

Obesity, Abdominal Obesity, and Insulin Resistance

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The correlation of body mass index (BMI) with both adiposity and risk for type 2 diabetes mellitus (DM) is positive. An elevated BMI is also associated with increased mortality from cardiovascular disease (CVD). However, for any given BMI measurement, some persons are at risk for type 2 DM and CVD, while others are not. This disparity of risk may relate to differences in age, fitness, and body composition, including body fat. Obesity—excess body fat—is associated with insulin resistance. Abdominal obesity, in particular, places people at higher risk for developing insulin resistance and, consequently, is associated with an increased risk for type 2 DM and CVD. The association between obesity and insulin resistance is largely due to changes in the function of adipose tissue, specifically, increased release of free fatty acids and abnormalities in adipokine secretion. The properties of visceral adipose tissue may cause these dysfunctions to become magnified. Weight loss has the potential to improve insulin sensitivity through alterations in adipose tissue function. (*Clinical Cornerstone*. 2008;9[1]:23–31) © 2008 Elsevier. All rights reserved.

The rapidly increasing prevalence of obesity in the United States and abroad continues to be a problem of great concern. In 2004, the proportion of obese adults in the United States was estimated to be 32.2%.¹ This statistic is alarming because obesity is associated with a substantial risk for abnormal glucose tolerance, hypertension, dyslipidemia, heart disease, osteoarthritis, and sleep apnea syndrome.² Some of these conditions may result from the physical effects of excess fat, whereas others may result from changes at the molecular level, as well as obesity-mediated changes in adipose tissue homeostasis.

KEY POINT

Obesity is associated with a substantial risk for abnormal glucose tolerance, hypertension, dyslipidemia, heart disease, osteoarthritis, and sleep apnea syndrome.

The influence of body fat on insulin action is important, and the relation between obesity and insulin resistance/

type 2 diabetes mellitus (DM) has been recognized for quite some time.³ The link between abdominal obesity, in particular, and insulin resistance may further increase the risk of developing type 2 DM and cardiovascular disease (CVD), and it is believed by some that abdominal obesity is a major contributor to the development of metabolic syndrome.⁴ Furthermore, metabolic syndrome is associated with an increased risk of developing type 2 DM and CVD. *Metabolic syndrome* is defined by the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) as ≥ 3 of the following: waist circumference ≥ 40 inches for a man or ≥ 35 inches for a woman; triglyceride levels ≥ 150 mg/dL; high-density lipoprotein cholesterol (HDL-C) levels < 40 mg/dL in a man or < 50 mg/dL in a woman; blood pressure levels $\geq 130/85$ mm Hg or treatment for hypertension; and fasting plasma glucose levels of 100 to 125 mg/dL.⁵

KEY POINT

The link between abdominal obesity and insulin resistance may further increase the risk for type 2 DM and CVD.

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DEFINING OBESITY

Obesity is characterized by excessive accumulation and storage of fat in the body; however, clinically, an accurate quantification of excess body fat is difficult to achieve. Body weight can provide an indirect estimate of fat stores, but the variability of body build and composition makes it difficult to define a specific level for obesity.⁶

Generally, the correlation between percentage of body fat and body mass index (BMI) is positive, especially when body fat is measured in the research setting.⁷ Thus, despite some limitations, BMI is considered a valid measure for defining obesity and identifying those individuals at increased risk for obesity-associated morbidity and mortality.⁸ Obesity is generally defined as a BMI ≥ 30 kg/m² for adults.^{2,8}

OBESITY-ASSOCIATED MORBIDITY AND MORTALITY

The current epidemic of obesity is the major factor underlying the growing prevalence of type 2 DM. The strong relation between elevated BMI and risk for type 2 DM was identified in 2 large epidemiologic studies—the Nurses' Health Study⁹ and the Health Professionals' Follow-up Study.¹⁰ Other studies^{11–14} indicate that obesity may reduce a person's life expectancy. Data from the Framingham Study¹¹ show that a nonsmoking obese woman will lose 7.1 years of life and a nonsmoking obese man will lose 5.8 years because of obesity compared with a normal-weight cohort. Prospective cohort studies^{12–14} have shown that even a moderate elevation in BMI is associated with increased mortality due to CVD.^{12,14}

