Chapter 34
Insulin Resistance and the Metabolic Syndrome

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Introduction

This chapter focuses on insulin resistance and its role in diabetes, obesity, and cardiovascular (CV) disease. There is significant evidence that both CV disease and diabetes have common metabolic antecedents.[1,2] The metabolic syndrome and its relation to insulin resistance, cardiovascular disease, and diabetes will be critically reviewed with a focus on current clinical controversies.

Insulin Action and Insulin Secretion

To maintain normal glucose homeostasis, there must be adequate insulin secretion synchronized with target tissue insulin responsiveness. Following the ingestion of a meal, insulin, secreted from the pancreas, permits the circulating blood glucose to be transported to muscle and adipose cells for metabolism or storage and also suppresses the release of glucose from the liver.[3]

Insulin acts to increase glucose uptake for storage and metabolism in muscle and adipose cells via the tissue-specific glucose transporter glut-4 and in liver via glut-2. Insulin also decreases lipolysis and promotes lipogenesis. In liver, insulin decreases gluconeogenesis and glycolysis and promotes glycogen synthesis. Insulin also regulates amino acid uptake and protein synthesis, has important actions on the vasculature and endothelial cells and, among its least understood functions, acts on the brain to integrate fuel and energy homeostasis.

Insulin activates its receptor by binding to its two alpha subunits[4,5] (Figure 34.1). This auto-phosphorylates and activates *tyrosine kinases* intrinsic to the beta subunits, to promote phosphorylation of other tyrosines on downstream molecules known as insulin receptor substrates (IRS) and Shc. The IRS family of molecules consists of tissue-specific subtypes, for example, IRS-1 in muscle and IRS-2 in liver. IRS and Shc in turn activate phosphatidylinositol-3 kinase (PI-3-kinase) and mitogen-activated protein kinase (MAP kinase). The PI-3-kinase path is involved with metabolic activity and glucose transport via Glut-4 transporters in muscle and the MAP kinase pathway regulates mitogenesis and growth. Other metabolic activities controlled by the PI-3-kinase pathway include glycogen synthesis, lipolysis, fatty acid, and protein syntheses. Defects in this pathway are likely to reflect a combination of genetic and acquired defects.[6,7] One example of a defect in the pathways involves phosphorylation of serine or threonine residues of the IRS-1 complex instead of tyrosine which results in decreased downstream insulin receptor activity.

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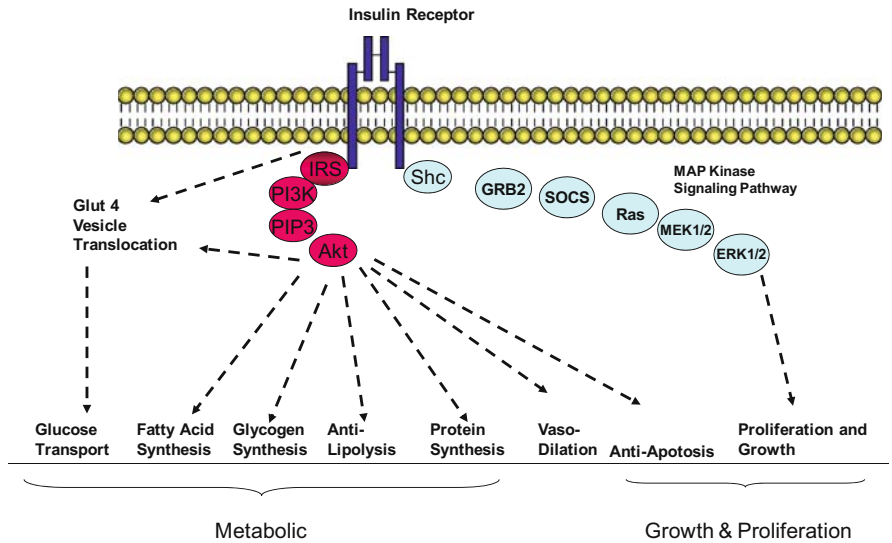

Fig. 34.1 Conceptual pathways of insulin receptor signaling show a simplified scheme for key insulin receptor pathways for metabolic actions and growth and proliferative action. *Dashed lines* represent intermediates which are not shown. (modified from ref [4,5])

Physiological Effects of Insulin Resistance

Resistance to insulin's effects may occur in different tissues.[8] In muscle, decreased insulin-mediated glucose uptake causes elevated blood glucose. Usually, a compensatory increase in insulin secretion develops which results in hyperinsulinemia sufficient to maintain normal glucose homeostasis. Without this, hyperglycemia and diabetes ensue. This compensatory increase in insulin or hyperinsulinemia while perfectly appropriate for maintaining the blood glucose level, may result in the enhancement of other actions of insulin.[9,10]

In the liver, a decreased insulin effect results in a lower suppression of hepatic glucose output and may lead to increased blood glucose. In adipose tissue, increased lipolysis and free fatty acids occur. Increased blood glucose and free fatty acid in turn promote further beta-cell dysfunction, decreased insulin secretion, and action. This negative amplification is also known as glucose toxicity and lipotoxicity.[11] In the brain, insulin resistance may be involved in altered feeding and energy regulation. In endothelial cells, insulin action via the PI-3-kinase pathway promotes the release of nitric oxide from endothelial cells. Nitric oxide, a *vasodilator*, increases blood flow and aids in peripheral glucose uptake. In contrast, insulin, working through the MAP kinase pathway, also promotes the release of endothelin-1 which is a potent *vasoconstrictor.* Normally, the vasodilator and vasoconstrictor aspects of insulin are in balance. However, in insulin resistance, hyperinsulinemia sufficient to maintain normal blood glucose through the PI-3-kinase and glut-4 pathway overactivates the MAP kinase pathway resulting in vasoconstriction. Activation of MAP kinase also promotes proliferation of vascular smooth muscle cells, an early vascular abnormality.[12,13]

Measuring Insulin Action in Humans

Although insulin regulates many physiological functions, our understanding of defects in insulin action in humans centers around muscle glucose uptake which has become a defining feature. Dynamic measures of insulin action include the euglycemic insulin clamp,[14,15] the insulin suppression test with steady-state plasma glucose determination,[16] the frequently sampled intravenous glucose tolerance test,[17–22] and the insulin tolerance test. Estimates of insulin sensitivity can also be obtained during an oral glucose tolerance test and include the Avignon, Matzuda, Gutt, and Stumvoll indices and the $IS_{0,120}$.[23–26] Static measures use fasting plasma insulin

Table 34.1 Measurements of insulin sensitivity

	Direct steady-state measurements
Hyperinsulinemic euglycemic clamp	Glucose infusion rate at steady state = M
	Possible variations include use of specific tracers for endogenous glucose output or lipid metabolism and adjustments for actual insulin concentrations achieved
Insulin sensitivity test	Steady-state plasma glucose concentration during constant infusions of insulin and glucose with suppressed endogenous insulin secretion
	Direct non-steady-state measurements
Insulin tolerance test	Measures a disappearance rate (k) of glucose following an intravenous bolus of insulin
Minimal model analysis of FSIVGTT[a]	The minimal model identifies model parameters that determine a best fit to glucose disappearance during the modified FSIVGTT. S_I: fractional glucose disappearance per insulin concentration unit; S_G: ability of glucose itself to facilitate its own disposal and inhibit hepatic glucose production in the absence of an incremental insulin effect (i.e., when insulin is at basal levels)
	Indices derived from fasting conditions
G/I ratio	Ratio of fasting plasma glucose (mg/dl) and insulin (μU/ml)
HOMA	HOMA-IR = $([I_{0\ \mu U/ml}] \times [G_{0\ mmol/l}])/22.5$
QUICKI	QUICKI = $1/[\log (I_{0\ \mu U/ml}) + \log (G_{0\ mg/dl})]$
	Indicies derived from oral glucose tolerance test
Matsuda index	$10{,}000/[(G_{0\ (mg/dl)} \times I_{0\ (mU/l)}) \times (G_{mean} \times I_{mean})]$
Gutt index	$75{,}000 + (G_0 - G_{120})_{(mg/dl)} \times 0.19 \times BW/120 \times G_{mean(0,120)\ (mmol/l)} \times \log (I_{mean(0,120)})_{(mU/l)}$
Stumvoll index	$0.157 - 4.576 \times 10^{-5} \times I_{120\ (pmol/l)} - 0.000299 \times I_{0\ (pmol/l)} - 0.00519 \times G_{90\ (mmol/l)}$

