattractant properties of chemerin, it is thought that a reduction in circulating chemerin may diminish the infiltration of proinflammatory immune cells in adipose tissue leading to restrained adipose tissue growth, thus, exerting both direct and indirect effects on peripheral tissues to regulate insulin action.

Adipsin is also known as adipocyte trypsin, factor D, or complement factor D (547). The protein encoded by the *CFD* gene is a member of the trypsin family of peptidases and a protein component of the alternative complement pathway. Recent evidence shows that this serine protease is expressed at high levels in adipose tissue and is secreted by adipose tissue explants. Furthermore, tissue expression levels and circulating concentration levels in the blood are elevated in obese subjects. In addition, adipose tissue also releases a protein derived from the interactions of adipsin with complement C3 and factor B known as acylation-stimulated protein (ASP). ASP is produced in a two-step process in which the aforementioned three proteins of the alternative complement system in which the enzyme adipsin causes cleavage of the parent protein C3 to C3a, which is followed by desargination of the carboxyl terminus to generate C3adesArg or ASP (124). Adipocytes are one of the few cell types that contain all three complement factors necessary for the generation of ASP. ASP is thought to represent the most biologically active component of this system and circulating levels are thought to be modulated by insulin, cytokines, and the fatty acid components of chylomicrons as reflected by dietary fat consumption. ASP is shown to exert potent effects to stimulate TG synthesis and inhibit lipolysis in adipocytes. ASP administration to obese or diabetic rodents enhanced TG clearance by as much as twofold;

similar but less robust findings were also observed for lean control mice (457, 562). In part, TG synthesis is promoted by ASP-stimulated increases in diglycerol acyltransferase activity and glucose uptake into adipocytes, and these effects may be mediated by activation of specific adipocyte protein kinases, for example PKC (39). Mice with a homozygous null mutation for C3, and therefore ASP, showed altered postprandial TG clearance (456). When fed a normal chow or high-fat diet, KO mice were leaner with reduced adipose tissue mass compared with wild-type littermates despite an increased caloric consumption by KO animals. In addition, KO mice had reduced circulating leptin, insulin, and glucose levels suggesting that ASP deletion may exert indirect effects to improve glucose homeostasis and protect against the detrimental effects of high-fat feeding (456). Similar to other adipose secreted factor, levels of adipsin and C3 are reduced following diet-induced weight loss in obese subjects (458,509). The direct cause underlying this reduction remains to be delineated. Thus, the rodent data supports that ASP may play an important regulatory role in energy balance; however, additional work in humans to better understand the mechanistic role of ASP in substrate handling and immune function are required.

Adipose-Secreted Proinflammatory Cytokines and Liver-Secreted Phase Reactant Proteins

TNFα

In the 1970s, TNFα was first described as an endotoxin-induced serum factor able to produce necrosis of tumors (104). Later in the 1980s, TNFα was found to be secreted by cultured macrophages treated with endotoxin and when TNFα was administered to rodents' tissue inflammation and cachexia were induced (642). The human gene, *TNFA*, was cloned in 1984 (475) and the protein was shown to be expressed as a 26-kDa plasma membrane-bound monomer. Proteolytic cleavage by TNFα converting enzyme produces a 17 kDa soluble trimer of the precursor protein. Two TNFα receptors have been described, *TNFR1* (55 kDa isoform) and *TNFR2* (75 kDa isoform), and the subsequent downstream signal is propagated by protein complexes with cytoplasmic adaptor proteins. In 1993, Hotamisligil and colleagues showed increased expression of TNFα mRNA in adipose tissue from four different rodent models of obesity and T2D and found a strong correlation between tissue expression levels and insulin resistance (285). TNFα protein was also elevated locally and systemically. Furthermore, antibody neutralization of TNFα in obese fa/fa rats caused a significant increase in the peripheral uptake of glucose in response to insulin (284). In agreement with neutralization studies, a targeted null mutation in the gene encoding TNFα and the two receptors led to significantly improved insulin sensitivity in both diet-induced and leptin-deficient ob/ob mice (656).

Follow-up studies in obese individuals recapitulated findings in rodents and showed that TNFα mRNA is elevated 2.5-fold in adipose tissue from obese subjects relative to the lean controls (282). Similar increases in TNFα protein concentrations in plasma and in conditioned medium from explanted adipose tissue were also observed; however, it is important to note that circulating levels of this protein are quite low. A strong positive correlation was observed between TNFα mRNA expression levels in fat tissue and the level of hyperinsulinemia, an indirect index of insulin resistance. Dietary treatment in obese

subjects resulted in improved insulin sensitivity and this was associated with a decrease in TNFα expression in adipose tissue. Taken together, these seminal studies conducted by Hotamisligil show that the abnormal regulation of this cytokine is involved in the pathogenesis of obesity-related insulin resistance (280, 282, 285, 656).

To understand the molecular action of TNFα on adipocytes several groups have performed incubation studies using the standard adipocyte cell line, 3T3L1. TNFα incubation has repeatedly been shown to induce lipolysis, as well as inhibit insulin-stimulated glucose transport. Inhibition of insulin action is thought to occur via alteration in phosphorylation status of key molecules in the insulin-signaling cascade (283, 284), which is purported to activate serine-threonine stress kinases as well as tyrosine phosphatases including PTP1B (462). In addition, TNFα is shown to antagonize central transcription factors that are involved in regulating substrate metabolism, insulin action, and adipogenesis (724). Furthermore, TNFα promotes the release of fatty acids from adipocytes and stimulates the production of other inflammatory cytokines, chemokines, and adipokines, for example, IL-6, PAI1, and leptin, all factors with purported insulin resistance producing actions (354). These adipose-secreted factors are elevated in circulation *in vivo* in mice treated with TNFα as well as in humans infused intravenously with the cytokine (660). Studies in TNFR mutant cells demonstrate that TNFα-induced lipolysis, as well as inhibition of insulin-stimulated glucose transport is predominantly mediated by TNFR1 and that the presence of TNFR2 is not necessary for these functions (585). Despite the extensive body of work that has been conducted to understand the biological role and involvement of TNFα and its receptors in the etiology of obesity and T2D, targeted therapies against this cytokine to ameliorate complications associated with these chronic diseases have yielded poor efficacy (470) [as reviewed by reference (447)].

IL-6

The precise role that IL-6 plays in the pathogenesis of obesity and insulin resistance remains controversial despite over a decade of intense research. Circulating levels of IL-6 are increased in obese subjects and are reduced with insulin sensitizing therapies (56, 376). Similar to leptin, IL-6 at rest is secreted primarily from adipose tissue and, thus, a reduction is adipose tissue mass leads to a reduction in circulating IL-6 concentration. Furthermore, variants in the *IL-6* gene are associated with adiposity in human subjects (23, 513). However, whether the correlation between IL-6 and obesity/insulin resistance syndrome reflects a causal relationship has yet to be confirmed. *In vitro* findings provided by several laboratories indicates that IL-6 induces insulin resistance in cultured hepatocytes and hepatoma cells (584), impairs insulin action, and promotes lipolysis in adipocytes (376, 554, 646). Furthermore, IL-6 neutralization *in vivo* leads to improved insulin action in obese ob/ob leptin deficient and high-fat-fed mice (360). While these findings support a negative role for IL-6, recent work by Sadagurski et al. from the laboratory of White, show that mice with transgenic overexpression of IL-6 are more insulin sensitive and display increased energy expenditure compared to wild-type animals despite comparable fat pad mass and food consumption (560). Transgenic mice fed a high-fat diet were also partially protected against insulin resistance and adipose tissue weight gain. When the *IL-6* transgene was expressed in leptin deficient ob/ob mice, these animals showed improved glycemia and a

reduction in fed and fasting insulin levels. A role for I-L6 in energy expenditure and improved glucose uptake in rodents and humans is previously supported (101, 647).

Taken together the notion that IL-6 can exert both pro- and anti-inflammatory actions is gaining scientific support. Work by Rose-John and colleagues may resolve some of the confusion related to IL-6 function *in vivo* in that the pro- and anti-inflammatory actions of IL-6 may be ascribed to differences in signaling from the soluble and membrane bound IL-6 receptors. The activities of IL-6 via the soluble IL-6R, referred to as IL-6 "transsignaling" is largely responsible for proinflammatory IL-6 signaling since all cells express the gp130 receptor (gp130R), but many cells lack the membrane bound IL-6R. A disintegrin and metalloproteinases (ADAMs) are important enzymes involved in "ectodomain shedding" of a diverse group of molecules including growth factors, cytokines, receptors and adhesion molecules, and altered expression of specific ADAMs are associated with disease pathophysiology. Specifically, the membrane bound IL-6R is shed via ADAM10 and ADAM17. As a consequence of receptor shedding, the IL-6/IL6R complex can travel to sites of inflammation or cellular dysfunction and transduce a signal via the gp130R (550). Overexpression of a soluble form of gp130 (sgp130) either by administering a dose of sgp130Fc protein exogenously or by generating a transgenic mouse overexpressing this protein (515) in both cases blocked IL-6 transsignaling and inflammation to a similar extent as described for IL-6 null mice. These data support the notion that the sIL-6R is responsible for most of the tissue inflammation brought about by IL-6 signaling. Thus, in pathological cases where IL-6 signaling is heightened, it is proposed that blocking IL-6 transsignaling, by downregulation of sheddase activity using specific small molecule inhibitors, or by squelching/mopping up the soluble receptor, may serve as an effective way to repress inflammation and restrain disease progression. This notion is supported by studies conducted in human patients harboring a single nucleotide polymorphism (Gly148Arg) for the IL-6 signal transducer (IL-6ST)/*gp130* gene, which is associated with decreased IL-6 responsiveness and a significantly reduced odds ratio for heart disease (61). Clinical trials are currently underway to investigate the impact of reduced inflammatory signaling via ADAM inhibition on cancer progression. Whether this mechanism may also be exploited for treatment or prevention of T2D requires further investigation.

IL1β and IL-1Ra

IL-1 is linked with various autoimmune diseases and now metabolic dysregulation. Eleven ligands and ten receptors have now been identified in the IL1 family. IL-1β is mainly produced by immune cells including blood monocytes, tissue macrophages, dendritic cells, B lymphocytes, NK cells; however there is some evidence for production by β-cells within pancreatic islets as well (264, 413). IL-1β is implicated in β-cell destruction that is purportedly mediated by ER stress and activation of apoptotic pathways. Furthermore, endogenous production or exogenous administration of the IL-1 receptor antagonist (Ra) or anti-IL1β monoclonal antibody (XOMA 052) protect against diet-induced insulin resistance and β-cell death (174, 375, 485, 572). IL-1β is induced and IL-1Ra is repressed in human islets cultured in high glucose or treated with leptin suggesting a role for adipose secreted factors in the pathogenesis of islet destruction (414). In human subjects, a strong association between variation in the *IL-1* gene family and indices of glucose homeostasis and T2D

prevalence have been documented (408) and circulating IL-1β levels are elevated in type 2 diabetic patients and subjects with the MS, however, show a direct causal role for IL-1β and IL-1Ra in insulin resistance and β-cell destruction have yet to be confirmed.

PAI-1

Plasminogen activator inhibitor (PAI)-1 is a 47-kDa serine protease inhibitor protein and the principal negative regulator of tissue plaminogen activator and urokinase, activators of plasminogen and hence fibrinolysis. PAI-1 is mainly produced by the endothelium but is also produced and secreted by adipose tissue and macrophages (298). Thus, circulating levels of PAI-1 are elevated with obesity and the MS (367). Therefore, the risk of thrombosis is elevated in humans with increased circulating levels of PAI-1. During inflammatory conditions fibrin is deposited at the site of injury and PAI-1 is thought to exert and important profibrotic role. ANGII as well as cytokines and growth factors are shown to promote PAI-1 synthesis, thus adipose secreted factors appear to work in concert to promote atherosclerotic lesion development and thus constitute an important nexus by which obesity elevates CVD risk.

Weight loss induced by bariatric surgery performed on morbidly obese subjects significantly diminished tissue factor, PAI-1 and prothrombin fragment 1.2 levels and the thrombotic lag phase was significantly extended which correlated well with improved insulin sensitivity (35). This relationship is supported in rodents in which PAI-1 null mice are protected against high-fat diet-induced accretion of fat and insulin resistance (409). Additional studies are needed to better understand the role of PAI-1 in the pathogenesis of obesity and insulin resistance.

Angiotensin

Angiotensin (ANG) is produced by adipose and transcript levels are elevated in adipose tissue from obese subjects (662). ANGII is a potent vasoconstrictor and may underlie the increased incidence of obesity-associated hypertension. This notion is supported in rodent models where hypertension and increased fat mass were observed in animals with an adipose selective overexpression of ANGII (419). In addition, the same group also showed that adipose selective ablation of ANGII is protective against diet-induced obesity and in part this observation was explained by increased locomotor activity (419). Given that ANGII is shown to promote cellular oxidative stress and stimulate NF-κB leading to the increased secretion of PAI-1, leptin, IL-6, and IL-8 in human primary adipocytes suggests that ANGII-induced inflammation may underlie the association between ANGII expression and increased adiposity. Given that treatment with ANG converting enzyme inhibitors (ACEIs) reverses inflammation, increases circulating adiponectin levels, and protects against high-fat diet (HFD)-induced adipose tissue weight gain supports a role for the renin-ANG pathway in the etiology of obesity and the MS (145, 193, 393, 394). Further studies in the clinic must be performed to determine whether pharmaceutical targeting of this system is efficacious and practical in ameliorating complications associated with T2D.

CRP

CRP is a member of the pentraxin family of acute phase proteins produced by liver in response to secreted factors from macrophages and adipocytes, including IL-6. CRP is thought to link chronic inflammation with atherosclerosis. Its putative role is to bind dead or dying cells to activate the complement system via c1q thus promoting cellular removal by macrophage phagocytosis. CRP is the best characterized and well-standardized marker of systemic inflammation, and several studies now confirm that CRP levels are elevated in patients with the MS. Furthermore, as many as six major prospective clinical trials support the hypothesis that CRP contributes to increased CVD risk. In the insulin resistance and atherosclerosis study, CRP was highly associated with central adiposity and insulin resistance, and additionally with blood pressure, LDL cholesterol, and TGs. Administration of recombinant CRP causes impaired insulin action and endothelial nitric oxide synthase (eNOS) production in endothelial cells (704). Syk and JNK are thought to mediate CRP-induced insulin resistance as inhibitors of these kinases (Y27632 and SP600125, respectively) restored in part insulin action and eNOS production (704). Similar findings of CRP-induced insulin resistance by a JNK-mediated mechanism to inhibit IRS-1 were observed for L6 muscle cells (140). In monocytic immune cells, CRP is shown to promote inflammation by induced expression of tissue factor, cytokines (IL-6 and TNFα), ROS, CCR2, and matrix metalloproteinases (157, 158, 263, 596). While clinical findings strongly support a relationship between CRP levels and various features of the MS, experimental studies to clarify the specific sites and molecular modes of CRP action *in vivo* are still needed. Additionally, CRP is inversely related to fitness level (31, 32, 587), and circulating levels are reduced in healthy and T2D patients following lifestyle intervention, including chronic aerobic exercise (15, 142); as reviewed in reference (278). Additionally, some evidence indicates that resistance training (RT) may also induce a reduction in circulating CRP (163, 262, 477). However, other evidence suggests exercise training does not alter CRP levels (131, 359, 623, 731).

Adipose tissue-secreted chemokines

Chemokines are a family of small (8–10 kD) cytokines that are involved primarily in promoting the migration, chemotaxis, of immune cells to sites of infection, cellular damage, inflammation, or altered metabolism; however, nonchemotactic homeostatic functions have also been described. In addition to the small size, many in the chemokine family members also possess conserved amino acid sequence homology including four well-characterized cysteine residues that are important for creating the characteristic chemokine three-dimensional structure. Chemokine proteins are typically produced as propeptides, in which a signal peptide of approximately 20 AA is cleaved upon mature peptide release. Members of the chemokine family are divided into four groups defined by the spacing of the first two cysteine residues: CC chemokines, CXC chemokines, C chemokines, and CX_3C chemokines. Chemokines bind to cell surface G-protein coupled receptor containing on average seven transmembrane domains. As many as 20 chemokine receptors have been characterized and these are classified into four groups based upon the type of chemokine they bind. With respect to the cross talk between adipose tissue and the immune system in the regulation of whole body insulin action, the CC chemokines including monocyte

chemoattractant protein (MCP)-1 (CCL2), MIP1α (CCL3), and regulated-upon-activated-normal-T-cells expressed and secreted (RANTES or CCL5) have been studied the most extensively.