Despite evidence that shows obese people to be at increased risk for type 2 DM and CVD, there is a heterogeneity in risk among obese people. Although there is a

positive correlation between BMI and risk for type 2 DM, not everyone who is obese has type 2 DM, and not everyone who has type 2 DM has an elevated BMI.^{9,10} Furthermore, some obese patients may have normal metabolic profiles, whereas some nonobese patients (ie, those of normal weight or those having relatively small amounts of excess fat) may display metabolic characteristics that put them at risk for type 2 DM and CVD.^{15,16}

KEY POINT

Some obese patients may have normal metabolic profiles, whereas some nonobese patients may display metabolic characteristics that put them at risk for type 2 DM and CVD.

Studies that link obesity with increased risk for metabolic complications often have confounding variables, such as physical activity, that impact that risk. For example, obese people who are physically active may be at lower risk for morbidity and mortality than are those of normal weight who are sedentary.^{17,18} In a study by Wei et al,¹⁷ lean but unfit men were shown to have a higher mortality risk than men who were obese but fit. A recent prospective study¹⁸ of adults aged ≥ 60 years showed that fitness was a significant mortality predictor, independent of both overall and abdominal obesity.

The association of BMI with morbidity and mortality also may be influenced by age. Obesity-related mortality risk has been reported to be lower at older ages. One study¹⁹ that demonstrated such a decline in risk showed no correlation between BMI and mortality after the age of 74 years.

KEY POINT

Data from the Framingham Study show that a nonsmoking obese woman will lose 7.1 years of life and a nonsmoking obese man will lose 5.8 years because of obesity compared with a normal-weight cohort.

LOCATION OF FAT DETERMINES METABOLIC RISK

From the standpoint of metabolic risk, the location of excess fat is important. Evidence from epidemiologic and metabolic studies^{20,21} has shown that adverse metabolic consequences of excess fat are more closely related to the *location* of fat than to the *amount* of fat. Indeed, central accumulation of fat may be a better predictor of increased risk for type 2 DM and CVD than is absolute fat mass.²² Conversely, accumulation of fat in the gluteofemoral areas is not associated with

increased cardiovascular risk and may even be metabolically protective.^{23,24}

KEY POINT

Adverse metabolic consequences of excess fat are more closely related to the location of fat than to the amount of fat.

Abdominal obesity has been shown to increase a person's risk for developing type 2 DM.²² This increased risk has been largely attributed to the association of insulin resistance with the accumulation of abdominal adipose tissue.^{22,23} Even lean people may show variability in insulin sensitivity because of differences in body fat distribution. For example, those who have a more peripheral distribution of fat are more insulin sensitive than are those whose fat is predominantly central.²⁵ Thus, even people who are not clinically obese may be at risk for insulin resistance and metabolic dysfunction if their fat is centrally located.

Abdominal fat can be characterized as either *subcutaneous* or *visceral*. Among the various fat depots, the amount of intra-abdominal, or visceral, fat best correlates with insulin sensitivity.^{26,27} Studies that have quantified the amount of fat in subcutaneous and visceral adipose depots with computed tomography (CT) or magnetic resonance imaging (MRI) have demonstrated that centrally located visceral fat has more influence on insulin resistance than does centrally located subcutaneous fat.^{28,29}

KEY POINT

Centrally located visceral fat has more influence on insulin resistance than does centrally located subcutaneous fat.

Furthermore, the amount of visceral adipose tissue (VAT) has been shown to be predictive of fasting insulin levels, as well as insulin and glucose responses to oral glucose loads, independent of both the degree of obesity

and the amount of subcutaneous abdominal fat.²³ Among identical twins discordant for obesity, only those who differed most in amounts of visceral fat—not subcutaneous abdominal fat or overall adiposity—had major differences in insulin sensitivity and glucose tolerance.³⁰ These studies suggest that, among obese patients, those with visceral obesity are a subgroup at particular risk of developing insulin resistance and type 2 DM.