[a]FSIVGTT = frequently sampled intravenous glucose tolerance test
BW= body weight in kilograms
G_0 = fasting plasma glucose
G_{120} = plasma glucose at 120 min after 75 g oral glucose ingestion
G_{90} = plasma glucose at 120 min after 75 g oral glucose ingestion
I = plasma insulin; I_0 = fasting plasma insulin

alone or, together with glucose values, result in indices such as the insulin/glucose ratio, HOMA-IR, and the QUICKI. All correlate to varying degrees with clamp-derived insulin sensitivity[27–34] (Table 34.1).

The euglycemic insulin clamp, considered the gold standard, involves infusing a constant amount of insulin and a variable amount of glucose over time so that the plasma glucose concentration remains constant.[14,15] By quantitating the amount of glucose required, the effect of insulin on whole-body glucose uptake is determined and reported as milligrams of glucose per kg body weight (or lean body mass) per minute. The higher the number of mg/kg/min of glucose infused, the greater the sensitivity at any particular insulin infusion. Adjustments may be made for plasma insulin concentration. Usually data from the last 30 min are used to calculate glucose disposal after a steady-state plasma glucose has been achieved. In its simplest form, the euglycemic insulin clamp method measures whole-body glucose uptake largely in *muscle*. In general, a glucose uptake above 5 mg/kg/min during a 1 mU/kg/min insulin infusion, which achieves a circulating insulin concentration of approximately 100 μU/ml, is usually considered normal insulin sensitivity, although this should be determined in individual populations. The choice of insulin dose infused during the clamp depends upon the hypothesis being tested. Liver glucose output is suppressed at low insulin concentrations while glucose uptake in muscle occurs at higher insulin concentrations. By combining this method with tracer techniques (labeled glucose or glycerol), the effect of insulin on the liver (suppression of hepatic glucose production, gluconeogenesis) and adipose tissue (lipolysis) can also be determined.[35,36] The procedure is reproducible, time consuming, and requires a degree of experience. A variation on the euglycemic insulin clamp, popularized by Reaven, involves the infusion of a fixed dose of insulin and glucose and the resultant steady state plasma glucose is the measure of insulin sensitivity with suppressed insulin secretion.[16]

The frequently sampled intravenous glucose tolerance test (FSIVGTT) relies on a rise of endogenous insulin in response to a bolus infusion of intravenous glucose (0.3 g/kg of 50% dextrose) delivered over 1 min with plasma samples obtained at 0, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 22, 25, 30, 40, 50, 60, 70, 80, 90, 100, 120, 140,

160, 180 min.[17–22] The minimal model mathematical analysis of the kinetics of the resulting plasma glucose and insulin concentrations determines the fractional glucose disappearance rates per unit of insulin, termed S_I. Another parameter describes the effect of glucose on its own disposal at basal insulin concentrations, termed S_G. Parameters from the standard FSIVGTT correlate moderately well with clamp-derived insulin sensitivity.[8] One limitation is its reliance on release of endogenous insulin which may not be robust in patients with diabetes. Thus, a modification of the technique evolved which uses a bolus of insulin (30 mU/kg) 20 min after the test begins. This improves the *overall* correlation of the FSIVGTT parameters with the clamp technique (r=0.62, p<0.0001). Subgroups with impaired glucose tolerance or diabetes may not correlate as well (r=0.48, p=0.016 and r=0.41, p=0.03, respectively).[18,20,22]

Measures based on the oral glucose tolerance test, the Avignon, Matsuda, Stromvoll, and Gutt indexes,[23–26] are simpler to perform but may be affected by different and variable rates of gastric emptying and incretin effects. Measures which rely on a fasting glucose and/or insulin are simplest and lend themselves to large population studies.

Correlations of fasting plasma insulin with clamp-derived insulin sensitivity show coefficients of 0.56, p=0.01.[33] The HOMA-IR or homeostatic model assessment is calculated using the following formula: fasting plasma glucose mmol/l × fasting plasma insulin μU/ml/22.5. The number 22.5 is a factor derived from the product of a normal glucose of 4.0 mmol/l and a normal insulin 5.0 μU/ml. Thus the value of 1.0 would be found in a "normal" individual and higher numbers indicate insulin resistance. HOMA-IR correlates well with clamp-derived insulin sensitivity, r= 0.88, p<0.0010.[30] The HOMA-IR is less accurate in diabetes and, because fasting insulin and glucose reflect liver metabolism, this test assumes that hepatic and peripheral insulin resistance are comparable. The log of HOMA-IR provides more consistent results (correlation with clamp data produces in healthy controls r=–46, p=0.056 and in obese subjects r=–0.79, p<0.0001). Another variation is the QUICKI or the Quantitative Insulin Sensitivity Check Index =1/(log insulin (μU/ml) + log glucose (mg/dl)).[31] It demonstrates a good correlation with clamp-derived data but appears to be less robust in non-obese subjects (overall r=0.78, p<0.00001; normal, r=0.49, p=0.01; obese, r=0.8, p<0.008; diabetics, r= 0.7, p<0.0001). Modifications of QUICKI include free fatty acid or glycerol determinations and improve the relationship with the euglycemic clamp-derived insulin sensitivity: QUICKI FFA = 1/(log fasting insulin [μl/ml] + log fasting glucose [mg/dl] + log fasting FFA [mmol/l]).[32,34] Limitations may include decreased ability to measure *change* in insulin sensitivity and reduced accuracy in uncontrolled diabetes. Thus, there are numerous ways to determine insulin sensitivity, each with its own advantages and limitations. The key is choosing one that is both feasible and best addresses the hypothesis being tested.

Insulin Resistance, Type 2 Diabetes, and Metabolic Abnormalities: Physiological Studies

Following the discovery of the radioimmunoassay technique by Berson and Yalow,[37,38] insulin resistance was identified as important in type 2 diabetes. It is present in the majority of type 2 patients with type 2 diabetes, their first-degree relatives, individuals with impaired glucose tolerance and obesity.[39–44] For years debates raged about whether insulin resistance or insulin secretion was more important in the pathogenesis of diabetes.[39] Most arguments supported insulin resistance since most patients and their relatives were insulin-resistant and nondiabetic individuals without diabetic relatives were not. Fewer arguments supported defective insulin secretion, although it was known that when matched for obesity, patients with type 2 diabetes had lower insulin responses than nondiabetic obese individuals. An important concept was the hyperbolic nature of the relationship between insulin resistance and insulin secretion in maintaining normal glucose tolerance: beta cell function varied reciprocally with the degree of insulin resistance as a constant, called a "disposition index" or DI. Thus mis-matches of beta cell function relative to insulin requirements were predicted to result in hyperglycemia and the development of diabetes.[45]

Longitudinal studies tracking the progression from normal to impaired to diabetic glucose tolerance provided clearer answers.[46–49] Among insulin-resistant Pima Indians, who were followed for 5 years, individuals who remained with normal glucose tolerance developed a slight worsening of insulin resistance and a complementary

increase in insulin secretion. In contrast, in those individuals who developed diabetes, there was a slight worsening of insulin resistance but a very dramatic decrease in insulin secretion. Thus, even in the presence of insulin resistance, the key and essential physiological abnormality leading to hyperglycemia was a relative or absolute *decrease in insulin secretion* relative to insulin requirements.