CC chemokine MCP1

MCP-1 is expressed in a number of cell types including skeletal muscle, endothelial cells, smooth muscle cells, and adipocytes. MCP-1 exerts its action through CC motif receptor (CCR) 2 that is also expressed in a variety of tissues including skeletal muscle, adipocytes, and macrophages. MCP-1 was first described as a monocyte and endothelial secretory product involved in the pathogenesis of atherosclerosis (581). In addition, MCP-1 is insulin and TNFα responsive as expression levels and rates of secretion from adipocytes were markedly increased with hyperinsulinemia or TNFα treatment (567). Furthermore, MCP1 is overexpressed in adipose from obese rodents and insulin action as well as expression levels of several adipogenic genes (LPL, adipsin, GLUT4, aP2, β3-adrenergic receptor, and PPARγ) are reduced in cells treated with MCP-1 (567). Secretion of MCP-1 from adipocytes is thought to prompt the diapedesis or movement of monocytes from the vascular compartment into adipose tissue. Once differentiated, these tissue resident macrophages/ professional phagocytes exert a host of functions to regulate tissue remodeling, inflammation, and substrate metabolism. The phenotypic role of tissue resident macrophages has received increasing attention in the past decade and despite the increased exploration, many unresolved issues remain.

Given the increased MCP-1 expression and secretion from adipose taken from obese, diabetic, and high-fat-fed mice, Kanda et al. (329) generated animals with an adipocyte selective overexpression of MCP-1. These mice exhibited whole body insulin resistance, had increased macrophage infiltration in adipose tissue, and hepatic TG accumulation (329). Consistent with this observation, MCP-1 homozygous null mice were protected from high-fat-diet-induced insulin resistance, hepatic steatosis, and adipose tissue macrophage infiltration. A similar amelioration of these measures was observed in d*b*/d*b* with a dominant negative MCP-1 mutation. Similar adipocyte-specific MCP-1 overexpression studies conducted by Kamei et al. (328) yielded identical findings.

Collectively, this work is further supported by several investigations in which the elimination or inhibition of CCR2 was protective against insulin resistance and complications associated with T2D (628,629,682). Until recently, it was unknown as to whether MCP-1 could induce insulin resistance *in vivo* independent of alterations in adipose tissue inflammation or obesity. Tamura et al. (628) recently showed that acute administration of purified MCP-1 to circulating levels comparable to those observed in obese rodents, was sufficient to cause insulin resistance measure by glucose clamp; this was independent of adipose tissue inflammation.

Studies in visceral adipose tissue from lean and obese human subjects show that macrophage specific markers and CC chemokines in monocyte chemotaxis as well as their receptors are elevated in obese visceral fat compared with lean controls. Furthermore, adipose tissue expression of these chemokines and receptors correlated positively with increased systemic inflammation and insulin resistance (297).

CX chemokine CXCL5

CXCL5 or epithelial neutrophil-activating peptide (ENA-78) belongs to a family of chemokines that is mainly shown to recruit and activate neutrophils to sites of inflammation through interaction with the CXCR2 receptor (671). Although this chemokine has been implicated in lung cancer, pulmonary diseases and arthritis, recent work by Aquilante et al., show that CXCL5 is highly expressed in adipose tissue from obese subjects and that circulating levels of the chemokine are elevated almost twofold over levels observed in lean subjects (24, 112). Adipose tissue explants harvested from obese and diabetic rodents support observations of increased circulating levels of CXCL5 in obese humans. Fractionation analyses performed in both rodent and human white adipose tissue shows that the stromal vascular fraction, specifically tissue resident macrophages are the primary source of CXCL5. Furthermore, this group also shows that the CXCR2 receptor is most highly expressed in skeletal muscle compared with adipose tissue and liver, suggesting that CXCL5 acting through its putative receptor, CXCR2, may exert its deleterious effects on glucose homeostasis by inhibiting insulin action in skeletal muscle. In support of this notion, Chavey et al. (112) showed that treatment of muscle *ex vivo* with recombinant CXCL5 markedly inhibited insulin-stimulated glucose uptake and signaling. Similar observations were made in mouse embryonic fibroblasts. Follow-up mechanistic analyses suggest that CXCL5 activates the JAK/STAT pathway and SOCS2, which were shown previously to inhibit proximal insulin signal transduction. Use of CXCL5 neutralizing antibodies and inhibitors against Jak2(AG490) and the CXCL5 receptor CXCR2 support this mechanism of action.

Interestingly, an 800 kcal/d caloric deficit that led to an average 7% reduction in body weight in obese women was correlated with a significant decrease in serum CXCL5 concentration (112). A more pronounced reduction in CXCL5 was observed following treatment with the insulin sensitizing compound rosiglitazone (112). Taken together, CXCL5 is an important adipose tissue secreted chemokine that is elevated with obesity and exerts effects directly on skeletal muscle to cause insulin resistance via JAK/STAT inhibition of proximal insulin signaling. A direct role of exercise to suppress adipose chemokine secretion independent of adipose tissue weight loss warrants further attention.

Immune Function and Regulation of Insulin Action and Adiposity

Chronic low-grade inflammation is a central underpinning in the development of obesity and insulin resistance and cells of both the innate and adaptive immune system are shown to play an important role in the pathogenesis of metabolic disease (Fig. 5). In 2003, two seminal papers were published showing an accumulation of F4/80-positive immune cells in adipose tissue of obese mice and animals fed a diet rich in fat (683, 703) (Fig. 6A). These F4/80+ adipose tissue macrophages obtained from obese animals were found to secrete proinflammatory, insulin resistance-producing factors including TNFα, IL6, IL1β, serum amyloid A3 (SAA3), and CCL2 (i.e., MCP-1) to name a few (684) (Fig. 6B). These two publications sparked a fervent burst of investigation into the role of the immune system in the regulation of glucose home-ostasis and adiposity. Subsequent studies have demonstrated that lymphocytes including regulatory T cells, effector T cells, and B cells are recruited

during various stages in the expansion of adipose tissue as well (168, 463, 473). Many propose that regulatory T cells, TH2-polarized T cells as well as alternatively activated anti-inflammatory macrophages are most abundant in adipose tissue from lean rodents, whereas diet-induced adiposity is associated with the orchestrated trafficking of B cells, TH1-polarized T cells, and effector T cells with later stages of adipose tissue expansion showing the accumulation of classically activated proinflammatory macrophages and natural killer cells (168, 169, 473).

Despite the burgeoning research in this field, the metabolic factors regulating immune responses in glucoregulatory tissues including adipose, liver, and skeletal muscle remain poorly defined. To date, much of the work in this field implicates macrophages as major effectors in the pathogenesis obesity-insulin resistance phenotypes. Early studies clearly show that ablation of genes involved in inflammatory signaling within macrophages is protective against diet-induced obesity and insulin resistance (28, 94, 559), while conversely, hematopoietic/myeloid-specific ablation of transcription factors involved in inflammation repression promotes diet-induced obesity and whole body insulin resistance (267, 469) as well as accelerated atherosclerotic lesion development (538). In later part of the past decade, a theme emerged in which immune cells were rigidly ascribed as either phenotypically anti-inflammatory, alternatively activated "M2" or proinflammatory, classically activated, "M1." Although the appealingly simplistic binary classification of M1 versus M2 macrophage phenotype has been readily accepted by the obesity/diabetes research community, the diversity and complexity of immune cell type and function favors a spectral classification taking into account the required functionality of the immune cell and the specificity of chemotactic signal and environmental milieu unique to the recruiting tissue (125, 232).

Altering the chemotactic signal from a given tissue is shown to exert either health benefit or pathogenic repercussions. For instance, there is some suggestion that deletion of MCP1 or its receptor, CCR2, confers protection against adipose tissue macrophage accumulation, insulin resistance, and atherosclerosis during high fat feeding (329, 471, 682) whereas adipocyte-specific overexpression of MCP1 promotes macrophage infiltration, inflammation, insulin resistance and atherosclerosis (328).

Work over last past decade clearly shows a critical role for the immune system in the regulation of glucose homeostasis and the pathogenesis of adiposity and atherosclerotic lesion development. In addition, more recent evidence shows that diet/caloric restriction and/or exercise are potent interventions to promote adipose tissue weight loss and alteration of immune cell phenotype (30,344,364). Thus, the key for future studies will be to further delineate the tissue-selective aspects of immune cell recruitment and function, and determine how each cell type may be exploited to ameliorate disease complications without compromising innate immunity.

Chronic exercise exerts potent anti-inflammatory effects (40, 335, 502) and these effects are likely mediated by direct effects on the immune system and a reduction in visceral fat including diminished release of proinflammatory cytokines and chemokines from adipocytes [as reviewed by reference (223)]. In part, endurance exercise reduces toll-receptor

expression on monocytes and macrophages (200), and experimental reduction in Tlr expression is associated with reduced induction of proinflammatory signaling and diet-induced obesity (144, 559, 650). Furthermore, treadmill exercise reduces adipose tissue macrophage infiltration and promotes an M2 anti-inflammatory immune cell phenotype (344). During exercise, skeletal muscle is thought to produce and secrete a host of anti-inflammatory cytokines that are thought to produce and secrete a host of anti-inflammatory cytokines that are shown to experimentally alter immune cell function and phenotype. Muscle-secreted factors are discussed below.

Muscle as an Endocrine Organ—Myokines and Insulin Action

Mounting evidence suggests that skeletal muscle is an endocrine organ capable of secreting a variety of factors that act on peripheral tissues to alter metabolic function. Myokines are skeletal muscle specific-secreted factors able to exert humoral effects *in vivo* and may underlie the health benefits associated with daily physical exercise. Muscle-derived factors including IL-6 (100, 101, 492, 493) IL-15 (514), BNDF (365, 424, 520), FGF21 (29, 64, 132, 164, 311, 349), and Follistatin-like 1 (482, 484), and SPARC (466) are a few putative myokines currently under investigation. IL-6, one of the first myokines identified, is shown to increase in expression over 100-fold during prolonged exercise and stimulate the appearance of other circulating anti-inflammatory cytokines such as IL-1Ra and IL-10, and inhibit the production of the proinflammatory cytokine TNFα (494, 603). In addition, IL-6 enhances lipid turnover, stimulating lipolysis as well as fat oxidation (16, 101). Moreover, contrary to conventional wisdom IL-6 infusion stimulates glucose disposal in humans and rodents (101, 719), while in contrast, homozygous deletion of IL-6 promoted systemic insulin resistance in mice (423). Novel secreted proteins of the human and mouse muscle proteome are being vigorously studied and indeed several of these are now associated with improvements in immune cell function (442) and restraint of cancer cell proliferation (270). Whether these observations in culture translate directly to the reduction in cancer risk associated with exercise requires further investigation. Considering that skeletal muscle comprises approximately 40% of total body mass and is the primary tissue contributing to insulin-mediated glucose uptake and fatty acid oxidation, identification of signals emanating from muscle to regulate whole body energy balance and metabolism will likely prove to be of therapeutic benefit.

Exercise and the Metabolic Syndrome

Epidemiology/observational evidence

As previously discussed, MS is clearly a significant public health problem in the US with both fitness and physical activity playing vital roles in preventing and treating MS. Numerous studies have clearly demonstrated that the pathogenesis of the MS is largely attributable to a lack of fitness and physical activity. Some of these studies are described below. Cross-sectionally, several studies have indicated greater prevalence of MS in subjects with lower fitness. Lakka et al. (378) noted associations of leisure-time physical activity and cardiorespiratory fitness (CRF) with MS in a population-based sample of 1069 middle-aged men without T2D, CVD, or cancer. Men who engaged in moderate-intensity leisure-time physical activity 1.0 h/wk or less were 60% more likely to have MS than those engaging in

3.0 h/wk or more. In addition, men with a VO_{2max} equal to 29.1 mL/kg/min or less were approximately seven times more likely to exhibit MS than those with a VO_{2max} is equal to 35.5 mL/kg/min or more. Across CRF quintiles, as measured by maximal treadmill exercise test, prevalence of MS in a population of 7104 women was lower as fitness increased, with prevalence ranging from 19.0% in the least fit quintile to 2.3% in the most fit quintile (189) (Fig. 7). Additionally, the prevalence of MS in the different age groups for women who achieved a maximal metabolic equivalent (MET) level of 11 or higher was one-third to one-fourth that of women who achieved lower maximal MET levels (189). An additional study in middle-aged men noted age and BMI-adjusted OR for MS of 0.55 and 0.26 for moderate and high fitness, respectively (103).

In a prospective population-based study, LaMonte et al. (379) noted that in 9007 middle-aged men and 1491 women, multivariate OR for incident MS in the low, middle, and upper third of fitness were 1.0, 0.74, and 0.47 for men and 1.0, 0.80, and 0.37 for women, respectively. Similar patterns of significant inverse associations between fitness and MS incidence were seen when men were stratified according to categories of BMI, age, and number of baseline metabolic risk factors. Because lifestyle factors potentially exhibit similar patterns and/or exercise may impact food choices, Finley et al. (197) noted that adjustment for macronutrient intake and other potential confounding variables did not alter the association between CRF and prevalent MS. It is also important to note that in most cases controlling for obesity does not impact the link between fitness and MS.

Muscle strength and lean body mass (LBM) are also related to MS. Jurca et al. (320) demonstrated in men from the Aerobics Center Longitudinal Study (ACLS) that greater muscle strength is associated with lower prevalence of abnormal MS components. Each of the five MS components were inversely associated with muscular strength, as determined by one-repetition maximum (1-RM) bench press and leg press when adjusted for age and smoking status. The OR for MS was 0.33 in the quartile with the highest versus the quartile with the lowest muscle strength. Interestingly, the effects of muscle strength and CRF were independent of each other and largely of BMI (Fig. 8A). The effects of muscle strength were modestly attenuated when controlling for CRF, likely due to the overlap between muscular and aerobic fitness. This suggests that both aerobic fitness and muscular strength have preventive effects on MS risk. In this analysis for CRF, the OR for MS with the highest fitness was 0.08 compared to the lowest. This group followed up their work to demonstrate that muscle strength was inversely associated with incident MS in men, independent of age (319) (Fig. 8B). In addition, in a cohort of 1019 adults, muscle strength was inversely associated with MS risk score; although, adjustment for aerobic fitness attenuated this inverse association (692). Atlantis et al. (33) also noted increased prevalence of MS (by both the ATP III and IDF criteria) in subjects with low peak handgrip strength.