Regardless of the relative contributions of visceral and subcutaneous abdominal fat to insulin resistance, the pattern of central abdominal obesity correlates more strongly with insulin resistance than does lower-body obesity. Although waist circumference does not distinguish between amounts of visceral and subcutaneous fat, techniques using CT and MRI are able to distinguish precisely visceral fat depots from subcutaneous depots. Waist circumference, therefore, is the best physical attribute to correlate with amount of VAT.³¹ Measurement of waist circumference can help clinicians determine which patients may be at especially high metabolic risk. Guidelines developed by the NCEP ATP III define a waist circumference of ≥ 40 inches in a man and ≥ 35 inches in a woman as central obesity.²⁵

KEY POINT

Obese patients with visceral obesity are a subgroup at particular risk of developing insulin resistance and type 2 DM. Furthermore, the pattern of central abdominal obesity correlates more strongly with insulin resistance than does lower-body obesity.

OBESITY AND INSULIN RESISTANCE

Adipose tissue, as the body's major energy depot, stores energy in the form of triglycerides and releases energy in the form of free fatty acids (FFAs) and glycerol.³² Adipose tissue plays an important role in metabolic homeostasis not only through its direct control over large stores of energy but also through its secretion of various bioactive proteins that collectively are called *adipokines*.^{33–35} Obesity has been shown to affect the production of FFAs

and adipokines³⁶ and to be associated with increased release of FFAs and abnormal secretion of adipokines.^{36–38} Both of these obesity-related changes—the increased FFA release and the abnormal secretion of adipokines—can have adverse effects on insulin action; therefore, both have the potential to link obesity with insulin resistance.

KEY POINT

Adipose tissue plays an important role in metabolic homeostasis not only through its direct control over large stores of energy but also through its secretion of various bioactive proteins that collectively are called *adipokines*.

The elevated level of FFAs commonly seen in obesity is an important connection between obesity and insulin resistance.^{36–38} The increased release of FFAs from adipose tissue is associated with the expansion of adipose mass.^{38,39} Visceral and subcutaneous fat differ somewhat with respect to their contribution to this expansion. Visceral fat is less sensitive to insulin's antilipolytic effect and therefore is more lipolytic than is subcutaneous fat.³⁶ Furthermore, FFAs that are released from visceral fat drain into the portal circulation and go directly to the liver, whereas FFAs derived from subcutaneous fat are secreted into the systemic circulation.^{40,41} The increased flux of FFAs from visceral fat through the liver can promote gluconeogenesis and hepatic insulin resistance and lead to an accelerated synthesis of very-low-density lipoprotein and increased triglyceride levels.^{39,41}

It is hypothesized that triglycerides in obese persons are diverted from adipose tissue and stored in nonadipose cells and tissues, such as hepatocytes and skeletal muscle.^{37,38,42} This redirection may occur either because the adipose tissue is already so packed with fat that triglycerides need to be stored elsewhere or the adipose tissue is “set” to release FFAs and not to store triglycerides. In either case, the accumulation of fat in nonadipose cells and tissues contributes further to insulin resistance in these areas, probably by interfering, either directly or indirectly, with insulin signaling pathways.⁴³

As noted earlier, adipokine secretion may be a link between obesity and insulin resistance. Adipose tissue is able to alter insulin action through its secretion of proinflammatory cytokines and other factors,^{33–35} the most widely studied of these being adiponectin, leptin, plasminogen-activator inhibitor-1 (PAI-1), tumor necrosis factor (TNF)- α , and interleukin-6 (IL-6). Leptin, PAI-1, TNF- α , and IL-6 levels are elevated in obese subjects and are associated with insulin resistance.^{33,40} There is evidence that TNF- α and IL-6 may promote insulin resistance via pathways that interfere with the transduction of glucose transporter 4 to the plasma membrane.⁴³ Adiponectin, on the other hand, has insulin-sensitizing properties, and its levels have been found to be reduced in obese persons.^{33,36,40} Adiponectin may act as an insulin sensitizer primarily by stimulating fatty acid oxidation.^{33,36,37} Production of these proteins appears to differ between subcutaneous and visceral adipose depots. For example, expression and secretion of IL-6 and PAI-1 are relatively greater in VAT, whereas that of leptin and adiponectin are relatively greater in subcutaneous fat.⁴⁰