Studies in a different ethnic group further illustrate this concept of insulin deficiency in diabetes. Among African-Americans, type 2 diabetes is heterogeneous: there are insulin-resistant *and* insulin-sensitive variants.[50] Nearly 30% of African-Americans with a BMI < 28.5 kg/m^2 exhibit the *unusual insulin-sensitive variant*.[51] Individuals with the insulin-sensitive variant had fasting plasma insulin levels markedly lower than that in those with the insulin-resistant variant. Postprandial insulin levels were also lower in the insulin-sensitive subgroup suggesting that insulin deficiency was a significant defect in this group. Insulin responses in the typical insulin-resistant variant were lower than that in controls leading to the conclusion that this group had at least two defects, insulin resistance and insulin deficiency, similar to the Pima Indians.

Several important metabolic features distinguish the *variants*. The insulin-resistant variant is associated with metabolic abnormalities including high plasma triglyceride and low plasma HDL cholesterol levels[52] while the insulin-sensitive variant exhibits normal plasma triglycerides, HDL cholesterol, and free fatty acid levels. Body composition also distinguishes the variants. There is a greater amount of visceral adipose tissue volume in the insulin-resistant variant compared with the BMI and age-matched insulin-sensitive variant.[53] Increased visceral adipose tissue is inversely associated with insulin-mediated glucose disposal while total subcutaneous adipose tissue is not (Figure 34.2). Increased visceral adipose tissue volume is also associated with increased plasma triglyceride levels, intramyocellular fat, and liver fat[54–56]. These and other data show that the insulin-resistant form of type 2 diabetes is characterized by increased cardiovascular risk factors with fat in abnormal locations.

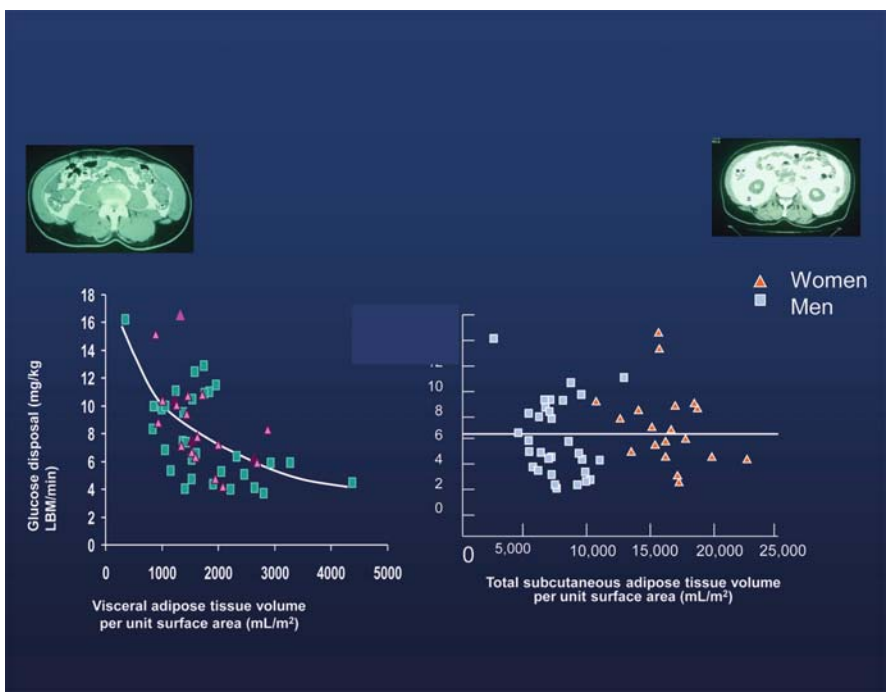

Fig. 34.2 *Left Panel* shows the inverse nonlinear relationship of insulin action to visceral adipose tissue ($r = –0.58$, $Pp < 0.0001$; men $r = –0.60$ (*squares*) and women $r = –0.59$ (*triangles*); the slope and intercept were not different in men and women). *Right panel* shows there is no significant relationship between insulin-mediated glucose disposal and total subcutaneous adipose tissue volume. *Insets* shown above the *left* and *right panel*, respectively, are a cross section of an abdominal CT image highlighted to show a small compared to a large visceral adipose tissue area.[62]

Insulin resistance and increased myocellular fat are also associated with abnormalities in muscle mitochondria number, size, and function.[57,58] Myocellular ATP production is decreased somewhat in the fasting state and abolished during insulin stimulation in individuals with type 2 diabetes, in their relatives, in obesity and nutrient overload.[59] Both increased FFA and glucose may decrease mitochondrial fitness and expression of genes for oxidative phosphorylation, including PGC-1α.[60,61] It is difficult to determine whether the fundamental cellular decrease in energy production is a result or a cause of obesity or insulin resistance.

There are population differences in the prevalence of insulin resistance in type 2 diabetes. For example, among Japanese, the insulin-sensitive form has a high frequency (∼60%) with decreased non-traditional cardiovascular risk factors.[63] In contrast, South Asian Indians have a high prevalence of insulin resistant diabetes.[64] In the US NHANES data, 85% are insulin resistant and only 15% are insulin sensitive.[65]

Insulin resistance has been associated with multiple metabolic abnormalities (Table 34.2), several of which are traditional CV risk factors (high LDL cholesterol, hypertension, obesity, and diabetes), while the rest are known as nontraditional CV risk factors. Because of the link between insulin resistance and these CV risk factors,[66,67] it has been attractive to consider that insulin resistance is the underlying pathophysiological cause of increased CV disease in diabetes and obesity. These metabolic abnormalities include increased inflammatory markers such as increased hsCRP (highly sensitive C-reactive protein), interleukin-6, increased plasminogen activator inhibitor-1 (PAI-1) and increased fibrinogen (predisposing to thrombosis), increased uric acid and endothelial dysfunction with increased microalbuminuria and homocysteine levels.[63–77] The association between insulin resistance and hypertension appears to be population specific as it is not present in all ethnic groups[78–80] and because among individuals with essential hypertension, only 50% are insulin resistant. Many of these metabolic changes found in insulin resistance are also observed with obesity and will be discussed below. It is difficult to know which is of primary importance, obesity or insulin resistance.

Table 34.2 Insulin resistance syndrome and its components

Obesity[a]
Central obesity
Increased liver fat
Increase muscle fat
Glucose intolerance and type 2 diabetes[a]
Altered lipids
High triglyceride concentrations
Low HDL cholesterol concentrations
Dense LDL cholesterol[a] particles
Hypertension[a] – variable expression
Increased inflammation – CRP and others
Increased coagulation
Increased PAI-1
Increased fibrinogen
Increased vascular disease
Microalbuminuria
Endothelial dysfunction

[a]Traditional cardiovascular risk factors

Insulin Resistance and Obesity

In the 1940s and 1950s, Jean Vague of France described two types of obesity, both occurring in men and women: android or central obesity and gynoid or peripheral obesity.[81] The android form was associated with increased rates of diabetes, hypertension, and coronary artery disease while the gynoid form was not.