Obviously, investigation of mortality outcomes related to MS and fitness is important. Along these lines, in the ACLS, Katzmarzyk et al. (337) investigated the effects of CRF and mortality in 19,223 men 20 to 83 years old, separated into "healthy" men and those with MS. During 196,466 man-years of follow-up RR of all-cause and CVD mortality were 1.29 and 1.89, respectively, for men with the MS compared with healthy men. However, after accounting for CRF, the associations were no longer significant (0.98 for all-cause and 1.23

for CVD) (Fig. 9). The RRs for all-cause mortality comparing unfit and fit men were similar in men deemed healthy and in those with MS (2.18 and 2.01 vs. fit groups, respectively). Overall mortality risk was 5.18% in the healthy unfit group compared with 1.95% in the healthy fit group and the number needed to treat (NNT) to prevent one death was 31. In those with MS, overall mortality risk was 5.15% in the unfit MS group compared with 2.69% in the fit MS group, with an NNT of 40.6. More importantly, the results indicated that unfit healthy men exhibited higher all-cause and CVD death rates per 10,000 man-years of follow-up than fit men with MS (Fig. 10A and B). Additionally, a significant dose-response relationship between CRF and mortality was observed in men with MS. These data indicate that CRF may be as powerful of a predictor of mortality as all the MS characteristics combined, indicating that CRF should be included as a feature of MS (257). This group went on to demonstrate in 19,173 men (338) that at baseline 19.5% of the men had MS, and the ORs of MS at baseline were 4.7 in overweight and 30.6 in obese men compared with normal weight men. In an average 10-year follow-up, the risks of all-cause mortality were 1.11 in normal weight, 1.09 in overweight, and 1.55 in obese men with MS compared with normal weight healthy men (Fig. 11A). Corresponding risks for CVD mortality were 2.06 in normal weight, 1.80 in overweight, and 2.83 in obese men with MS compared with normal weight healthy men (Fig. 11B). However, after inclusion of CRF in the statistical model, the risks associated with obesity and MS were no longer significant. This data suggests that fitness is likely a better predictor of CVD mortality than obesity or MS. Given the aforementioned increased risk of cardiovascular and all-cause mortality with MS (454), it is likely that a significant portion of this risk is explained by low fitness. These data are compelling evidence that exercise provides protection against mortality risk in subjects with MS.

The odds of having risk factors for MS (elevated systolic blood pressure, serum TG, fasting glucose, and central adiposity) was reported as 3.0 and 10.1 for least-fit men compared to moderately fit and most-fit men, respectively (685). Furthermore, in the Coronary Artery Risk Development in Young Adults (CARDIA) study, low fitness predicted risk of MS as powerfully as conventional factors (102). Additionally, in a study of 5159 men ages 40–59, physical activity level was associated with MS factors, as well as risk of CAD and T2D (676). CRF has been consistently associated with many components of MS, including insulin resistance, HDL cholesterol, TG levels, and blood pressure (685).

While fitness quantitation is the optimal measure when assessing risk, physical activity questionnaire data can be helpful when assessing large datasets. Nevertheless, physical activity energy expenditure is inherently difficult to measure precisely, and previous epidemiological studies have primarily relied on self-reported physical activity when examining associations with MS. Several studies have demonstrated that the pathogenesis of MS is largely attributable to activity levels. Cross-sectionally, Churilla and Fitzhugh (123) used NHANES 1999–2004 data from 5620 adults and the newer AHA/NHLBI definition, again, similar to ATP III except for the fasting glucose cutpoint of more than 100 mg/dL, estimated MS prevalence among US adults at 21.9% and 36.3% for the WHO and AHA/NLHBI criteria, respectively. The highest quintile of physical activity predicted an OR of 0.54 in men and 0.50 in women, compared to the lowest (123). In the Whitehall II study comprising 5153 Caucasian Europeans, the ORs for having MS among participants

engaging in vigorous (METs 5) and moderate (3 METs <5) activity were 0.52 and 0.78, respectively (532). The OR for MS in the high leisure-time physical activity group (intense activity more than two times per week, at least 30 min each time) was 0.33 among 4228 60-year-old Swedish men and women (251). In the Second Manifestations of ARTerial disease (SMART) study examining 1097 patients, the prevalence of MS was lower in physically active patients (>15 MET/h per week) compared to those who were physically inactive (OR: 0.50) (82). Using self-reported physical activity data obtained from 2164 participants, aged 18 to 92 years old living in Portugal, both higher total physical activity during transportation, work, and household (OR: 0.63 in women; OR: 0.55 in men) and higher leisure-time physical activity levels (OR: 0.86 in women; OR: 0.59 in men) were significantly associated with a lower prevalence of MS (566). Ford et al. (203) noted in 1626 men and women from NHANES 1999–2000 that participants who did not engage in any moderate or vigorous physical activity during leisure-time had approximately twice the odds of having MS (OR: 1.90) as those who reported engaging in 150 min/wk or more of such activity. Adjustment for age, sex, race or ethnicity, educational status, smoking status, and alcohol use attenuated the OR (1.46). The adjusted odds ratio for having MS in the high leisure-time physical activity group was 0.33 using the low leisure-time PA group as reference. However, no such inverse association was noted for work-related PA. In the aforementioned study by Carroll et al. (103), findings for CRF were also found for physical activity index (OR for moderate: 0.28 and high fitness 0.12). Interestingly, although CRF is generally considered more precise in the determination of the relationships between exercise training status and disease risk, Franks et al. (206) noted the association between physical activity and MS was much greater than for CRF. Although CRF modified the relationship between physical activity energy expenditure and MS, it suggested a strong inverse association between physical activity and MS, especially in unfit individuals.

These relationships were extended to African-American and native American women, as the OR for MS was 0.18 for women in the highest category of physical activity compared with the lowest, while the OR was 0.07 comparing the duration of groups with the shortest versus longest maximal treadmill time (306). In urban Mexican adults (428), where prevalence of MS was 24.4% (25.3% in men and 21.8% in women), MS risk was reduced among men (OR: 0.72) and women (OR: 0.78) who reported 30 min/d or more of leisure-time activity, and among women who reported an amount of 3 h/d or more of workplace activity (OR 0.75). Furthermore, similar relationships were noted in Asian men for both CRF (390) and physical activity (116) in men and women. These results indicate that the fitness/MS relationship holds across ethnicity. Furthermore, DuBose et al. (166) noted that aerobic fitness modified the BMI-MS relationship, with higher fitness decreasing MS score in normal weight, overweight, and obese children.

Longitudinal studies have also confirmed the development of MS is related to physical activity levels. Over a 4-year follow-up period, the Kuopio Ischemic Heart Disease Risk Factor Study reported an inverse relationship between leisure-time physical activity (defined as >3 h/wk of structured or lifestyle physical activity of 4.5 METs) and the development of MS in middle-aged men (374) (Fig. 12). In the Medical Research Council Ely Study, over 5.6 years of follow-up, the physical activity energy expenditure measure predicted a

progression toward MS that was independent of aerobic fitness, obesity, and other confounding factors in middle-aged healthy Caucasians (175). In the Oslo study, leisure-time physical activity was a significant predictor of incident MS (OR: 0.65) over 28 years of follow-up in men (275).

In addition to the link between MS factors and fitness or physical activity, other risk factors in subjects with MS are also linked with fitness. For instance, greater white blood cell count is noted in subjects with MS factors and low CRF (517). In another example, Pitsavos et al. (505) noted that after controlling for various potential confounders, physically active individuals with MS had lower levels of CRP, white blood cells, serum amyloid A, TNFα, and IL-6 when compared to sedentary subjects. Additional data indicates that in subjects with MS, higher CRF is associated with lower CRP concentration (31).

Intervention Effects on Metabolic Syndrome

Early on it was suggested that physical activity and exercise prevented or controlled MS (51, 180), and numerous studies have investigated the effects of exercise on MS. Many studies should be acknowledged as they have investigated MS components, such as insulin resistance/hyperglycemia, dyslipidemia, hypertension, and obesity, and/or have assessed markers of metabolic health other than those that makeup the definition of MS. Many of these studies were not designed to test effects of physical activity on MS *per se,* given its more recent characterization. Relatively few studies, have investigated the effects of exercise on MS *per se*, which we discuss here, while the individual components of MS are discussed in Chapter by Booth et al. (76).

The Studies of a Targeted Risk Reduction Intervention through Defined Exercise (STRRIDE) study noted that a low amount of moderate intensity exercise (~19 km/wk of walking) and a high amount of vigorous intensity (~32 km/wk of jogging), but not a low amount of vigorous intensity (~19 km/wk of jogging), improved MS compared to controls, with only the high-vigorous reporting a decrease in BMI (316). Katzmarzyk et al. (340) investigated the efficacy of exercise training in treating MS, as defined according to the NCEP criteria in 621 Black and White participants (males and females, age 17–65 years) from the HERITAGE Family Study. The presence of MS and component risk factors were determined before and after 20 weeks of supervised aerobic exercise training (3 d/wk at 55% of VO_{2max} for 30 min and progressing up to 75% VO_{2max} for 50 min). The prevalence of the MS using ATP III criteria was 16.9% in this sample (105/621) of apparently healthy participants. Of the 105 participants with MS at baseline, 30.5% were no longer classified as having MS after training.

Kemmler et al. (347) using 4 d/wk group exercise sessions combining aerobic (20 min, 70–85% HR_{max}) and RT (2 sets, 12–15 repetitions) in older women with MS noted that although several components of MS decreased significantly in the women, a nonsignificant decrease ($P = 0.15$) in the number of MS factors by IDF criteria was noted. Stewart et al. (613) investigated the effect of a combined strength and endurance exercise protocol (3 times per week, seven exercises, two sets of 10–15 repetitions at 50% 1-RM; 45 min of endurance exercise at 60–90% HR_{max}) on MS prevalence in older subjects (55–75 years

old). There was no significant difference in the number of subjects without MS in the intervention versus control groups, although the number of subject MS factors decreased by 0.65 factors in the exercise group and 0.30 in the control group ($P = 0.06$).

No studies on RT alone have investigated effects on MS *per se*. However, among 137 subjects who participated in RT in the Finnish Diabetes Trial, MS components of hyperglycemia, hypertriglyceridemia, and low HDL were favorable in individuals who were in the upper third of participation rate (median 51 times per year) compared with individuals in the lowest third (median 8.5 times per year) (305).

Regarding interval training, a recent study compared moderate-intensity AT (70% of HR_{max}) to interval training (90% HR_{max}) three times per week, and noted decreases in number of MS criteria (5.9-4.0 for interval training vs. 5.7-5.0 for AT), independent of differences in body weight changes, which were similar. Interval training was superior to AT in enhancing endothelial function, insulin signaling in fat and skeletal muscle, skeletal muscle biogenesis, and in reducing blood glucose, and lipogenesis in adipose tissue, which likely contributed to mechanisms underlying the beneficial effects of interval training on MS (640).

Overall, aside from the STRRIDE and HERITAGE Family Study, relatively few studies have investigated the effects of exercise training on MS *per se* and in those that have, decreases in MS components are noted; however, the effects on MS *per se* need to be investigated further.

Although not the focus of this review, numerous other intervention studies have suggested that combined interventions with diet and exercise/activity help in the treatment and prevention of MS. Combined studies tend to show better effects, with some comparisons made between isolated and combined interventions, and likely the mechanisms for improvements with diet and exercise being, at least in part, independent. Anderssen et al. (22) evaluated the effect of a supervised endurance program (3 d/wk, 60 min at 60–80% HR_{max}) with or without caloric restriction on IDF-defined MS prevalence in middle-aged men recruited from the larger Oslo Diet and Exercise Study. In the exercise group, the MS prevalence was reduced 24% (1% drop in body weight) and the combined caloric restriction and exercise group noted a 67% prevalence reduction (7% drop in body weight), although the MS reduction in exercise group was not significantly different from the control group (12%). Although exercise was not investigated alone, Okura et al. (474) noted that exercise plus a low-calorie diet reversed MS in 36 of 38 subjects compared with 15 of 21 subjects with a low-calorie diet alone who completed a 14-week intervention (eight subjects did not complete the intervention).

In the Diabetes Prevention Program, lifestyle intervention resulted in 3-year cumulative diabetes incidence of 51%, 45%, and 34% in placebo, metformin, and lifestyle groups associated with a 41% reduction in the lifestyle group and a 17% reduction in the metformin group (478). In the Finnish Diabetes Prevention Study, after adjustments for changes in dietary intakes of total and saturated fat, fiber, and energy, and change in BMI, increased moderate-to-vigorous leisure-time physical activity was associated with a greater likelihood

for diabetes resolution (29.7 vs. 19.1% in the upper vs. lower third of change) and a lesser likelihood for development (23.5 vs. 44.7%) of MS (305). Additionally, the prevalence of MS decreased (OR: 0.62) in the intervention group compared to the control group throughout the intervention (304).

Lifestyle intervention significantly reduced MS compared with standard physician information (OR = 0.28), with a 31% absolute risk reduction, corresponding to 3.2 patients needing to be treated to prevent 1 case after the 12-month intervention (72). Camhi et al. (95) noted that a 1-year combined diet and exercise intervention improved MS score compared to control, with the authors suggesting changes in body fat explaining the intervention effects. Roberts et al. (542) noted reversal of MS in 9 of 15 subjects with an intensive 21-day diet and exercise intervention. The latter study incorporated truly intensive programs that require follow-up randomized-controlled studies to determine if interventions of this magnitude can be translated to a large segment in the population who might benefit from rapid reductions and maintenance of reduced risk for MS-related complications. Similar findings have demonstrated that combined interventions are also effective in children in some (113, 448, 530) but not all studies (690). In a nonrandomized 14-day intervention that incorporated an *ad libitum* high-fiber, plant-based diet along with approximately 2 h/d of exercise and game play, Chen et al. (113) noted reversal of MS in seven of seven children. In a 1-year multidisciplinary intervention including aerobic exercise and nutrition therapy, prevalence of MS was 27% prior and 8% after the intervention (98). It is interesting to note that in these studies, despite reversal of MS, the subjects remained obese. In addition, Thomas et al. (638) noted that in subjects who underwent a caloric restriction and aerobic exercise intervention to improve MS factors (and elicit 10% weight loss), in subjects that continued to exercise during a subsequent regain phase, improvements in some MS and other related risk factors were maintained compared with subjects that did not exercise during the regain phase.

It is important to note that other factors, the more salient being diet as well as smoking, sleep, alcohol intake, and stress all may contribute to MS; and there are potential interactions between several of these lifestyle factors (566, 678), as alluded to above. In many subjects, these other factors are not considered but are likely related to patterns of lifestyle in individuals. In addition, treating individual risk factors with lifestyle change might be as beneficial as treating MS as a separate disease.

Exercise and Insulin Sensitivity

As discussed above, insulin resistance has been suggested as the major underpinning link between physical inactivity and MS. It is well known that trained subjects and those with high levels of physical activity exhibit high levels of insulin sensitivity/insulin action. Additionally, changes in exercise through initiation or cessation of training programs and increases or decreases in physical activity modify insulin action. We will touch on exercise training *per se*, rather than acute exercise and briefly discuss the effects of aerobic, resistance, and interval training as well as increased and decreased physical activity levels. Below is a discussion of selected studies in these areas. The majority of studies discussed will focus on studies using the EHC, FSIGT, or OGTT. We will only discuss training studies

with the caveat that the timing of the insulin sensitivity measure after the last bout may impact the effects noted, as considered below.

Aerobic Training

It is well known that AT results in increases in insulin action in skeletal muscle of healthy individuals. The effects of AT on insulin sensitivity have been noted both cross-sectionally in exercise-trained compared to untrained individuals and for untrained subjects after periods of training. One of the earliest demonstrations of increased insulin action was a cross-sectional study of trained and untrained men, which noted lower insulin and glucose during an OGTT in the trained subjects (70). Several other studies early on noted that aerobically/endurance-trained subjects exhibit improved insulin responses to intravenous glucose (388,405), even differing in highly trained versus trained (387), and higher insulin sensitivity using the EHC in younger (353,569) or older (273) trained compared to untrained subjects, including whole body and nonoxidative glucose disposal (172).

Many studies have subsequently demonstrated that aerobic/endurance training elicits increases in insulin sensitivity, in general, from 25% to 50% in a variety of age and population groups, including normal healthy men (153, 289) and women (183), overweight and obese (149, 227, 591), young (712), middle-aged (291), and older subjects (160), in addition to first degree relatives of T2D patients (55, 483, 498), subjects with T2D (152), and even adolescents using GCMS (658).