IMPROVING INSULIN SENSITIVITY IN OBESITY

Weight loss and physical activity are known to improve insulin activity and glucose homeostasis.³ Clinical trials have proven that weight loss with lifestyle modification can prevent people at high risk from developing type 2 DM and reduce their risk of developing metabolic syndrome.^{44,45} Treatment with metformin was also shown to prevent these problems but was not as successful as lifestyle modifications. Weight reduction also has been shown to reduce levels of PAI-1, TNF- α , and IL-6 and increase levels of adiponectin.^{33,34}

KEY POINT

Weight loss and physical activity are known to improve insulin activity and glucose homeostasis. Weight loss with lifestyle modification can prevent people at high risk from developing type 2 DM and reduce their risk of developing metabolic syndrome.

Thiazolidinediones (TZDs) lower glucose levels in type 2 DM by improving insulin sensitivity. The mechanism by which this occurs may be via the promotion of fatty acid storage in adipose tissue, which would lower FFA levels and redistribute lipids away from the liver and muscle tissue.³⁷ Although use of TZDs is associated with lower glucose levels and improved insulin sensitivity, their use also is generally associated with weight gain.

Rimonabant, a CB₁ receptor antagonist, has been shown in clinical trials⁴⁶ to reduce weight and improve parameters associated with metabolic syndrome, including waist circumference, HDL-C levels, triglyceride levels, blood pressure, and glucose tolerance. These improvements have translated into a significant ($P < 0.001$) reduction in the prevalence of metabolic syndrome in subjects receiving rimonabant 20 mg daily compared with placebo.⁴⁷ It has been suggested that, independent of its association with weight reduction, beneficial metabolic effects might be mediated through an influence on adipocyte function. For example, an increase in adiponectin levels beyond what would have been expected in association with weight loss itself has been observed with the use of this agent.⁴⁷

The effect of weight reduction with lifestyle modification might involve changes in adipokines that, in turn, affect insulin sensitivity. Pharmacologic agents such as TZDs and rimonabant may have beneficial effects on insulin sensitivity due to their effects on adipocyte function, which occur regardless of any improvement in weight. Because visceral and subcutaneous adipose tissues have different properties, changes in their respective masses have varying impacts on insulin sensitivity. Together, these observations could be interpreted as indirect evidence that the association of insulin resistance with obesity involves more than body fat mass per se. Instead, it requires the development of abnormalities at the molecular level of adipose tissue homeostasis. These abnormalities are more likely to occur in people who are obese, particularly in those with abdominal obesity, but they could also occur in nonobese individuals who may, for example, have an increased amount of visceral fat.

CONCLUSIONS

Obesity is a complex disorder. This is especially apparent when the connection between obesity and insulin resistance is examined. There appear to be important differences in the metabolic effects of adipose depots,

KEY POINT

The association of insulin resistance with obesity involves more than body fat mass per se. Instead, it requires the development of abnormalities at the molecular level of adipose tissue homeostasis.

depending on their location (ie, peripheral or central) and whether they are characterized as visceral or subcutaneous. Obesity-related changes in adipocyte function are associated with abnormalities in FFA levels and adipokine expression, which in turn are important promoters of insulin resistance. Therefore, what might emerge as a more reliable predictor of obesity-associated morbidity and mortality is not necessarily the amount of adipose tissue present, or even its location, but rather the degree of dysfunction associated with it.

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Dialogue Box

EDITORIAL BOARD

The Framingham study indicated a reduced life expectancy for obese patients (body mass index [BMI] >30 kg/m²). Are there any data regarding changes in life expectancy for subjects whose BMI places them in the category of “overweight”?