Obesity is excess of body fat and is most simply defined by a body mass index (BMI) or weight in kilograms divided by the height in meter squared [(weight (kg)/height (m)^2]. By convention, an individual with a BMI of less than 25 kg/m^2 is lean, with a BMI of 25–29.9 kg/m^2 is overweight, and with a BMI greater than 30 kg/m^2 is obese. Because of racial differences in body composition in South Asian Indians, an individual with a BMI

< 23 is defined as normal, 23–25 is defined as overweight, and > 25 is defined as obese. The BMI is an imperfect measure and for a greater understanding of obesity and its relationship to metabolism, it is important to describe body composition. Total body fat can be estimated by body volume (using an underwater or an air displacement method), density, and weight or by using dual photon absorptiometry (DXA). Visceral and subcutaneous fat and muscle are measured using computed tomography or magnetic resonance imaging and in vivo measurement of metabolic activity of muscle can be obtained by NMR spectroscopy.

Obesity is related to insulin resistance.[82,83,87] In studies of obese persons (BMI 30–34.9), McLaughlin[84] showed that insulin-resistant individuals compared to insulin sensitive, had significantly higher systolic and diastolic blood pressures and serum triglyceride levels and low HDL cholesterol levels as well as a higher prevalence of impaired glucose tolerance (48% vs 2%). However, not all obese individuals are insulin resistant[84,85] as highlighted in Ruderman's concept of the metabolically "obese" normal-weight individual.[86] The European Group for the Study of Insulin Resistance (EGIR) examined the relationship of insulin resistance measured by the euglycemic insulin clamp and hyperinsulinemia in healthy European individuals without hypertension over a wide range of body mass indices.[85] Similarly, EGIR reported that only 25% of nondiabetic obese persons (BMI> 25 kg /m^2; mean of 29 kg /m^2) were insulin resistant based on the euglycemic insulin clamp measurements. This unexpected result suggests that 75% of obese (or non-lean) individuals are insulin sensitive. After correcting for age, sex, and BMI, the waist circumference and waist–hip ratio were no longer associated with insulin resistance. This is not surprising as the waist is highly correlated with BMI and reflects both the visceral and the subcutaneous adipose tissue compartments.

Whether visceral or the subcutaneous adipose tissue is most important relative to insulin resistance has been the subject of considerable debate. In a comprehensive review of studies in adults, correlating subcutaneous and visceral adipose tissue measurements made by CT or MRI to insulin resistance measured using either the euglycemic clamp or the steady-state plasma glucose by insulin sensitivity index, Reaven found that the majority (11 of 18 studies) showed that visceral adipose tissue was most highly correlated with insulin resistance in men and women, blacks, whites, and South Asians (with correlation coefficient ranging from –0.33 to –0.60). However five studies reported that subcutaneous adipose tissue had higher correlation coefficients and two had equivalent correlations between the two fat depots. In favor of subcutaneous adipose tissue is an observation that most circulating free fatty acids derive from this depot and have adverse metabolic effects on both insulin secretion and action and promote inflammation. Although, most of these cross-sectional studies suggest the importance of visceral adipose tissue, several well-constructed intervention studies and one longitudinal one provide the most convincing evidence that excess visceral fat has adverse effects.

An initial report from Goodpaster et al. noted that the subcutaneous but not visceral adipose tissue was most significantly correlated with insulin resistance (r= –0.61 vs –0.52).[88] Subsequently, these authors reported that, after diet-induced weight loss, it was the decrease in visceral (not subcutaneous) adipose tissue which correlated most significantly with the improvement in insulin sensitivity.[89] Thus, the visceral adipose tissue depot was clearly critical in determining insulin resistance. Lemieux followed a group of women for 7 years and reported on changes in body composition and insulin resistance.[90] Comparisons of two subgroups with similar increases in visceral fat despite large differences in subcutaneous fat showed that there was no difference in metabolic parameters including glucose levels and insulin secretion. Moreover, individuals with the largest increase in visceral adipose tissue had significant deterioration in glucose tolerance and increase in insulin levels. A different approach – surgically removing subcutaneous adipose tissue - leads to the same conclusion. Klein studied the effects of subcutaneous adipose tissue liposuction on cardiovascular and metabolic risk factors and insulin action in obese diabetic and nondiabetic patients, before and 10 weeks after the procedure.[91] The nondiabetic subjects had 10.5 kg of fat or 28% of the abdominal subcutaneous fat removed and the patients with type 2 diabetes had 9.1 kg of fat removed (44% of this depot); baseline BMIs were 39.9 and 35.1 kg/m^2, respectively. Visceral adipose tissue volume did not change. Klein reported that despite a substantial weight loss there was no improvement in metabolic parameters including lipids, glucose, insulin, adiponectin, insulin resistance measured by the euglycemic insulin clamp method or other measures of inflammation including hsCRP, interleukin-6, and tumor necrosis factor alpha (TNF-α). A follow-up study, performed to evaluate long-term metabolic and CV benefit possibly overlooked in the earlier data, showed nearly identical results.[92] Improved glycemic and metabolic control seen during the treatment of type 2 diabetes with thiazolidiendiones is frequently associated with increases in

subcutaneous fat and decreases in liver, visceral and blood fat suggesting specific roles of different fat depots.[95] Finally, a 10 year longitudinal study in Japanese Americans showed that visceral fat measured using the gold standard CT scanning was independently associated with the development of insulin resistance whereas total fat or subcutaneous fat was not.[93] The importance of a longitudinal study in well characterized subjects cannot be over emphasized.

Since human studies cannot always provide definitive information, a study in an animal model serves to clarify the role of *subcutaneous* adipose tissue. In female Syrian hamsters, surgical removal of greater than 50% of the subcutaneous adipose tissue, followed by a high-fat diet, resulted in a marked increase in serum triglycerides and visceral fat as well as a worsening of glucose tolerance and increase in serum insulin levels.[94] This demonstrates both the beneficial role of subcutaneous adipose tissue as a metabolic sink for excess calories and the adverse effects of storing calories in the viscera and in blood.[95]

Visceral adipose tissue has several unique metabolic properties. It demonstrates a high turnover, is more susceptible to catecholamine-induced lipolysis than subcutaneous adipose tissue,[96,97] and is under different sex hormone regulation. 1-Beta hydroxysteroid dehydrogenase type 1 activity may also differ. This enzyme converts inactive cortisone to cortisol and thus may cause local tissue changes in hormonal milieu.[98] Increased visceral adipose tissue is frequently associated with increased plasma triglyceride level, liver fat, and intramyocellular lipid.[55–101] These data suggest that ectopic fat (or fat in the "wrong places") may trigger inflammation with subsequent deleterious effects.

Adipose tissue is metabolically active and contributes to many factors which play a role in the adverse outcomes of obesity including insulin resistance, diabetes, and CV disease. These factors include increased resistin, increased visfatin, decreased adiponectin, increased inflammation, oxidative stress and increased reactive oxygen species[102–113] as well as free fatty acids, plasminogen activator-1 (PAI-1), fibrinogen, and uric acid. While weight loss decreases many of these biomarkers and suggests their importance, the finding that the adipose tissue-derived pro-inflammatory cytokines such as tumor necrosis factor α (TNF-α) can directly trigger inflammation points to a mechanism.[102] Several intracellular mediators of these inflammatory stimuli involve IKKβ/ NF-κB and the JNK pathways. Stimuli that activate the IKKβ/ NF-κB and JNK pathways include free fatty acid, glucose, reactive oxygen species, interleukin-6, ceramides, TNF-α, and advanced glycosylated end products (AGEs), as well as viral or bacterial elements. Activation of the pathways results in increased transcription of inflammatory moieties and the perpetuation of inflammation. Increased inflammation is associated with serine/threonine phosphorylation of IRS-1 and contributes to insulin resistance. Activation of macrophage can set in motion an inflammatory cascade of events leading to the vascular atheroma development and CV disease. In this context, two studies serve as proof of concept. Dandonna showed that treatment with insulin immediately after a myocardial infarction decreased inflammation (hsCRP and interleukin-6) and improved cardiac outcomes.[114] Goldfine treated obese nondiabetic individuals with salsalate, an anti-inflammatory agent, and reported a decrease in inflammation as well as a decrease in C-peptide and glucose suggesting that decreasing inflammation improves insulin resistance.[115] These data show some of the interrelationships of obesity, inflammation, insulin resistance, and CV disease.