Differences in aerobic exercise intensity have also been investigated. For example, Seals et al. (578) noted in older subjects that oral glucose tolerance was not significantly changed after training, although the area under the curve (AUC) for insulin was 8% lower after 6 months of lower intensity training (walking 30 min, 3–4 d/wk, ~40% of $HR_{reserve}$), and decreased an additional 23% after an additional 6 months of higher intensity training (jogging 30–45 min, 3–4 days/wk, ~75% of $HR_{reserve}$), although the study design was sequential as opposed to crossover. More recently, in a 9-month study of older women, DiPietro et al. (160) noted that only high-intensity training (~80% Vo_{2max}) elicited an increase in insulin sensitivity (21%) compared with moderate-intensity (~65% Vo_{2max}) training (16%), independent of changes in body composition or Vo_{2max} with the same training volume. Second, in a 12-wk program in overweight elderly women, despite similar changes in fitness and no changes in body fat or BMI, high-intensity training (75% of Vo_{2max}) led to a 28% increase in glucose disposal via EHC when compared to no change with moderate intensity at 50% Vo_{2max}, mediated by increase in nonoxidative glucose disposal (128). On the other hand, in the aforementioned STRRIDE study, Houmard et al. (290) suggested that duration should be a consideration, as low volume/moderate intensity and high volume/high intensity exhibited a greater response than low-volume high-intensity AT in sedentary, overweight subjects. In addition, Braun et al. (81), using an insulin suppression test, noted similar changes in insulin sensitivity in women with T2D using different intensities of 50% and 75% of Vo_{2max}.

Also of note are the numerous studies that have found increases in insulin sensitivity independent of changes in body weight and/or body composition. For example, Duncan et

al. (170) noted increases in insulin sensitivity of 40% or more in middle-aged, previously sedentary adults after a moderate-intensity walking intervention, independent of any changes in BMI or waist circumference. These findings have also been noted in younger subjects with a training program for 1 year independent of any BMI changes (481), in older subjects without changes in LBM or fat mass (299) and subjects with T2D exhibited a 44% improvement during an ITT without a change in body weight. Furthermore, a decrease AUC for insulin during an OGTT was shown in children, with no changes in body weight, LBM, or visceral fat (461).

Because of the timing of the posttraining test of insulin sensitivity, it has been difficult to dissect the acute versus chronic effects, and thus one aspect to consider is the timing of the measure of insulin sensitivity after training to establish the acute versus chronic effects of exercise on insulin sensitivity. This conundrum is complex given that there are likely effects of a single bout (388) and accumulated bouts that are difficult to separate, as training results in a diminished insulin response during an OGTT more so than does a single exercise bout (261). This also has implications for what constitutes "inactivity" as discussed below. Hence, there is a fine line between the "training" effect *per se* and the effects that can be attributed to the last exercise bout. For example, Mikines et al. (435) noted that trained subjects exhibited higher insulin sensitivity compared to untrained subjects, and although less pronounced, one bout in untrained subjects did lead to increased insulin sensitivity of glucose uptake, an effect that lasted 48 h, but not 5 days (434). While waiting 4 to 5 days will allow for studying the training effects *per se*, it might actually be at a time when the training effects have waned and therefore underestimate the effect. To complicate matters, it is also evident that the time frame for this effect has been highly variable across studies, with some showing affects waning after as little as 38 to 60 h postfinal bout (92,431,480) and others, such as LeBlanc et al. (388), demonstrating that when trained subjects did not exercise for 3 days, intravenous glucose induced greater elevations in insulin, however, still remaining smaller than chronically sedentary subjects. Interestingly, 1 week of vigorous aerobic-exercise training produced increases in both insulin sensitivity and responsiveness of glucose disposal, as well as enhanced suppression of hepatic glucose production in overweight patients with T2D, without weight loss (posttesting was performed 18–20 h after last bout) (356). This finding was also noted by Mikus et al. (438), who used CGMS to document improved glycemic control with 1 week of training, independent of changes in fitness or adiposity.

Mechanisms

As previously discussed, many studies have documented that AT improved whole body insulin sensitivity. Skeletal muscle, the most important target tissue for insulin action, has received the most attention for mechanistic studies with emphasis on insulin signaling pathway studied from biopsy samples. While the effects of AT-induced increases in glucose disposal have been attributed primarily to increases in insulin signaling protein and/or activities, the data are not consistent. Studies comparing endurance-trained subjects versus untrained subjects have indicated differences in glycogen storage in response to insulin (172), insulin signaling proteins, such as increased GS, GLUT4, GLUT4 vesicle-associated

protein (insulin-regulated aminopeptidase), and PI3-K activation, but decreased IRS-1, IRS-2, insulin receptor, and no difference in AKT (172, 286, 355, 716).

Using 31P NMR spectroscopy, Perseghin et al. (498) noted that despite lower glucose transport phosphorylation in offspring of T2D patients compared with normal subjects, both exhibited increases in whole body insulin sensitivity after AT by 40% or more and whole body nonoxidative glucose metabolism by 60% to 70%, mediated by an increase in glucose transport-phosphorylation (leading to greater glycogen synthesis). The training-induced improvement in glucose disposal has been attributed, at least in part, to increased insulin-stimulated glucose storage and GS fractional velocity, which correlated with insulin-stimulated glucose storage (119). Dela et al. (152) also noted increases in nonoxidative glucose disposal associated with increased GS mRNA and Frosig et al. (211) noted increased GS activity with short-term training. Ferrara et al. (195) noted similar effects on GS fractional activity in response to insulin, with no change in total activity. Dela et al. (150) noted maximum insulin binding and that basal- and insulin-stimulated receptor kinase activity did not change; however, GLUT4 protein concentration increased and the training-induced increase in GLUT4 (26%) matched the increase in maximum insulin-stimulated leg glucose uptake (25%) in the same subjects (153), and individual values of the two variables were correlated (r=0.84). In subjects with IGT, independent of changes in body composition, glucose disposal at high insulin concentration during an EHC increased approximately 60% and GLUT4 and glycogen increased after training (299). Several additional studies have noted increases in GLUT4 content. For example, 60% in middle-aged subjects (291), approximately 80% in nondiabetic men (289), 38% and 22% in overweight nondiabetic and diabetic men (119), 40% in healthy men and 23% in men with T2D (154) (mRNA also increased). Short et al. (592) noted increases in GLUT4 mRNA and protein content, independent of age in subjects ranging from age 21 to 87. Furthermore, short-term training increased GLUT4 protein similarly in both younger and older subjects (133).

Frosig et al. (211) noted AT-induced increases in insulin-stimulated glucose uptake of 60% and increases in muscle Akt1/2, AS160, GLUT4, HK2 and insulin-responsive aminopeptidase protein content and activities Akt1, GS and AS160 phosphorylation. However, IRS-1-associated PI3K activity was reduced. Short-term training studies reported no change in mRNA expression of IR, IRS-1, IRS-2 and the p85α-subunit of PI3K (668), but there were noted increases after short-term training in insulin receptor autophosphorylation (714) and PI3K activity (288, 355) in concert with increased insulin sensitivity, and PI3K activity in chronic-trained young men (288, 355). On the other hand, Christ-Roberts et al. (119) noted along with increased insulin sensitivity increased GS fractional activity, AKT protein expression but not IRS-1-associated PI3K activity after AT in both insulin-resistant, nondiabetic and type 2 diabetic subjects. Furthermore, Tanner et al. (633) also noted that short-term training did not increase PI3K activity with increased insulin sensitivity. Other pathways have also been investigated, such as those related to mitochondrial biogenesis (PPAR, PCG1α, etc), inflammation and stress kinases (JNK, IKKβ, etc), and AMPK, but it is unclear if modulation of these pathways directly caused the increase in insulin sensitivity with AT. For example, Frøsig et al. (210) also noted increases

in AMPK $\alpha 1$, $\beta 2$, and $\gamma 1$. Therefore, it is apparent that there are not generalized improvements in insulin signaling after AT.

One issue to acknowledge in these studies is that the timing of the biopsy after the last bout of exercise may contribute to differences noted (675), given that biopsies taken within the first day may in part reflect acute effects of the last bout and the time course and effects of training may differ for different types of proteins.

Other factors such as fiber type changes (289), increased oxidative capacity/mitochondria or blood flow (152, 172), altered muscle lipid metabolism (86, 88), and endocrine/paracrine mediators and reduced visceral obesity (592) may also contribute. For example, Ebeling et al. (172) noted that skeletal muscle GS fractional activity was highly correlated ($r = 0.88$) with blood flow, suggesting they may be causally related.

Interval Training

An additional modality of training that has received renewed interest is high-intensity sprint interval training (SIT), also referred to as high-intensity interval training (HIT or HIIT). Although it has long been known to induce muscular adaptations, for example, increase in peak power output, VO_{2max}, glycolytic (hexokinase, phosphofructokinase) and aerobic [citrate synthase, succinate dehydrogenase) enzyme activities (410) and as reviewed by (552)], since 2005 SIT has been the subject of greater investigation (90). However, in 1994, Tremblay et al. (644) noted that 20 weeks of SIT led to greater reductions in skinfold thickness as an indicator of body composition, compared with AT. Interestingly, these improvements were despite the SIT having <50% of the total energy cost compared to AT, demonstrating that changes in fat mass are not a function of exercise energy expenditure. Of note, recent studies have demonstrated increased insulin sensitivity with SIT. For example, Babraj et al. (36) noted that six sessions of four to six 30-s Wingate cycling sprints in healthy, young recreationally active men led to 12% and 37% decreases in AUC of glucose and insulin, respectively during an OGTT. Whyte et al. (689) performed a similar study design, and noted decreased AUC for insulin, but not glucose, 24 h, but not 72 h after the last training session. Again, using a similar 2-wk paradigm, SIT increased glucose infusion rate by 21% in young men and women 72 h after the last training session during EHC (539). More recently, eight patients with T2D performed six sessions of HIT (10×60-s cycling bouts at ~90% HR_{max}) over 2 wk, and average 24-h blood glucose concentration was reduced after training, as was the three meal sum 3-h postprandial glucose AUC (400) (as determined by CGMS). Additionally, Metcalfe et al. (430) used a $3\times$/wk for 6-week protocol that consisted of 10-min-exercise sessions which included progressing to 2 to 20 s all out sprints and noted a 28% increase in insulin sensitivity in males, but not females, a finding that requires further study.

As for potential mechanisms, SIT was found to increase IR phosphorylation more than moderate AT (640). Little et al. (401) used a more practical six sessions of 8 to 12 60-s cycle sprints at 100% of peak power output achieved during a VO_{2max} test and noted 119% increases in GLUT-4. Also from the Gibala laboratory, Hood et al. (277), using a similar protocol in middle-aged subjects, noted a 2.5-fold increase in GLUT-4 content and Little et

al. (400) noted a similar increase in GLUT-4 in older subjects with T2D. It has also been suggested that glycogen depletion during SIT may induce the improvements in insulin sensitivity (36, 689), since its depletion correlated with several aspects of enhanced insulin signaling.

Resistance Training

Yki-Jarvinen and Koivisto (713) demonstrated cross-sectionally that weight lifters exhibited similar glucose disposal to long-distance runners. Szczypaczewska et al. (624) also noted that bodybuilders exhibit greater glucose tolerance and insulin action compared to controls. These findings led to research demonstrating that RT also enhances insulin sensitivity and improves glucose tolerance in a wide range of study groups, including younger (506, 586) and older individuals (721), postmenopausal women (558), those with hypertension (536) and T2D (308).

Insulin sensitivity has been demonstrated to improve with RT in several studies using the EHC (Table 2). For example, in healthy, middle-aged men, glucose infusion increased 24% during EHC after RT (440). In subjects with T2D (308) improvements in the glucose infusion rates have been noted, generally attributable to increases in nonoxidative glucose metabolism. Reynolds et al. (536) noted improved glucose disposal during EHC in older hypertensive subjects. Ryan et al. (558) noted an increase in a small cohort of post-menopausal women. Interestingly, the training program intensities and durations in these studies were highly variable, suggesting that multiple RT paradigms are capable of improving insulin sensitivity. In addition, Reynolds et al. (537) used the EHC and noted no significant changes in fractional glucose extraction or glucose clearance with RT. On the other hand, two studies (143, 557) found non-significant increases in insulin sensitivity. In the first (557), the increase was ~10% and did not achieve significance ($P < 0.06$). In the latter (143), the weekly training was 60 minutes in duration, suggesting that a potential threshold of overload may exist.

Several of these studies demonstrated an effect of RT without altering aerobic capacity or body weight/composition. In older men, Zachwieja et al. (721) noted a 33% increase in insulin sensitivity and an increase in glucose rate of disappearance, using a stable glucose isotope FSIGT, 7 days after the last bout of training, without a change in body weight, secondary to reciprocal increases and decreases in LBM and fat mass. In obese, middle-aged men, Klimcakova et al. (359) noted a 24% increase in glucose disposal rate, without any change in body weight, fat mass or VO_{2max}. Poehlman et al. (506) also noted a modest increase, which occurred independent of changes in total body, subcutaneous or visceral fat. In the study by Ryan et al. (558), body weight, fat mass, percent body fat, LBM, and VO_{2max} did not change with RT intervention. The addition of a calorically restricted diet augmented the response and induced weight loss, suggesting the possibility of additive effects with multiple lifestyle interventions. Increases in insulin sensitivity during an FSIGT have also been noted in children, despite no change in weight and an increase in LBM compared to a control group (586). Van Der Heijden et al. (659) noted highly variable responses in youth in peripheral insulin sensitivity, but a 24% increase in liver insulin

sensitivity. Additionally, improvement in adipose tissue insulin sensitivity has been noted (507).

Similar findings have been noted in subjects with T2D. Ishii et al. (308) noted that RT increased glucose disposal by 48% in lean subjects with T2D without a change in VO_{2max}, weight loss or body composition. In older men with T2D, a 2 d/wk RT program led to a 45% increase in insulin sensitivity and a 10% decrease in abdominal fat, without a change in body weight (302) and an estimated increase in energy intake of 15%. In addition, Misra et al. (446) noted improved insulin sensitivity by an ITT in South Indians with T2D.

Many RT studies have also used an OGTT as an index of insulin action, and some (599, 600), but not all (134, 301, 440,441), have noted improvements in glucose tolerance after RT. Plasma insulin concentrations have been demonstrated to decrease during an OGTT (134, 440, 441, 599, 600). Using the OGTT method, RT improves insulin action including subjects with IGT or T2D (137, 171, 276, 600). Alternatively, glucose and insulin AUCs were not altered by 6 weeks of RT in women with T2D (192). Another aspect to consider is while the EHC estimates glucose disposal and the FSIGT insulin secretion and β-cell function, the OGTT has classically been used to estimate glucose tolerance via AUCs or the Matsuda index (421) of insulin sensitivity. However, given the advantages of the technique, Abdul-Ghani et al. (3) validated a muscle insulin sensitivity index (ISI) and hepatic insulin resistance index (IRI) with EHC data and oral DI (4, 534), an estimate of β-cell function, from FSIGT testing. Roberts et al. (unpublished observations) recently demonstrated that 12 weeks of RT improved muscle ISI and oral DI, without a change in hepatic IRI, suggesting that RT affects insulin sensitivity in skeletal muscle, but not liver.

Overall, a systemic review of 20 studies found that supervised resistance exercise training improved glycemic control and insulin sensitivity in a wide variety of study groups (231). However, without supervision, RT compliance and glycemic control are generally less, suggesting either the need for supervision or alternative incentives to maximize training-induced benefits.

Aerobic Versus Resistance Training

A handful of studies have directly compared the effects of AT and RT on insulin action. Smutok et al. (599) noted that both modalities led to decreased AUC for both glucose and insulin and that no significant difference between the interventions were noted, nor were there any changes in body weight, although body fat percentage dropped slightly in the AT group. This group also studied the effects of AT or RT in subjects with T2D or IGT, noting similar results (600). Cauza et al. (107) reported greater benefits of RT as opposed to endurance training, on glycemic control (mean blood glucose decreased 15%) in patients with T2D using CGMS. Also RT and AT were compared in older obese men 3 days/wk for 6 months and noted similar 20–25% increases with EHC in both groups, despite a decrease in body weight of 2% in the aerobic group and an increase in body weight of 2% in the RT group (195). In subjects with T2D, both AT and RT for 4 months resulted in increases in glucose disposal rates during EHC (37). Cuff et al. (137) did not compare the effects of AT versus RT; however, they did investigate the effects of added RT to an AT intervention in

postmenopausal women with T2D and noted greater glucose infusion rate during the combined intervention, in the absence of an effect of AT alone. In addition, the effects of combined training versus each modality in isolation noted that combined was superior to RT, but not to AT (143). It should be noted that the total exercise time was 60 min/wk in the RT group and 150 min/wk in the aerobic and combined groups, and suggests when making comparisons of different training modalities, attempting to match the training overload is critical. However, given differences in energy expenditure that exist with different RT prescriptions, there is inherent difficulty in trying to match the overload of the different training modalities. Because of this conundrum, from a feasibility standpoint, one option is to match the duration of the training. Thus, we propose it is important to report the exercise time and to attempt to match the relative intensity when comparing these different training modalities.