WESTPHAL

Yes, this was addressed in data from the Framingham study as well. If they were overweight, 40-year-old female nonsmokers lost 3.3 years of life expectancy, and 40-year-old male nonsmokers lost 3.1 years.

EDITORIAL BOARD

What is the mechanism for obesity-related mortality risk being lower at older ages?

WESTPHAL

It may reflect a selection process that has allowed these people to survive to an older age. For example, their constitution is such that they haven't had problems from coronary artery disease despite being obese. In addition, in the elderly, maintaining a particular BMI may be a sign of overall good health, as it indicates that they have not had problems with potentially life-threatening illnesses that are often associated with weight loss.

EDITORIAL BOARD

What is the major determinant of whether a fat cell elaborates more adiponectin than inflammatory cytokines?

WESTPHAL

Adiponectin is recognized as an anti-inflammatory cytokine and appears to have protective metabolic properties, unlike the inflammatory cytokines. There is an inverse relation between adiponectin levels and insulin resistance: levels of adiponectin decrease with the conditions of obesity, insulin resistance, and type 2 diabetes and increase when insulin sensitivity improves, as occurs with weight loss. Adiponectin levels tend to move in the direction opposite that of the inflammatory cyto-

kines, and decreased levels of adiponectin are a manifestation of adipocyte dysfunction.

EDITORIAL BOARD

What determines whether a patient accumulates subcutaneous rather than visceral fat?

WESTPHAL

Genetic factors play a role in determining body fat distribution. Whether fat is in the subcutaneous versus the visceral depot is probably a reflection of the interaction between a person's genotype and his or her environment.

EDITORIAL BOARD

Do you see a role for thiazolidinediones (TZDs) in nondiabetic patients?

WESTPHAL

There are potentially a couple of roles for TZDs in patients who do not have diabetes, for example, in patients with nonalcoholic steatohepatitis and in patients with impaired glucose tolerance. Concerns have been raised about the long-term safety of TZDs regarding potential cardiovascular disease, congestive heart failure, and bone loss. Thus, although these agents appear to be promising, more work is needed to assess their long-term safety and efficacy in these settings.

EDITORIAL BOARD

Is the process of oxidation of free fatty acid (FFA) a normal part of the uptake of FFA into the liver or muscle cell, or is oxidation of FFA a component of a different process?

WESTPHAL

There are 2 major pathways for FFA disposal: (1) mitochondrial β -oxidation to adenosine triphosphate and ketone bodies; and (2) secretion into the blood as triglycerides in very-low-density lipoprotein particles. Impaired β -oxidation of FFAs—either because of a functional problem at the level of the mitochondria or because of the excess FFA load placed on the mitochon-

Dialogue Box

dria of hepatocytes—has been implicated in nonalcoholic fatty liver disease, a complication associated with obesity and type 2 diabetes.

EDITORIAL BOARD

Where do insulin and other adipokines work in the FFA oxidation metabolic pathway?

WESTPHAL

Insulin and other adipokines probably have the largest impact at the level of FFA supply. Insulin resistance and the increased production of proinflammatory cytokines are associated with excessive lipolysis and FFA flux from adipose tissue. This increased flux of FFAs into the mitochondria of hepatocytes is thought to stress the mitochondria, as they have limited ability to increase FFA oxidation. This is thought to generate reactive oxygen

species, which can cause lipid peroxidation and further promote the generation of cytokines.

EDITORIAL BOARD

Why is it that starvation or calorie deprivation does not result in an increase in FFA levels?

WESTPHAL

FFA levels are elevated normally in the fasting state. Insulin resistance in visceral adipose tissue leads to this chronic elevation, even in the postprandial state. Chronic elevation of FFA levels leads to a decrease in insulin sensitivity. Caloric restriction in obese patients with type 2 diabetes, even in the short term before any significant change in body weight occurs, will improve glucose homeostasis and insulin sensitivity. That is, the negative caloric state itself decreases insulin resistance.