Insulin Resistance, Obesity: Metabolic Heterogeneity

Insulin resistance and obesity are associated and are frequently assessed using the surrogate, hyperinsulinemia, especially in population studies. The European Group for the Study of Insulin Resistance (EGIR),[85] which reported on insulin resistance measured by the euglycemic insulin clamp and hyperinsulinemia in healthy European individuals as mentioned earlier, defined insulin resistance as the bottom 10% of the insulin lean group and hyperinsulinemia as the top 10% of fasting plasma insulin. Obesity was defined as a BMI > 25 kg/m^2. Insulin resistance was found in only 26% of obese subjects (mean BMI 29 kg/m^2), far fewer than anticipated. Hyperinsulinemia was observed in 41% of the obese subjects and *both* hyperinsulinemia and insulin resistance were present only among 14% of the obese subjects compared to 1.6% of the lean. The frequency of insulin resistance was low in obese individuals and was exceeded by hyperinsulinemia. Thus, hyperinsulinemia may

result not only from obesity and insulin resistance but also through other possibly central nervous system signals as well. Hyperinsulinemia, therefore, is not a precise surrogate for insulin resistance and the obese phenotype is heterogeneous in terms of insulin resistance and its metabolic abnormalities.

The heterogeneity of the obese phenotype is further demonstrated in the NHANES data of 5440 participants without known CV disease. Metabolic parameters assessed included fasting plasma glucose and insulin, insulin resistance measured by HOMA-IR, inflammation measured by hsCRP, lipids and blood pressure. Several interesting observations emerged. In the age-standardized group with *normal* body weight (BMI< 25 kg/m^2), 30%, were metabolically *unhealthy* with two or more abnormalities while in the groups which were *overweight* (BMI 25–29.9 kg/m^2) or *obese* (BMI $\geq$ 30 kg/m^2), 48.8, and 29%, respectively, were *metabolically normal* with 0–1 abnormalities. Racial sub-analyses were similar. Correlates of 0–1 metabolic abnormalities were younger age, black race/ethnicity, higher physical activity levels, and smaller waist circumference (Figures 34.3 and 34.4,[116]). A separate report confirms that obese individuals with high percent body fat can have favorable metabolic profiles characterized by normal insulin sensitivity, lack of high blood pressure, normal lipids, and adiponectin levels.[117] These subjects had less liver, visceral and muscle fat, as well as less intima–media thickness, a surrogate for CV disease. Finally, an intervention study of diet-induced weight loss suggested that the two phenotypes might respond differently: the metabolically

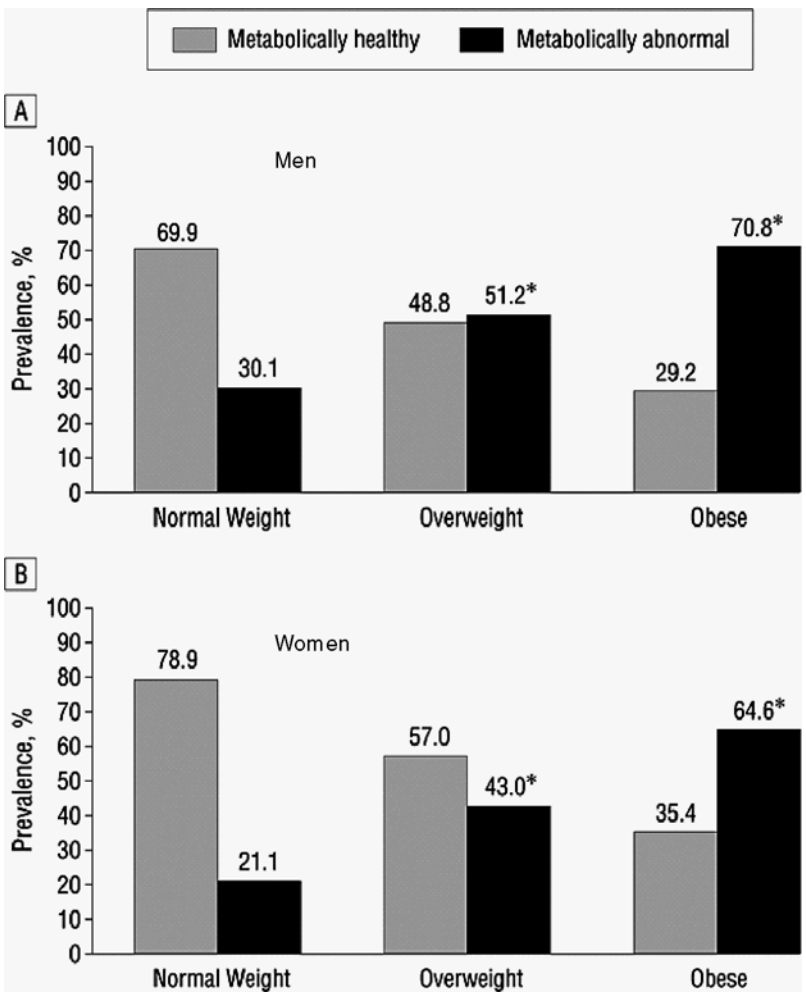

Fig. 34.3 Age-standardized prevalence of cardiometabolic abnormalities by body size and sex (A, men; B, women). $*p$ <.001 for proportion metabolically abnormal vs normal weight. (modified from ref[116])

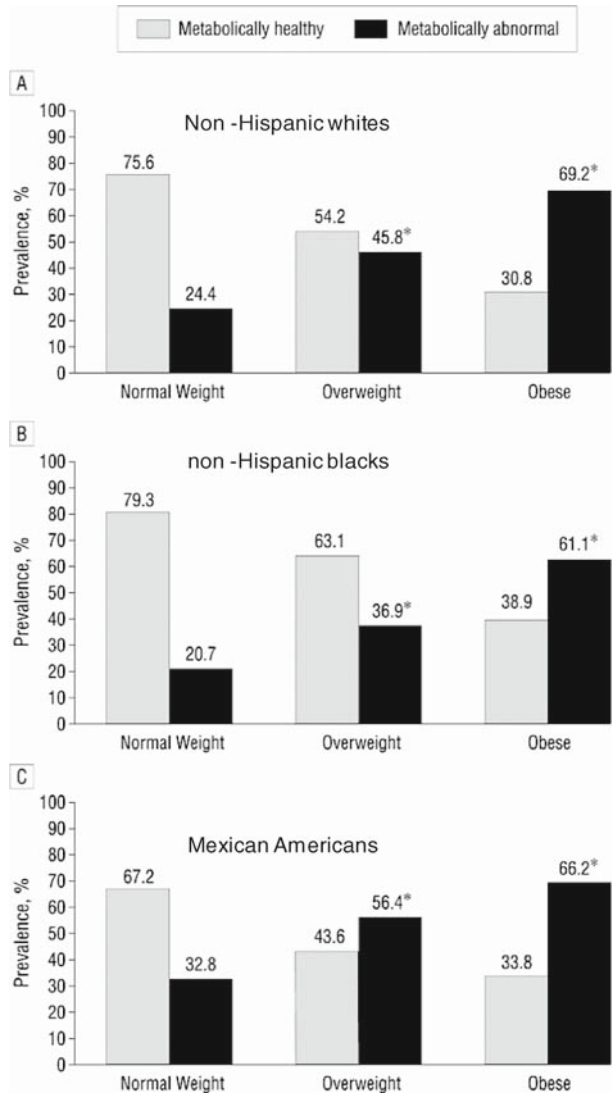

Fig. 34.4 Age- and sex-standardized prevalence of cardiometabolic abnormalities by body size and race/ethnicity. A, non-Hispanic whites; B, non-Hispanic blacks; and C, Mexican Americans. $*p$ <.001 for proportion metabolically abnormal vs normal weight. (modified from ref[116])

adverse group *improved* insulin sensitivity by 26% while in contrast, the metabolically normal group's sensitivity deteriorated by 11%.[118] Whether similarly divergent responses accompany exercise is not known.