Mechanisms

Although the mechanism for the increase in insulin sensitivity with aerobic exercise training has been often investigated, the increase with resistance exercise training is far less studied. Some insight has been provided by cross-sectional and comparison studies. Takala et al. (626) noted no effect of RT on insulin-stimulated glucose uptake per kilogram of muscle mass, and the positive effect of RT was attributed to the larger muscle mass. Yki-Jarvinen el al. (713) noted that both trained weight lifters and long-distance runners exhibited higher glucose disposal compared to controls during EHC; however, when calculating per LBM, only the runners exhibited higher values, suggesting that, at least in part, the mechanism for increased glucose disposal in resistance-trained subjects is due to increased skeletal muscle mass. This is in agreement with AT versus RT (506), which noted increases in glucose disposal rate during an EHC with both modalities of training and when these rates were express per fat-free mass (FFM), the improved insulin sensitivity persisted in the AT group, but not in the RT group. In other aforementioned studies, the EHC clamp increases were expressed relative to FFM (276, 308, 440), suggesting effects independent of LBM changes. Miller et al. (441) noted a significant correlation between insulin AUC and increase in LBM ($r = 0.89$).

These data suggest that the mechanism for the improvement with RT and AT, at least in part, may be distinct. Dela and Kjaer (151) suggested that RT improves insulin action by unknown mechanisms in addition to increased muscle mass. Despite numerous studies investigating the effects of RT on insulin sensitivity, few studies have attempted to investigate the mechanism(s) responsible for improved insulin sensitivity. Miller et al. (440) noted a 40% increase in nonoxidative glucose disposal during insulin infusion, suggesting increased glycogen synthesis. Holten et al. (276) noted, using the single-leg RT model, increased glucose clearance more than what could be explained by increases in LBM alone. In addition, these authors reported increased protein content of GLUT4 (T2D subjects only), insulin receptor, protein kinase B-α/β, GS, as well as GS total activity; however, no training effect was observed for protein content of IRS-1 or the p85 subunit of PI3K. On the other hand, RT did not alter muscle GS total activity, glycogen content, or levels of PI3K in overweight/obese older men (195). Roberts et al. (unpublished observations) recently demonstrated that 12 weeks of RT increased GLUT4 and HKII in obese young men.

Alternatively, GLUT4 was not altered in older Hispanic adults with T2D, although in the latter, sodium-dependent glucose cotransporter system (hSGLT3) transcript levels in the vastus lateralis muscle was positively correlated with glucose uptake (105). In subjects undergoing bed rest, GLUT-4 decreased in vastus lateralis after bed rest but increased in subjects undergoing RT during bed rest (625). Given the dearth of evidence in humans on the molecular mechanism, it is interesting to note that Krisan et al. (368) noted, using a rodent model of RT, increased GLUT4 content and IRS-1 associated PI-3K, Akt, and atypical PKC-ζ/λ activities. Some further insight has been provided by Andersen et al. (20), who noted that the decrease in leg glucose uptake, expressed relative to leg muscle mass, was associated with decreased glycogen content and increase myosin heavy chain IIx; however, GLUT4 mRNA, enzymatic changes, or capillary density did not change with detraining. Additionally, regarding the possibility that AMPK might be involved, RT resulted in similar changes to various AMPK subunit isoforms in subjects with T2D and healthy controls (698).

To try to gain some insight into the potential contribution of adipose tissue to altered insulin sensitivity in muscle, Klimcakova et al. (359) found no effects of RT on the mRNA levels of adiponectin, leptin, Il-1β, IL-6, and TNFα from subcutaneous adipose tissue. Overall, it is evident that there is a lack of clarity with respect to what are the molecular mechanisms responsible for the improvement in insulin sensitivity with RT, and this remains an important area for future research (Fig. 13).

Physical Activity

Although exercise training is typically imposed to assess the impact of physical activity on insulin sensitivity, physical activity levels *per se* are also related to insulin action. For example, Kriska et al. (369) noted that higher physical activity was associated with lower insulin concentration in more than 5000 Pimas and Mauritians of difference body compositions, suggesting influences of activity independent of body composition. In the IRAS study, insulin sensitivity determined by FSIGT was approximately 80% higher for those who participated in vigorous activity five times per week or more compared with those who rarely or never participated (426). More recently, objectively measured sedentary time, light-intensity physical activity, and moderate- to vigorous-intensity activity were all related to 2-h glucose after an OGTT (260). In addition, in a cohort of 801 men and women, the European Relationship between insulin sensitivity and cardiovascular risk study (42) demonstrated that total physical activity, activity intensity and sedentary time as recorded objectively by accelerometry were all associated with insulin sensitivity as determined by EHC. In addition, the dual-peak effects of accelerometry-measured physical activity and percent sedentary time suggest the potential for independent effects of activity and inactivity (Fig. 14). Interestingly, the most sedentary group exhibited a significant relation between insulin sensitivity and total activity; however, the effects in other quartiles of sedentariness, these trends were not as strong, nor were there trends between insulin sensitivity and sedentary time after accounting for physical activity. These data suggest that the interactions between sedentary behavior, physical activity, and structured exercise are very complex and relationships between sedentary behavior and physical activity are not simply inversely

associated. Furthermore, the interactions between exercise training and habitual activity (i.e., from ambulatory patterns, occupation, etc.) are generally unknown.

Decreased Physical Activity

Physical inactivity via either modification of habitual physical activity or from a trained state to training cessation also has effects on insulin action. For the former, several studies have suggested that becoming physically inactive may decrease insulin sensitivity. The original paradigm for this was bed rest, which demonstrated significant reductions in insulin action within 7 days (617) (432, 433). More recently, however, studies have indicated that simply decreasing ambulatory physical activity leads to blunted insulin action. For example, physical inactivity in a free-living environment decreases glucose tolerance during an OGTT after 1 week of daily step reduction from 6203 to 1394 and decreases glucose infusion rate during an EHC after 2 weeks of reducing daily step number from 10,501 to 1344 in healthy, young men (476). Mikus et al. (439) noted that 3 days of reduced activity (step reduction of 12,956 to 4319 steps/d) in healthy, young adult volunteers led to increased postprandial glucose responses as measured by CGMS, despite compensatory increases in insulin response to an OGTT. Peripheral uptake of 2-deoxyglucose was also reduced without change in hepatic insulin resistance after 2 weeks of reduced stepping (370). More recently, Knudsen et al. (361) noted that an average daily step reduction from 10,278 to 1,521 led to significant reductions in OGTT estimated Matsuda index, which preceded significant changes in fat mass.

In particular, previous studies have noted that training induced increases in insulin sensitivity could overcome effects of aging, leading to the concept that exercise and activity *per se*, as opposed to aging *per se* are largely the true underlying cause of insulin resistance commonly observed in older individuals (see inactivity section) (126, 577) (Fig. 15). In addition, as mentioned above, there is a fine line between the "training" effects of exercise training-induced increases in insulin sensitivity and when "detraining" or "inactivity" ensues. Nevertheless, it is evident that training effects are rapidly lost in response to training cessation. For example, one of the first studies in this area noted that AT effects were lost within 10 days of detraining in well-trained subjects, independent of any changes in CRF, body weight or body fat. Plasma glucose and insulin responses increased to levels similar to that commonly found in untrained subjects after 10 days of training cessation, and one bout of exercise significantly improved the response (Fig. 16) (261).

Studies using the EHC procedure (at submaximal insulin concentrations) demonstrated that elevated insulin-stimulated glucose disposal rates, and therefore the improved insulin sensitivity, in trained individuals disappear after as little as 2 (480), 3 (and sustained at 7 days) (92), or 10 days (352) of training cessation. Interestingly, 5 days of detraining decreased insulin action to levels comparable to untrained subjects (434, 436, 437), and this was reported to be associated with decreased GS activity (436). In addition, Dela et al. (153), using the well-known single-leg training model, noted that the cycling-induced increases in insulin sensitivity returned to near pretraining levels after 6 days of detraining. In a follow-up study by this group, the effect was lost after 6 days in T2D patients, but lasted longer in nondiabetic controls (152). Vukovich et al. (667) also noted decreased glucose

disposal after 6 days of detraining, as well as a decrease in GLUT4 content. However, Houmard et al. (287) noted that both AT and RT training cessation led to decreased insulin sensitivity to oral glucose, but GLUT4 remained unaltered. Andersen et al. (20) also noted cessation of RT training for 3 months after 3 months of training led to a drop in whole body glucose uptake of 11% and leg glucose uptake 33%, which occurred in concert with increased IIx fiber percentage, but no difference in GLUT4 or GS mRNA. The authors attributed this decrease to reduced nonoxidative glucose disposal.

On the other hand, Rodgers et al. (545) noted after 10 days of inactivity, glucose tolerance was still not at untrained levels, so there appears to remain a training component with longer term training (average 13 years). Evidently, the effects are highly variable depending on the degree of training of subjects, aspects of the training program performed, and maybe due to genetic contribution. Similarly, one way to avoid the effects of detraining is to continue to exercise, albeit at a reduced training load. For example, Houmard et al. (291) noted maintained insulin sensitivity and elevated GLUT-4 when subjects decreased training frequency by 50% for 2 weeks; however, training cessation led to a return of values to sedentary levels after 2 weeks.

Summary

MS, although only more recently defined and investigated, exhibits a prevalence of nearly 25% of the US adult population, and epitomizes the integrative nature of modern chronic disease, given its endocrine, metabolic, and cardiovascular underpinnings. Most notable is the relation between cardiovascular fitness and MS, given data that the mortality risk in unfit versus fit individuals with the MS is similar to the same comparison in healthy men. In addition, many studies not discussed, although not designed to investigate the effect of exercise on MS *per se*, have shown amelioration of risk factors comprising the MS, including insulin resistance, hypertension, dyslipidemia, inflammation, and endothelial dysfunction. Various modalities of training, including AT, RT, and SIT, as well as activity/ inactivity can alter insulin action in a short period of time.

Perspectives

Drug mimetics for exercise

Drug therapies and exercise training/physical activity have been utilized to ameliorate MS and its associated risk factors. In conjunction with this, there has been controversy surrounding the ability of exercise mimetics to target different phenotypes with hopes to reduce, among other diseases, MS-related disease outcomes (75, 99, 122, 228, 259, 540, 679). Although attempts have been made to engineer drugs to improve insulin sensitivity and ameliorate MS phenotypes, due to the myriad of beneficial effects that exercise and physical activity provide, virtually the entire population will benefit from increased physical activity levels. Although for select individuals physically unable to perform physical activity, drug mimetics for exercise might have credence for selected phenotypes; no drug therapies will be able to mimic the array of adaptations that occur with regular physical activity in the context of MS and its related causes and complications. Even if a polypill for

many of these adaptations was possible, it is likely that for many as discussed below, the pill would not even be taken.

Comparison with drug therapy

Studies have demonstrated that there are numerous barriers that invariably lead to discontinuance of exercise training programs and regular physical activity leading to MS and ultimately T2D and CVD. It is clear that translation of the efficacy studies clearly demonstrating benefits of a wide variety of exercise and activity modalities is vital. Case in point are studies suggesting that supervised training programs [commonly implemented in randomized controlled trials (RCTs)] yield superior results to unsupervised programs. Alternatively, it is assumed that for many, since exercise (and other lifestyle therapies, such as diet) is difficult to sustain, it will be easier for individuals to sustain health improvements through drug therapy. However, cohort studies of patients prescribed medications suggest variable but disappointingly high rates of discontinuation of therapy and poor adherence to drug regimens. As an example, lipid-lowering drugs are some of the most commonly prescribed drugs in many countries. Estimates have suggested that approximately 60% of patients discontinue their medication over 12 months, with half of the discontinuations occurring within 3 months. Main reasons for discontinuation included 32% unconvinced about need for treatment and 32% indicating poor efficacy (595). In accordance with this, approximately 60% of older patients discontinued statins for primary prevention within 1 year, and 75% after 2 years (312). Avorn and colleagues (34) noted that patients 65 years of age or more failed to fill prescriptions for lipid-lowering drugs for about 40% of the study year and that approximately 45% were adherent to statin medications after 6 months (60). Alternatively, age and standard of care may impact this effect as much greater discontinuation in younger Danish patients occurred within the first year (~60%) compared with older patients (~40%) (384). Whether other drug therapies for chronic disease risk factors exhibit similar patterns of discontinuation is largely unknown. This demonstrates that similar to RCTs, exercise in which shortcomings include ability to translate the intervention to the public at large, although underappreciated, clinical trials using lipid-lowering drugs likely succumb to the same shortcomings in the ability to translate the therapy to the population at large, albeit likely for different reasons. Even a therapy as simple as taking a pill, as opposed to changing physical activity, is also subject to high degrees of noncompliance. Ways to manage this conundrum should be investigated in the future.

Weight loss

As discussed above many of the changes in phenotypic outcomes, for example, insulin sensitivity and MS factors (HDL, TG, blood glucose, and blood pressure) can occur with aerobic, interval or resistance exercise training, independent of weight loss, and with or without accompanying changes in body composition and fat distribution. Nevertheless, at present there is a continued focus on weight loss and a misconception that weight loss is required for benefits. However, it is likely that the exercise-induced effects related to MS have mechanisms that, at least in part, are distinct from body weight loss *per se*. We need to understand the mechanisms for improvement of MS factors, as likely in some, fat loss may occur and contribute to the benefits noted; however, in others weight loss will not occur. Future studies should be carried out to investigate this question further.

Individualized programs

One aspect alluded to but not discussed in detail are individualized effects of training on insulin sensitivity and MS factors. It is apparent that in those with insulin resistance or MS, not all will respond similarly. Several studies, including the HERITAGE Family Study (77) and STRRIDE [Figure G2.4 in reference (2)] studies have noted this highly individualized effect. Case in point in the HERITAGE study, Boulé et al. (78) noted that although a majority of subjects exhibited an improvement in insulin sensitivity with aerobic training, the individual response was highly variable, with some subjects being unresponsive; additionally, they noted the change in insulin secretion was dependent on the baseline glucose tolerance. Therefore, as we learn more about the interaction between genetic variation and exercise, we can identify those that may respond to exercise interventions and better individualize training programs to optimize risk factor modification.

Future directions

Overall, future trials are needed to (i) establish the effects of long-term training programs on prevention and reversal of MS; (ii) compare long-term effects of exercise versus drug therapy sustainability, as well as the potential synergistic or antagonizing effects of common drug therapies (statins, metformin, etc.) on training-induced effects; (iii) explore further the mechanisms by which different training modalities increase insulin sensitivity (Fig. 13) and prevent MS; (iv) further investigate the potential of exercise to promote metabolic health independent of significant weight loss; and (v) provide insight into the factors and clues that will assist with optimization of individualized training programs.