Insulin Resistance and Cardiovascular Disease – Population Studies

A prodigious number of population studies have tested the hypothesis that insulin resistance is a risk factor for cardiovascular disease in an attempt to understand the 2- to 4-fold increase in CV disease mortality with diabetes.[119–121] Most used fasting plasma insulin or HOMA-IR to measure insulin resistance.

Small studies, using the euglycemic insulin clamp, showed a positive relationship between insulin resistance and CV disease. In a report of 208 persons followed for 6 years, those in the highest compared to the lowest tertile

had increased CV disease.[122] A report on the 6-year follow-up of 73 persons noted that CHD, hypertension, and microalbuminuria were increased in those with insulin resistance.[123]

Reports using the HOMA-IR showed variable results. The San Antonio Heart study which followed 2569 individuals for 7.5 years with 187 CV events. They reported an odds ratio (OR) of CV disease for the lowest versus the highest tertile of insulin resistance of 1.94 (95% CI 1.05–3.59) after adjustments for multiple confounders including sex, age, ethnicity, smoking alcohol use, physical activity, waist, blood pressure, HDL and LDL cholesterol, and triglycerides.[124] The VA HT study[125], The Study of Elderly Men[127] and the DECODE[126], the latter of which followed more than 10,000 individuals for 8.8 years also showed a positive association between insulin resistance and CVD.[126,127] In contrast, the Strong Heart Study and the Framingham Offspring Study did not show a relationship of insulin resistance and CVD[128,129]

The relationship of insulin to CV disease is not as strong as it was initially hypothesized. In 1998, Ruige's review showed an overall hazard ratio (HR) for insulin and CV disease of 1.18 (95% CI 1.08–1.29) for each 50 pmol/l of fasting plasma insulin and highlighted ethnic/racial heterogeneity.[130] In whites the association of insulin and CV disease showed a HR of 1.4 (95% CI 1.23–1.65) compared to non-whites (Nauruans and Pima Indians) of 1.04 (95% CI 0.93–1.16). Whites were older, with clinical outcomes of death or myocardial infarction instead of ECG changes. Several specific studies are worthy of review. The ARIC study of 13,446 men and women with 305 events followed over 6 years showed no relationship of fasting plasma insulin to CV disease.[131] Further follow-up revealed a relationship of fasting insulin to incident stroke with a HR of 1.54 (95% CI 1.01–1.3) for each 50 pmol/l of fasting insulin.[132] In contrast, the Helsinki Policeman study of 970 men followed up to 22 years did *not* show a relationship of hyperinsulinemia to stroke after adjustment for age and other CV disease risk factors [HR 1.54 (95% CI 0.9–2.64)] while blood pressure, upper body obesity, and smoking were significantly predictive [HR 1.36 (95% CI 1.18–3.06), 1.59 (95% CI 1.26–2.00), 1.88 (95% CI 1.16–3.04), respectively]. This study highlights an interesting aspect of long-term follow-up. After adjustment for age and other CV disease risk factors, hyperinsulinemia (defined as the highest quintile of insulin area under the curve during an OGTT) was associated with a HR for major incident coronary heart disease at 5, 10, and 15 years [HR 2.36 (95% CI 1.00–5.57), 2.29 (95% CI 1.31–4.02), 1.76 (95% CI 1.09–2.82), respectively] but not at 22 years [HR 1.32 (95% CI 0.89–1.97)]. This attenuation of effect suggests a changing relationship of insulin to CV risk over time. The concept of a changing temporal relationship of a risk factor to a disease as the pathogenesis evolves may explain the varied findings in different studies.[133,134] The Caerphilly study of 1056 subjects over 12 years with 127 events showed no relationship of fasting plasma insulin to CV disease.[135] Among elderly men born between 1913 and 1923, the risk of coronary heart disease increased 2.4-fold in those in the highest compared to the lowest quintile of fasting plasma insulin after 13-year follow-up.[136] The DECODE Study mentioned above,[126] also reported that the risk of *death* was predicted by the highest compared to the lowest tertile of fasting insulin [HR 2.66 (95% CI 1.45–4.9) for women and 1.54 (95% CI 1.16–2.03) for men].The HOMA-IR results were significantly similar [HR 2.35 (95% CI 1.16–2.03) for women and 1.58 (95% CI 1.2–2.09) for men].

A recent meta-analysis of 19 studies in Western populations with 3600 events showed an overall modest predictive effect of insulin on incident coronary heart disease. For fasting insulin, the RR was 1.2 (95% CI 0.98–1.28) and for non-fasting insulin the RR was 1.35 (95% CI 1.14–1.6). Figure 34.5 shows the effect of insulin for all the studies.[137]

Metabolic Syndrome: Risk for Type 2 Diabetes and Predictor of CV Disease

Although previously described, in 1988 Gerald Reaven's Banting Lecture popularized the "metabolic syndrome," linking insulin resistance as central to, if not the primary cause of a cluster of abnormalities including glucose intolerance, hypertension, and a distinct lipid profile of high triglyceride and low HDL cholesterol levels.[8,136–145] The "syndrome" was a plausible explanation linking diabetes and cardiovascular disease. Diabetes, like obesity, is associated with a 2- to 4-fold increase in CV mortality and since most people with diabetes are obese and insulin resistant, clarifying the contribution of the components of each to cardiovascular disease is challenging.

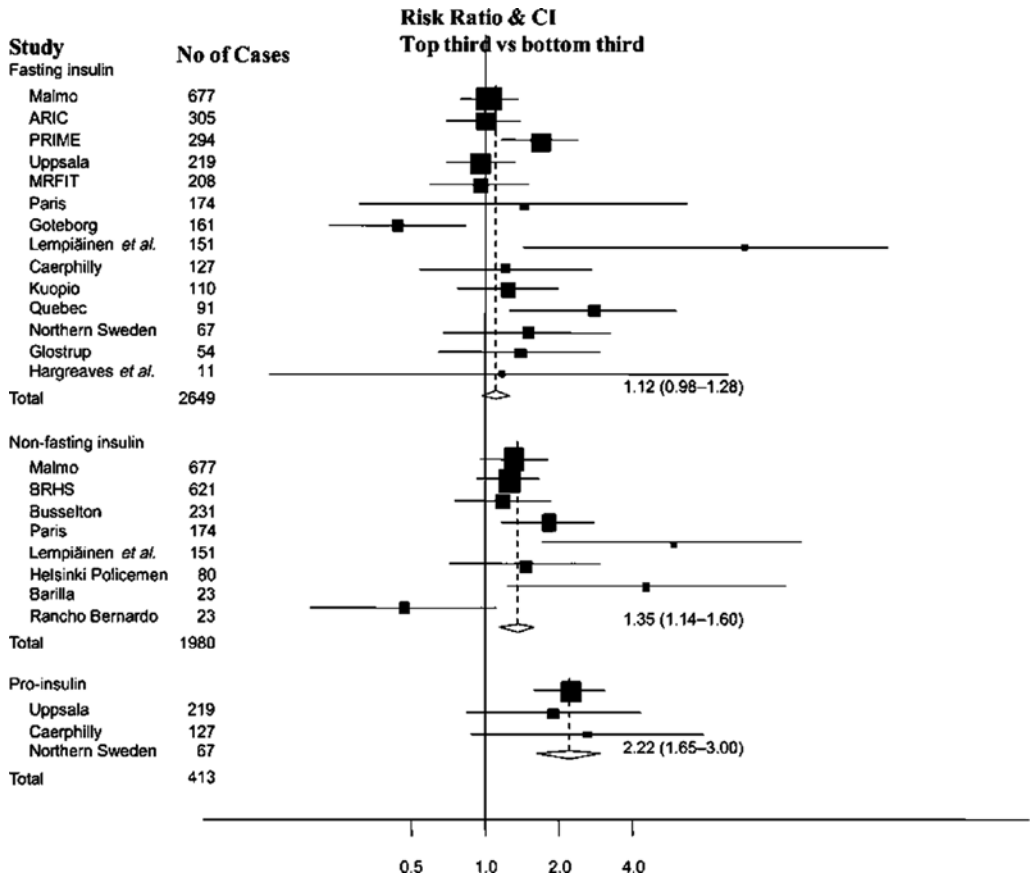

Fig. 34.5 Prospective studies of concentrations of circulating insulin markers and coronary heart disease (CHD) (nonfatal MI or coronary death) in Western populations in 19 prospective studies involving a total of about 3600 incident CHD cases. It shows the risk ratio (RR) for CHD and confidence intervals (CI) for the top third vs the bottom third for fasting insulin (1.12 [95%C 0.98–1.28] for raised fasting insulin) and for non-fasting insulin (1.35 [95% CI 1.14–1.60] for raised non-fasting insulin).[137] The *left inset* shows RR of various study characteristics. Specifically, *top* and *bottom insets* show RR of CHD: 1.12 [95% CI 0.98–1.28] for raised fasting insulin, 1.35 (1.14–1.60) for raised non-fasting insulin, respectively

Reaven presented the metabolic syndrome as a testable hypothesis and ever since, the challenge has been met with an avalanche of articles.

Metabolic Syndrome – WHO, ATP III, and IDF Criteria

The central feature of the Reaven's metabolic syndrome was insulin resistance measured by an insulin clamp. Since the insulin clamp was unwieldy, simpler measures were developed to assess if insulin resistance and metabolic syndrome were predictive of diabetes and increased CV. Various professional organizations devised clinically measurable but arbitrary sets of criteria as surrogates which were initially based on diabetes or insulin resistance. In chronological order these were the following: the World Health Organization (WHO, 1999), European Group for the Study of Insulin Resistance (EGIR, 1999), the National Cholesterol Education Panel (NCEP) of the American Heart Association (AHA), Adult Treatment Panel (ATP III) criteria (2001), the American Association of Clinical Endocrinologists (AACE) (2003), the revised AHA criteria (2005), and the International Diabetes Federation (IDF, 2005) (Tables 34.3 and 34.4).[146–151]

Table 34.3 Different definitions of the metabolic syndrome (modified from ref[150])

Clinical measure	WHO (1998)	EGIR	ATP III (2001)	AACE (2003)	IDF (2005)	AHA 2005
Insulin resistance	IGT, IFG, T2DM, or lowered insulin sensitivity[a] plus any two of the following	Plasma insulin >75th percentile plus any two of the following	None, but any of the following five features	IGT or IFG plus any of the following based on clinical judgment	None	Any three of the following five features
Body weight	Men: waist-to-hip ratio >0.90; women: waist-to-hip ratio >0.85 and/or BMI > 30 kg/m^2	WC ≥ 94 cm in men or ≥ 80 cm in women	WC ≥ 102 cm in men or ≥ 88 cm in women	BMI ≥ 25 kgm^2	Increased WC (population specific)[b] plus any two of the following	WC ≥ 102 cm men WC ≥ 88 cm women
Lipid	TG ≥ 150 mg/dl and/or HDL-C < 35 mg/dl in men or < 39 mg/dl in women	TG ≥ 150 mg/dl and/or HDL-C < 39 mg/dl in men or women	TG ≥ 150 mg/dl HDL-C < 40 mg/dl in men or < 50 mg/dl in women	TG ≥ 150 mg/dl and HDL-C < 40 mg/dl in men or < 50 mg/dl in women	TG ≥ 150 mg/dl or on TG Rx HDL-C < 40 mg/dl in men or < 50 mg/dl in women or ion HDL-C Rx	TG ≥ 150 mg/dl HDL-C < 40 mg/dl in men or < 50 mg/dl in women or treatment[c]
Blood pressure	≥ 140/90 mmHg	≥ 140/90 mmHg or on hypertension Rx	≥130/85 mmHg	≥130/85 mmHg	≥130 mmHg systolic of ≥ 85 mmHg diastolic or on hypertension Rx	BPs ≥ 130 or BPd ≥ 85 mmHg or treatment
Glucose	IGT, IFG, or T2DM[d]	IGT or IFG (but not diabetes)	> 110 mg/dl (includes diabetes)[d]	IGT or IFG (but not diabetes)	≥ 100 mg/dl (includes diabetes)	> 100 mg/dl
Other	Microalbuminuria			Other features of insulin resistance[e]		

[a]Insulin sensitivity measured under hyperinsulinemic euglycemic conditions, glucose uptake below lowest quartile for background population studied.

[b]See Table 344.

[c]HDL-C =HDL cholesterol, TG = triglyceride. Fibrates and nicotinic acid are the most commonly used drugs for elevated TG and reduced HDL-C. Patients taking one of these drugs are presumed to have high TG and low HDL.

[d]IGT = impaired glucose tolerance, IFG = impaired fasting glucose;T2DM = type 2 diabetes mellitus

The 2001 definition identified fasting plasma glucose of 110 mg/dl (6.1 mmol/l) as elevated. This was modified in 2004 to be 100 mg/dl (5.6 mmol/l), in accordance with the American Diabetes Association's updated definition of IFG

[e]Includes family history of type 2 diabetes mellitus, polycystic ovary syndrome, sedentary lifestyle, advancing age, and ethnic groups susceptible to type 2 diabetes mellitus

WC = waist circumference. To measure, locate top of right iliac crest. Place a measuring tape in a horizontal plane around abdomen at level of iliac crest. Before reading tape measure, ensure that tape is snug but does not compress the skin and is parallel to floor. Measurement is made at the end of a normal expiration.

Some US adults of non-Asian origin (e.g., white, black, Hispanic) with marginally increased waist circumference [e.g., 94–101 cm (37–39 in.) in men and 80–87 cm (31–34 in.) in women] may have strong genetic contribution to insulin resistance and should benefit from changes in lifestyle habits, similar to men with categorical increases in waist circumference. Lower waist circumference cutpoint [e.g., 90 cm (35 in.) in men and 80 cm (31 in.) in women] appears to be appropriate for Asian Americans.