Acknowledgments

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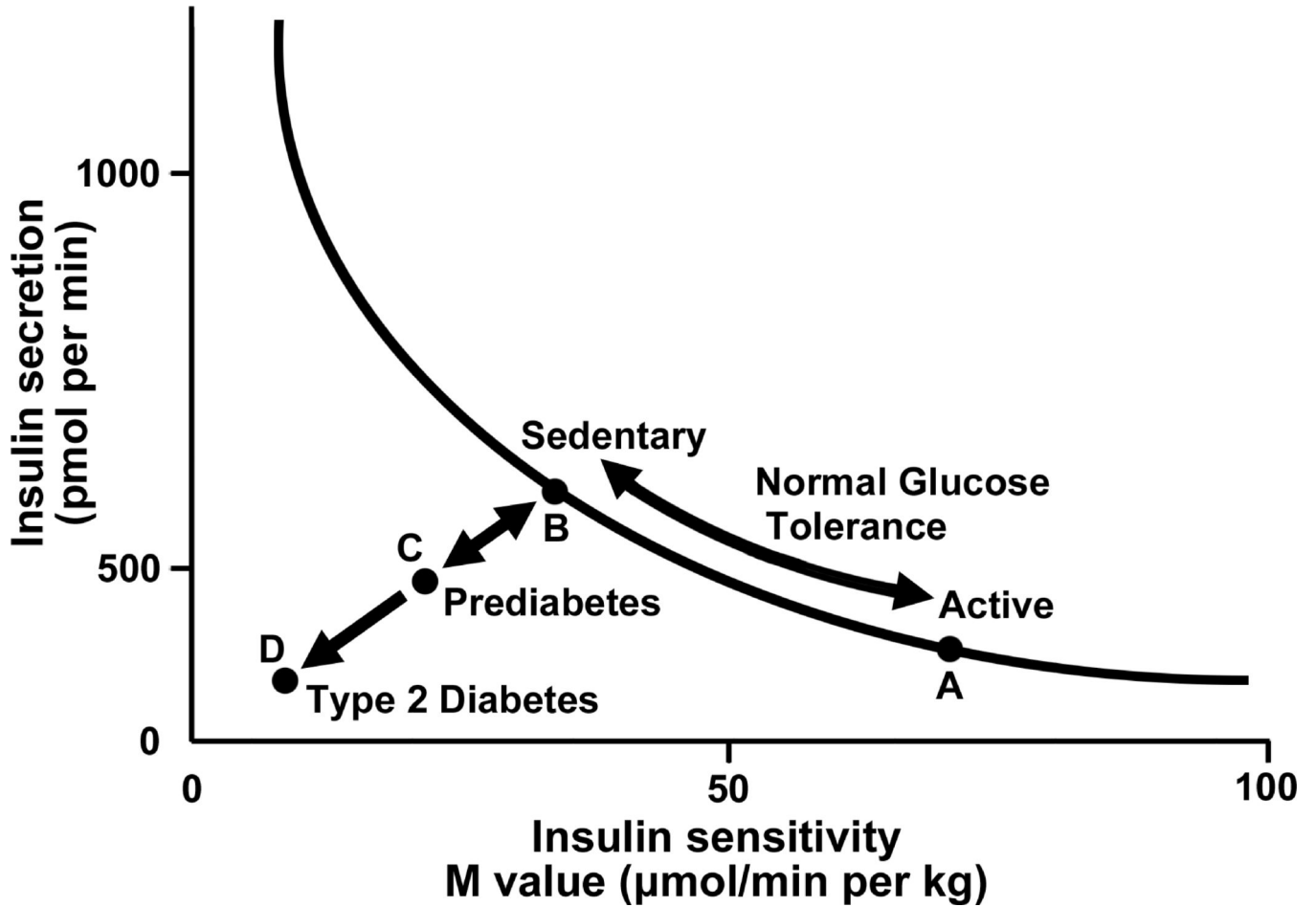
Figure 1.
Graph depicting the hyperbolic relation between insulin secretion and insulin sensitivity. Insulin secretion rises as insulin sensitivity falls when an individual goes from a state of exercise training/being physically active (point A) to detraining/sedentary (point B) and vice versa, that is, bidirectionality of the two arrows from B to A when undergoing exercise training/increasing physical activity levels. A failure of insulin secretion to compensate for a fall in insulin sensitivity is noted when both insulin secretion and insulin sensitivity decline from points B to C, leading to elevated fasting glucose and prediabetes (impaired glucose tolerance). A progressive decline in both insulin secretion and insulin sensitivity to point D indicates type 2 diabetes. Adapted from reference (9) with permission.
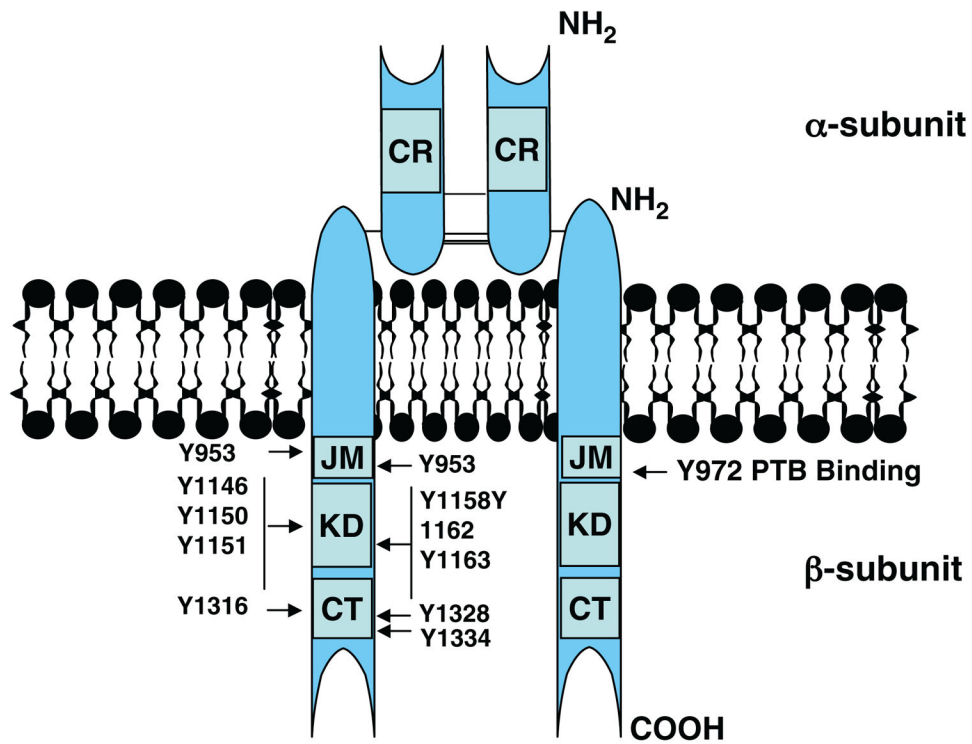
Figure 2.
Schematic of the insulin receptor and critical sites of tyrosine phosphorylation. CR, cysteine-rich region; JM, juxtamembrane; KD, kinase domain; CT, C-terminal domain; Y: tyrosine residue.
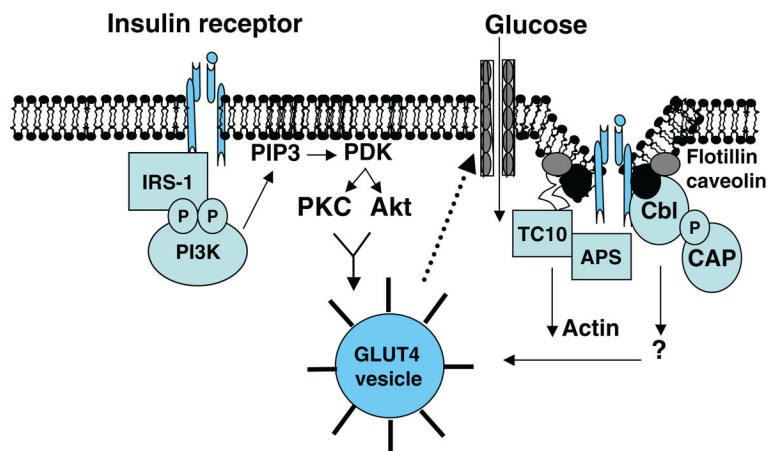
Figure 3.
Schematic of insulin signal transduction through canonical IRS1/PI3K pathway and through abbreviations: Cbl/CAP/TC10 pathway associated with lipid rafts in the plasma membrane. Akt or PKB, protein kinase B; APS, adapter protein with a PH and SH2 domain; CAP, c-Cbl-associated protein; Cbl, protooncogene; GLUT4, insulin responsive glucose transporter highly expressed in myocytes and adipocytes; IRS, insulin receptor substrate; PDK1, phosphoinositide-dependent kinase 1; PIP3, phosphatidylinositol (3,4,5)-trisphosphate; PKC, protein kinase C; TC10, small Ras-related GTPase, member of the Rho family.
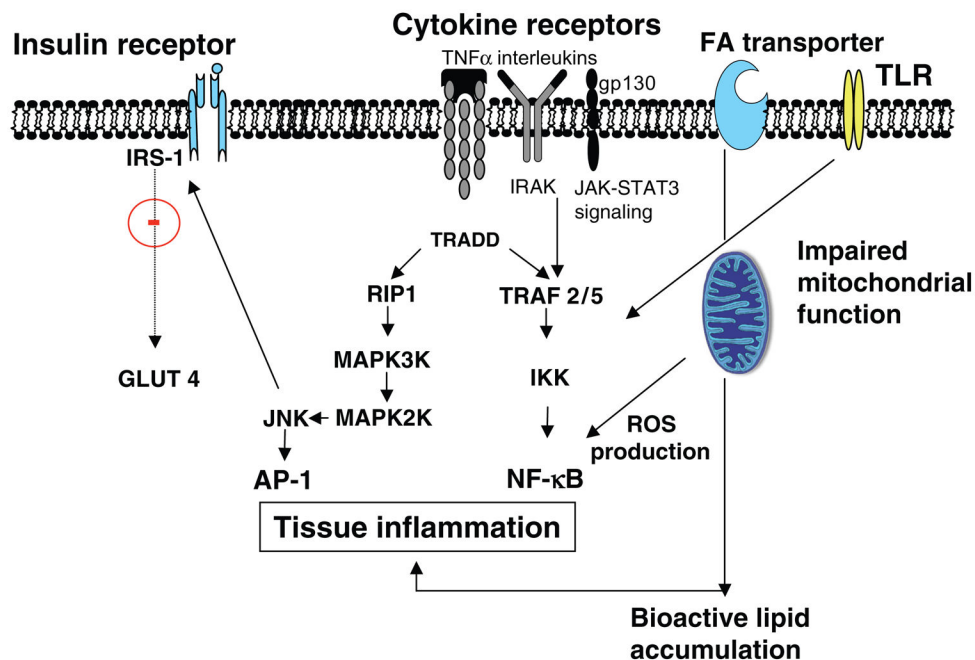
Figure 4.
Schematic illustrating mechanisms promoting inflammation that is now recognized as an important underpinning contributing in the pathogenesis of insulin resistance via impairment of insulin signal transduction. Abbreviations: AP-1, adaptor protein 1; IKK, I kappa B kinase; IKKkinase; IκB-α, inhibitor of kappa B; IL, interleukin; IRAK, interleukin receptor-associated kinase; JAK, janus kinase; JNK, c-Jun N-terminal kinase. Originally identified kinase family that binds and phosphorylates c-Jun on Ser-63 and Ser-73 within its transcriptional activation domain. MAPK2, mitogen-activated protein kinase 2; MAPK3, mitogen-activated protein kinase 3; NF-κB, nuclear factor κ B (nuclear factor kappa-light-chain-enhancer of activated B cells); RIP, receptor-interacting serine/threonine-protein kinase; ROS, reactive oxygen species; STAT, signal transducer and activator of transcription; TLR, toll-like receptor; TRADD, tumor necrosis factor receptor type 1-associated DEATH domain protein (adaptor protein); TRAF, TNF receptor associated factors.
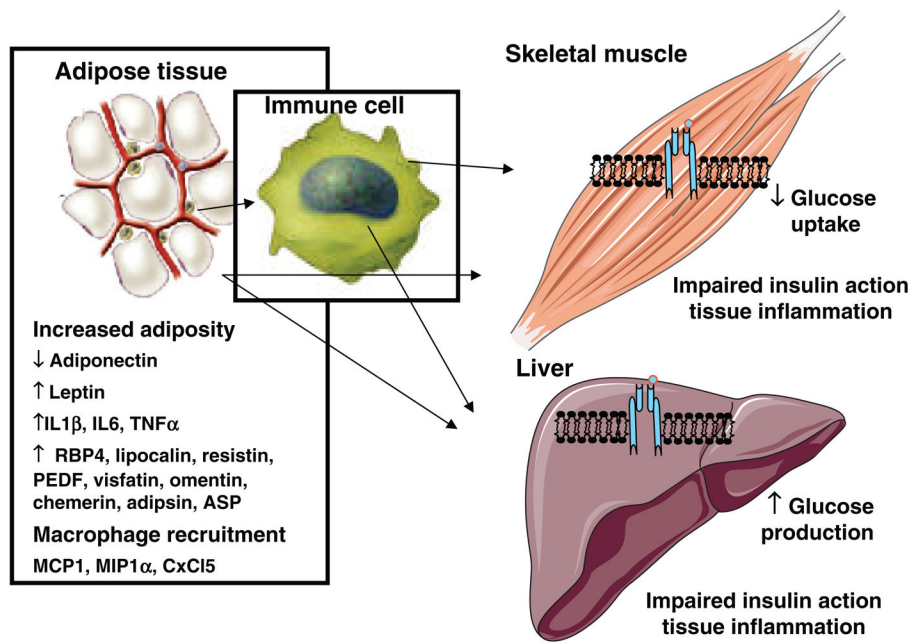
Figure 5.
Schematic of adipose tissue-secreted factors that act on muscle and liver to promote insulin resistance.
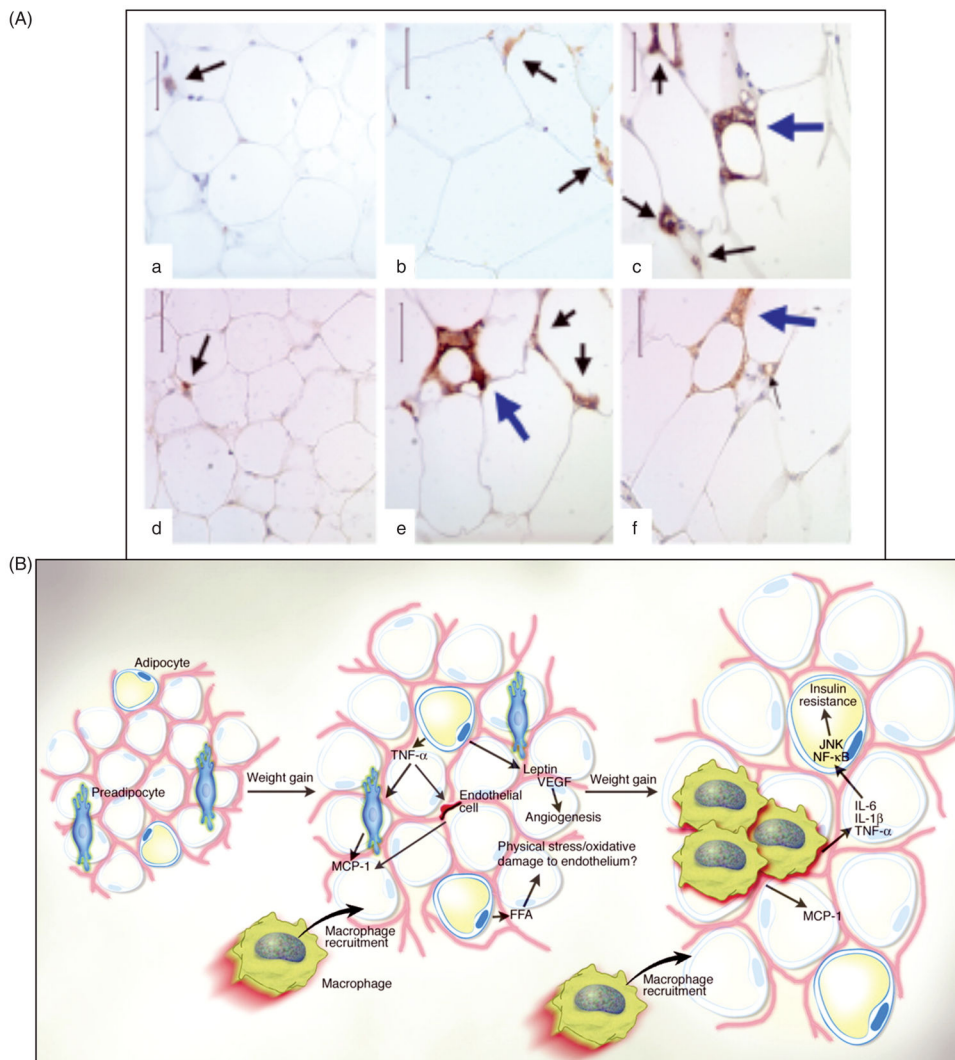
Figure 6.

The role of macrophages in the development of obesity. (A) Increased abundance of F4/80 positive macrophages in visceral perigonadal adipose tissue obtained from obese mice. (a) Lean female, (b) Ay/+ female, (c) Lep o/ob female, (d) lean male, (e) diet-induced obesity, and (f) Lep ob/ob male mice. F4/80 positive cells are small, dispersed and rarely aggregated in adipose tissue from lean animals (a and d), but found frequently in clusters "crowning" adipocytes in adipose tissue from high-fat fed and genetically obese mice (c, e, and f). Reprinted, with permission, from reference (683). (B) Schematic overview of the effects of adipose macrophage infiltration on the development of tissue inflammation and insulin resistance. Classically activated macrophages in adipose tissue from obese humans and rodents are shown to secrete insulin resistance producing proinflammatory cytokines and chemokines. Reprinted, with permission, from reference (684).
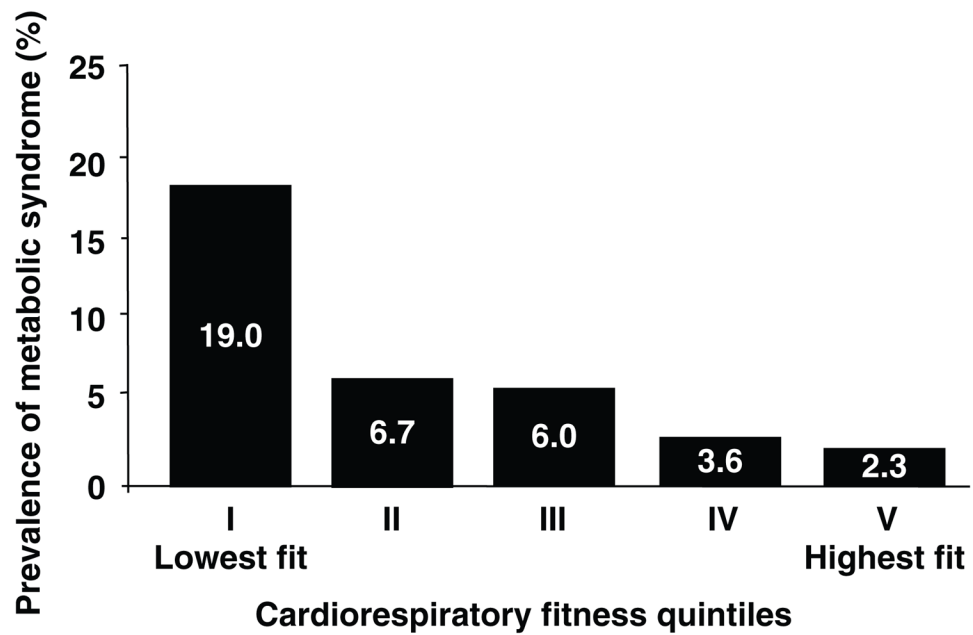
Figure 7.
Prevalence of metabolic syndrome according to cardiorespiratory fitness quintiles in more than 7000 women enrolled in the Aerobics Center Longitudinal Study from 1979 to 2000. Number of subjects in each quintile is I: 796; II: 1173; III: 1241; IV: 1754; and V: 2140. Adapted from reference (189) with permission.
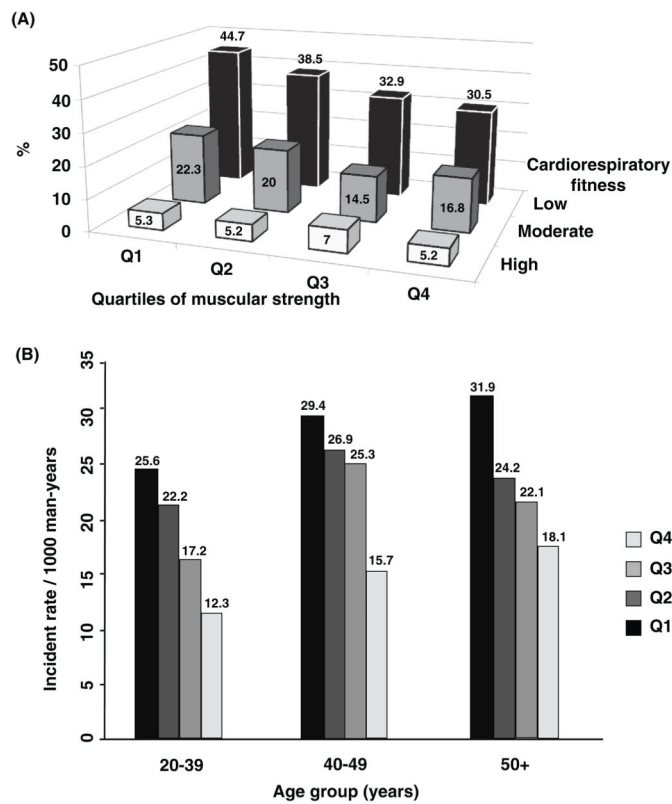
Figure 8.
(A) Age and smoking adjusted prevalence of metabolic syndrome in men according to level of muscular strength and cardiorespiratory fitness. Q1 represents the lowest and Q4 the highest muscular strength quartile. (B) Incidence of MS across muscular strength categories by age groups. Incidence rates per 1000 man-years are shown labeled with bars. The number of subjects for each age group is 20–39: 1239; 40–49: 1249; and 50+: 745. Q1 represents the lowest and Q4 the highest muscular strength quartile. The linear trend p values for the age groups 20–39, 40–49, and 50+ are less < 0.001, 0.01, and 0.05, respectively. Adapted from references (319, 320) with permission.
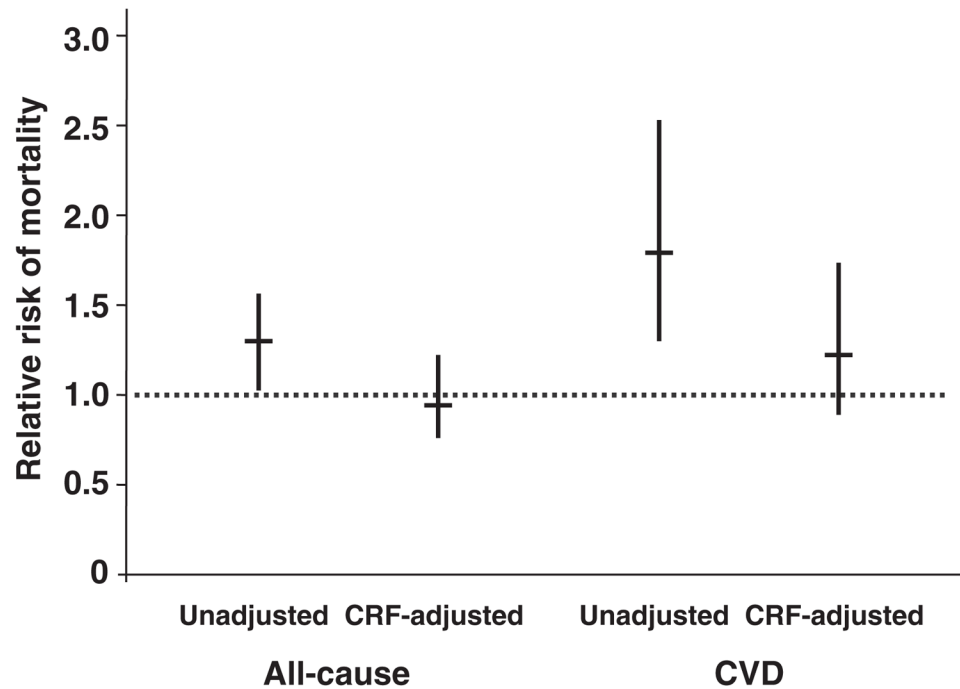
Figure 9.
Impact of fitness on relative risk for all-cause and cardiovascular disease (CVD) mortality associated with metabolic syndrome before and after the inclusion of cardiorespiratory fitness (CRF) as a covariate in more than 19,000 men 20–83 years of age from Aerobics Center Longitudinal Study. Error bars represent 95% confidence intervals and demonstrate that after inclusion of CRF as a covariate, all-cause and CVD mortality were no longer statistically significant. Adapted from reference (337) with permission.
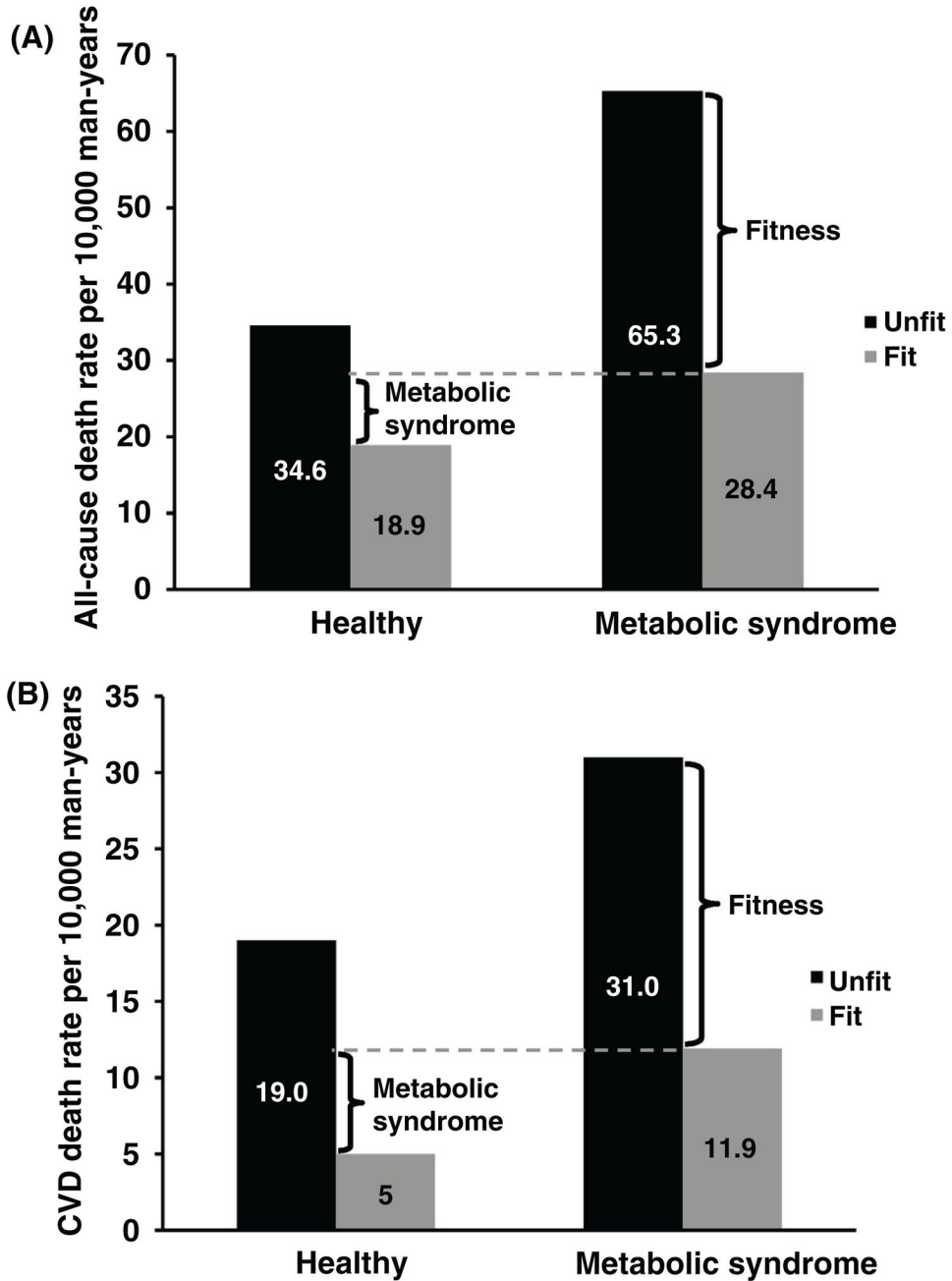
Figure 10.
All-cause (A) and cardiovascular disease (B) mortality death rates per 10,000 mean-years of follow-up in "healthy" and subjects with metabolic syndrome (MS), adjusted for age and year of examination more than 19,000 men 20–83 years of age from Aerobics Center Longitudinal Study. The theoretical contributions of fitness and MS are depicted by brackets. Adapted from reference (337) with permission.
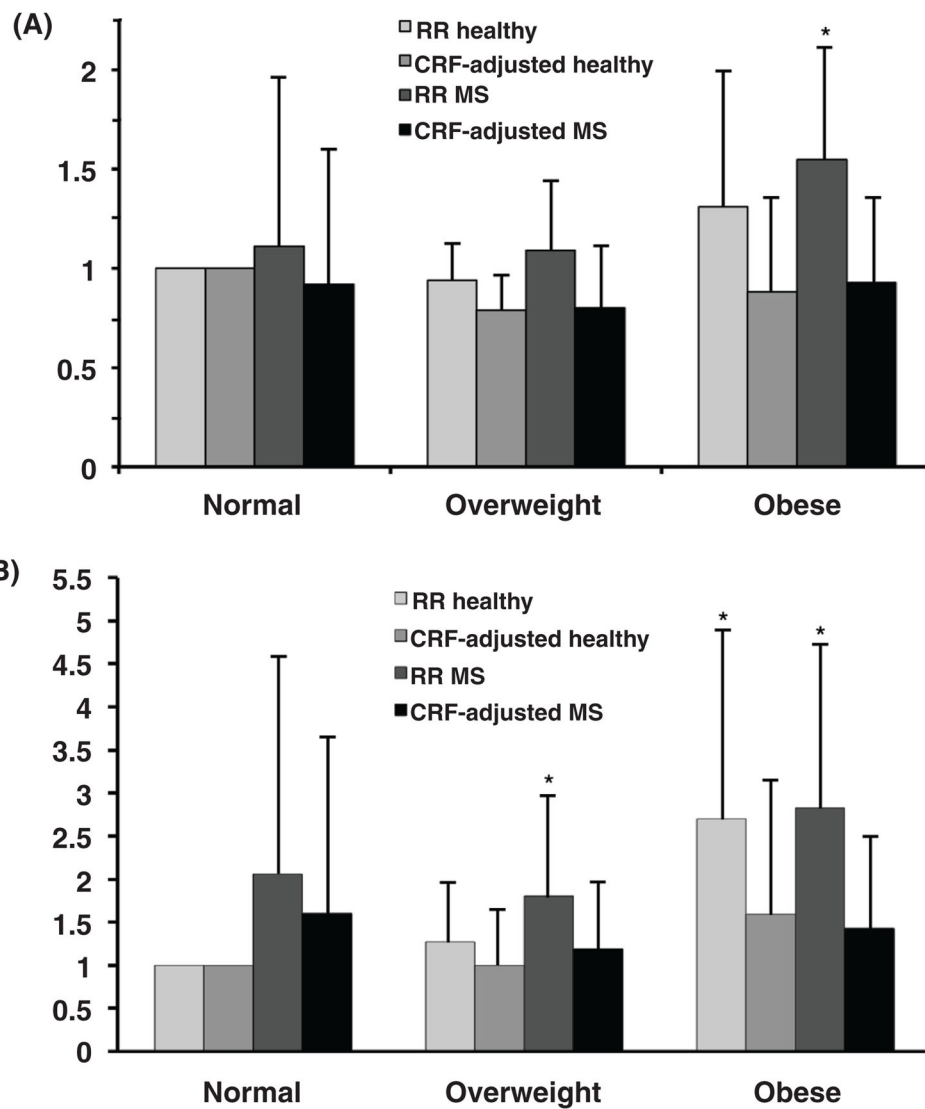
Figure 11.
Relative risk (RR) of (A) all-cause and (B) cardiovascular disease (CVD) mortality in more than 19,000 men from Aerobics Center Longitudinal Study, adjusted for age, examination year, smoking, alcohol consumption, possible existence of CVD, and parental history of premature CVD. Second and forth bars within a body mass index category refer to cardiorespiratory fitness (CRF)-adjusted RR's. Data, with permission, from reference (338).
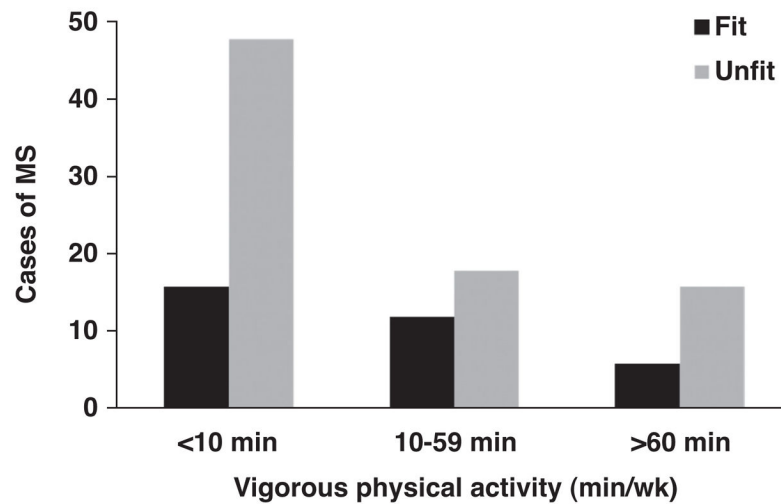
Figure 12.
Adjusted cases of metabolic syndrome (MS) based on minutes per week of leisure time physical activity in fit and unfit men after an average 4-year follow-up (374). Copyright 2002 American Diabetes Association. From Diabetes Care®, Vol. 25, 2002; 1612–1618. Reprinted by permission of the American Diabetes Association.
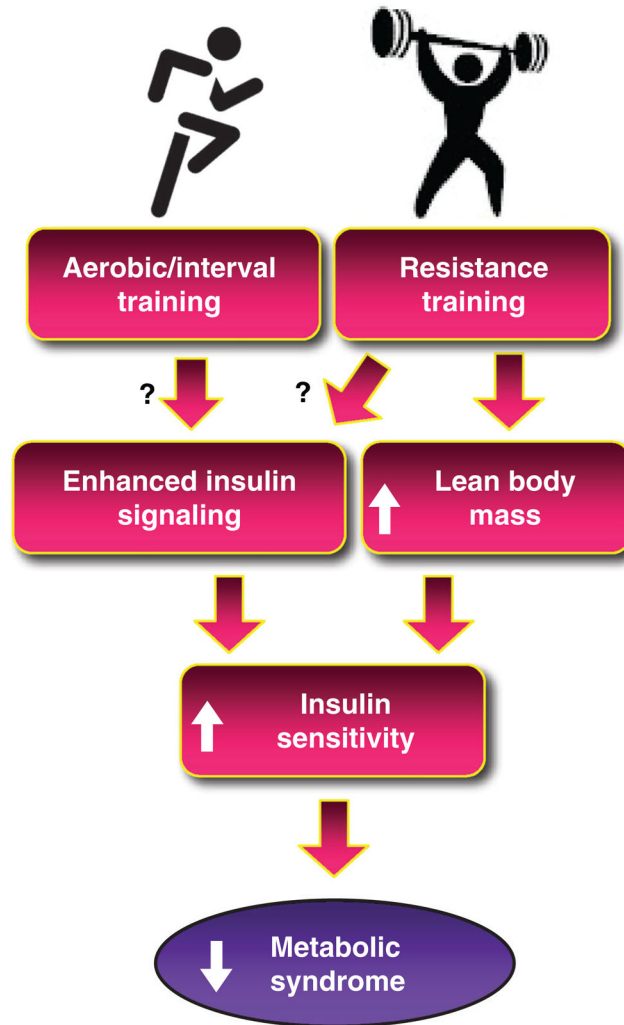
Figure 13.
Schematic diagram of future directions to determine mechanisms by which aerobic training (AT) and resistance training (RT) increase insulin sensitivity. Although there is preliminary evidence, more research is needed to clearly identify the mechanisms that are involved, as denoted by the question marks linking AT and RT to enhance insulin signaling.
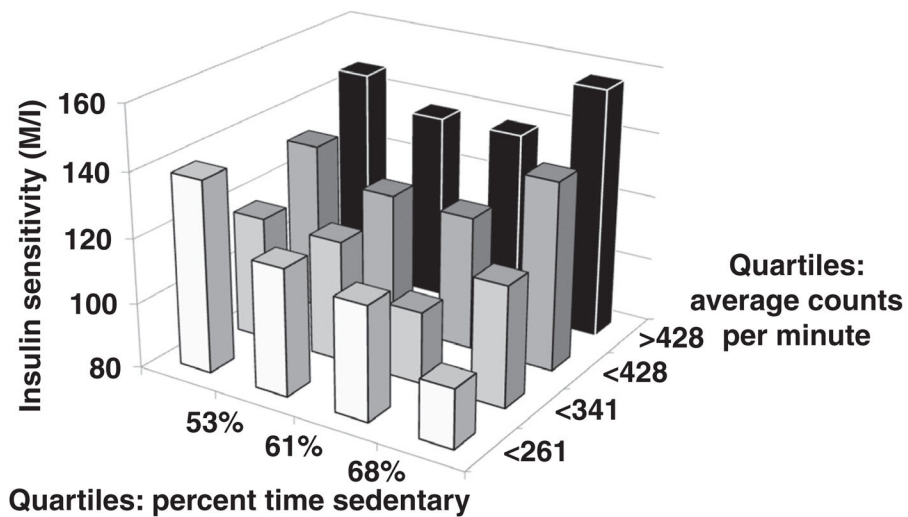
Figure 14.
Insulin sensitivity and physical activity measured by accelerometer by quartiles of average number of counts/min and quartiles of percent time sedentary in the insulin sensitivity and cardiovascular risk study. M/I is the unit measurement of insulin sensitivity ($\mu mol.min^{-1}kgFFM^{-1}nmol/L^{-1}$) (42). Copyright 2008 American Diabetes Association. From Diabetes Care®, Vol. 57, 2008; 2613–2618. Reprinted by permission of the American Diabetes Association.
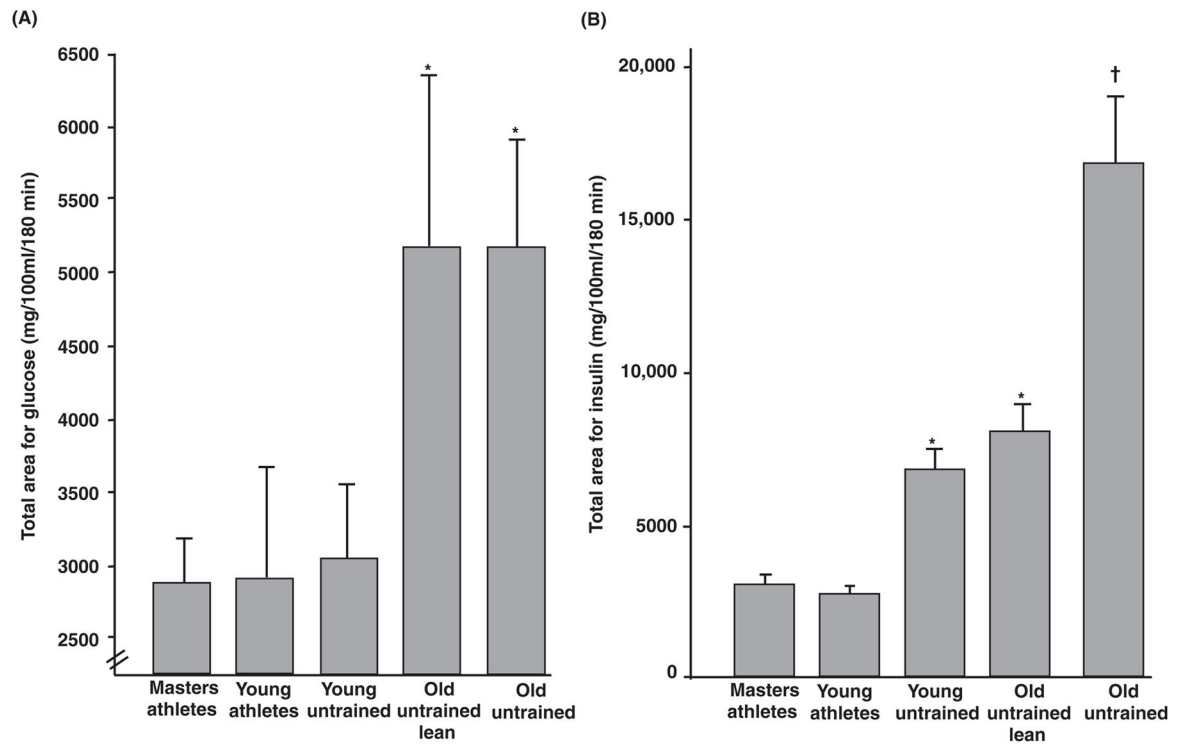
Figure 15.
Effects of training and age on area under the curve for (A) glucose and (B) insulin during an oral glucose tolerance test. Adapted, with permission, from reference (577).
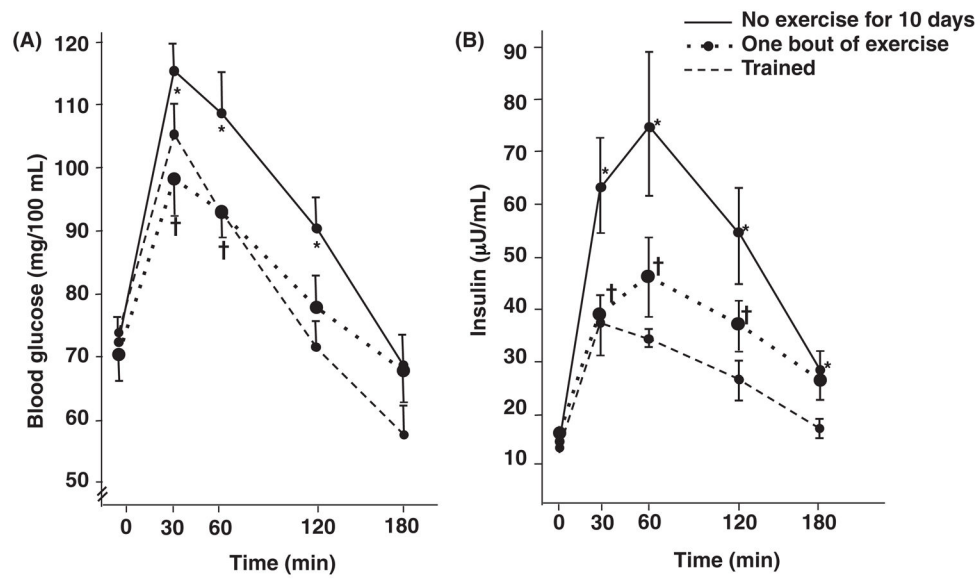
Figure 16.
Effects of chronic training (dashed line), inactivity (solid line) for 10 days and one single bout (dotted line) of aerobic exercise on (A) blood glucose and (B) insulin during an oral glucose tolerance test in well-trained subjects. Adapted, with permission, from reference (261).

Table 1

Established Criteria Proposed for Clinical Diagnosis of Metabolic Syndrome

Clinical measure	WHO (1998)	IDF (2005)	Joint IDR/NHLBI/AHA
Insulin resistance	IGT, IFT, T2DM, or lowered insulin sensitivity* Plus any two of the following	None	None But any three of the following five features
Body metric	Men: waist-to-hip ratio >0.90 Women: waist-to-hip ratio >0.85 and/or BMI >30kg/m^2	Increased WC (population specific) plus any two of the following	Population- and country-specific definitions
Lipid	TG 150 mg/dL and/or HDL-C <35 mg/dL in men or <39 mg/dL in women	TG > 150 mg/dL or on TG Rx	150 mg/dL (1.7 mmol/L)
		HDL-C <40 mg/dL in men or <50 mg/dL in women or on HDL-C Rx	<40 mg/dL (1.0 mmol/L) in males; <50 mg/dL (1.3 mmol/L) in females
Blood pressure	140/90 mmHg	130 mmHg systolic or 85 mmHg diastolic or on hypertension Rx	Systolic 130 and/or diastolic 85 mmHg
Glucose	IGT, IFG, or T2DM	100 mg/dL (includes diabetes)	100 mg/dL
Other	Microalbuminuria		

MS criteria as defined by WHO, IDF, and the joint IDR/NHLBI/AHA are compared. T2DM indicates type 2 diabetes mellitus; WC, waist circumferences; BMI, body mass index; and TG, triglycerides. All other abbreviations are in text.

*Insulin sensitivity measured under hyperinsulinemic euglycemic conditions, glucose uptake below lowest quartile for background population under investigation.

Table 2

Studies Incorporating Use of FSIGT or EHC Methodologies to Determine Effect of Resistance Training on Insulin Sensitivity

Study	Subject population	Design	Testing	Major findings	Hour after last bout
Zachwieja et al. (721)	64–75 years M	4×/wk, 16 weeks 4×4–10, 75–90% 1 RM	FSIGT	33% ⇑ in insulin sensitivity	168
Ibanez et al. (302)	66±3 years M, T2D	2×/wk, 16 weeks 50–70% 1 RM, then 70–80% 1 RM, 10–15 repetitions	FSIGT	25% ⇑ in insulin sensitivity, ⇓ fasting glucose	24
Shaibi et al. (586)	15±0.5 years M Hispanic	2×/wk, 16weeks Progressive increase in workload	FSIGT	45% ⇑ in insulin sensitivity	48–72
Van Der Heijden et al. (659)	15±0.5 years M/F Hispanic	2×/wk, 12weeks Progressive increase in workload	FSIGT (plus tracer)	⇑ peripheral in 8 of 12 subjects, but ⇓ in 4 of 12; hepatic insulin sensitivity ⇑ 24%	72
Miller et al. (440)	58±1 years M	1 set 90% 1 RM for three repetitions ⇓ load up to 15 repetitions 3×/wk, 16 weeks	EHC OGTT	24% ⇑ glucose infusion w/EHC ⇓ insulin during OGTT, fasting insulin ⇔⇒ glucose during OGTT	22–24
Ryan et al. (558)	58±2 years F	3×/wk, ~16 weeks 1–2 sets 15 repetitions	EHC	16% ⇓ in insulin response	24
Ishii et al. (308)	47±9 (SD) years, T2D	5×/wk, 4–6 weeks 2×10–20 repetitions 40–50% of 1 RM	EHC	48% ⇑ in glucose disposal	48
Poehlman et al. (506)	28±3 years F	3×/wk, 6 months 80% 1 RM	EHC	9% ⇑ in glucose infusion	96±24
Holten et al. (276)	61±2 years, healthy and T2D	3×/wk, 6 weeks, 1 legged training, 8–12 repetitions	EHC	~10% ⇑ in leg glucose clearance	16
Ryan et al. (557)	69±1 years M/F	3×/wk, 6 months 1–2 sets, 8–15 repetitions	EHC	Nonsignificant ⇑ in SI	24–36
Andersen et al. (20)	26±1 years M	RT cessation for 90 d, RT was 3×/wk, 3 months Periodized workload	EHC	11% ⇓ in insulin sensitivity	–
Reynolds et al. (536)	67±2 years M/F	3×/wk, 16 weeks 2×10–12 repetitions	EHC	15% ⇑ in glucose disposal ⇔⇒ insulin response, fasting insulin	24
Klimcakova et al. (359)	50±2 M	3×/wk, 3 months 1×12–15 repetitions	EHC	24% ⇑ glucose disposal	48–72
Davidson et al. (143)	60±4	3×/wk, 1 set up to 15 reps (20 min/session)	EHC	nonsignificant ⇑ in SI	36–48