Table 34.4 Population-specific waist circumference

Country/ethnic group	Waist circumference (WC)
Europids In the USA, the ATP III values (102 cm male; 88 cm female) – likely to continue in use for clinical purposes	Male ≥ 94 cm; female ≥ 80 cm
South Asians Based on a Chinese, Malay, and Asian-Indian population	Male ≥ 90 cm; female ≥ 80 cm
Chinese	Male ≥ 90 cm; female ≥ 80 cm
Japanese	Male ≥ 90 cm; female ≥ 80 cm
Ethnic South and Central Americans	Use South Asian recommendations until more specific data are available
Sub-Saharan Africans	Use European data until more specific data are available
Eastern Mediterranean and Middle East (Arab) populations	Use European data until more specific data are available

While the WHO and the EGIR were centered on diabetes, glucose intolerance, or insulin resistance, plus several other factors, the NCEP–ATP III version was developed by cardiologists with the express goal of targeting individuals at high risk for CV disease prevention. In NCEP–ATP III, three out of five equally weighted criteria defined the metabolic syndrome. Neither diabetes nor insulin resistance were necessary for the diagnosis of metabolic syndrome. In the IDF version, the central criterion was a high waist circumference (adjusted for differences in ethnic groups) plus two of four other elements. On the surface, these appear similar but the WHO, EGIR, AACE, and IDF are anchored hierarchically in diabetes/glucose intolerance/ insulin resistance or central obesity while in NCEP–ATP III all criteria are equal. Although conceptually NCEP–ATP III proposal appears simple, a large number of combinations of three out of five criteria raise the question of whether all combinations equally predict CV disease.[152]

Prevalence and Stability Over Time of the Metabolic Syndrome

The prevalence of metabolic syndrome varies by definition, population, and gender; reports suggest that its stability differs among populations. Its prevalence based on the NCEP–ATP III criteria was ∼24% in the US NHANES population of 1988–1994 and rose to ∼34% in 1999–2002 survey (Figure 34.6)[153,154]

The San Antonio Heart study followed two cohorts over 10 and 7 years and reported an increased prevalence of the metabolic syndrome by the NCEP–ATP III criteria.[155] Among nondiabetic individuals, percent rate increases were from 15.5 to 25.8% and 23.3 to 30.4% in men and 10.8 to 22.6% and 23.3 to 30.4 in women in the first and second cohorts. In diabetics these rates were significantly higher, ranging from 79 to 85% in the second cohort in men and 66 to 87% in both cohorts of women. In contrast, in Mexico, the rate in men was 38.9% without change over 7 years while in women there was no change over 3 years and a slight decrease (65–59%) over the final 4-year study interval.[156] A Finnish cross-sectional study done 10 years apart (1992 and 2002) shows the increasing prevalence of NCEP–ATP III metabolic syndrome (1992 and 2002); men had a higher prevalence of metabolic syndrome compared to women at baseline but only women had a significant increase in incidence over time (32–38% for women and 48.8–52.6% for men).[157] Among adolescents, the diagnosis of the metabolic syndrome is reported to fluctuate.[158]

Several important issues should be examined. (1) Is the metabolic syndrome useful in identifying individuals at high risk for diabetes and/or and increased CV disease in nondiabetic and diabetic populations? (2) Is insulin resistance the basis for the metabolic syndrome?

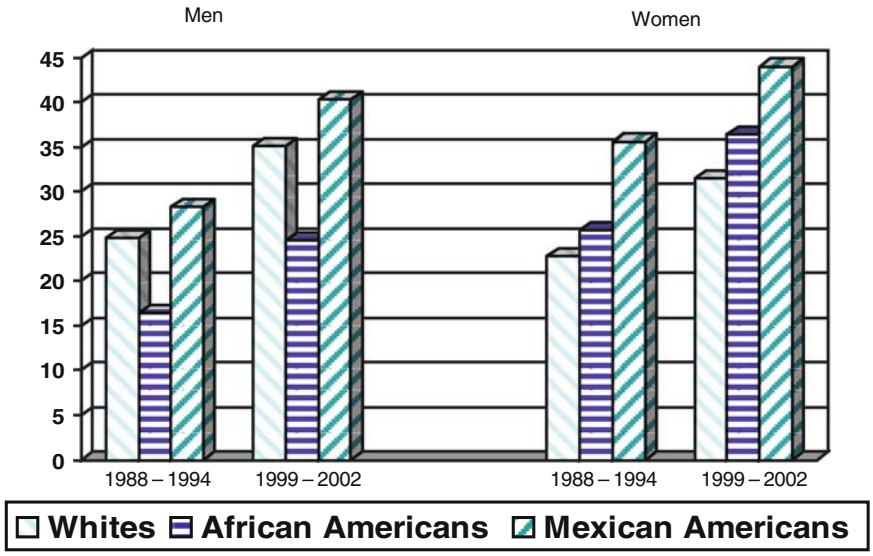

Fig. 34.6 Increase in metabolic syndrome over time in whites, African-Americans, and Mexican Americans

Does the Metabolic Syndrome Predict Diabetes in Nondiabetes Populations?

The metabolic syndrome strongly predicts diabetes. This may not be surprising because one component is an elevated blood glucose which alone has a similar predictive value.[159,160] Indeed, metabolic syndrome accounts for up to half of the new cases of diabetes in the Framingham offspring study among those who did not have diabetes at baseline and were followed for 8 years.[161] While the metabolic syndrome strongly predicts diabetes (HR ~4–6), fasting plasma glucose is far more predictive (HR ~18). The reader is referred to a recent review for more details.[162]

Does the Metabolic Syndrome Predict CV Disease in Nondiabetic Populations?

Early studies[143] enthusiastically reported robust associations of insulin resistance and CV disease but subsequent more rigorous examinations adjusting for components of the metabolic syndrome found it less informative.

Ford summarized 17 prospective studies from 1998 to 2002, and after adjusting for confounders, the metabolic syndrome by WHO and NCEP–ATP III criteria modestly and similarly predicted CV disease (RR for WHO was 1.93 (95% CI 1.39–2.07) and NCEP was 1.65 (95% CI 1.38–1.00) and all-cause mortality (RR for WHO was 1.37 (95% CI 1.09–1.74) and for NCEP was 1.27 (95% CI 0.09–1.78)). In contrast, metabolic syndrome was a much more robust predictor of diabetes (RR 2.60–2.99).[163] Among elderly Finns, followed for 13.5 years, Wang reported on the relationship of all the different definitions of metabolic syndrome and their ability to predict diabetes or CV mortality and disease.[164] WHO and IDF criteria predicted CHD and CV disease mortality significantly in men [(HR 1.97 (95% CI 1.27–3.05) and 1.70 (95% CI 1.19–2.43) and 1.58 (95% CI 1.02–2.44) and 1.34 (0.94–1.93)], respectively. None predicted all-cause mortality. The individual components themselves significantly predicted disease by a similar magnitude as the metabolic syndrome: impaired glucose tolerance [HR 1.55 (95% CI 1.17–2.0)] in WHO, IDF, and ATP III metabolic syndrome; low HDL cholesterol (<1 mmol/l) [HR 1.50 (95% CI 1.12–2.01)] and microalbuminuria (albumin creatinine ratio greater than 3.39 mg/mmol) [HR 1.86 (95% CI 1.40–2.47)] in metabolic syndrome by WHO. In another publication of the same population followed for 14 years,[165] metabolic syndrome predicted stroke with hazard ratios varying from 1.52 to 1.72 depending on the criteria used. This analysis also demonstrated that the individual components had nearly the same predictive value as the metabolic syndrome in predicting for outcomes and for CV disease risk.

The Malmo study followed over 5,000 Swedes for 11 years and showed a HR for a composite endpoint of MI and stroke of 1.11 (95% CI 0.86–1.44), 1.59 (1.25–2.03), and 1.35 (1.05–1.74), respectively, for the IDF, ATP III, and EGIR metabolic syndrome after adjusting for confounders.[166] Only the NCEP–ATP III criteria were predictive for men but not for women. Individual components had significant hazard ratios of a similar order of magnitude: 2.97, 2.01, 1.81, and 1.75 for blood pressure, HDL cholesterol, obesity, and current smoking. NCEP–ATP III was most predictive of CV disease; however, other studies showed IDF to be equivalent to NCEP–ATP III[167] and the DECODE study showed that WHO was better.[168]

Unlike the other studies, DECODE was a collaborative *mortality* analysis of 11 European studies of over 10,000 individuals, followed for 7–16 years.[168] The prevalence rates of metabolic syndrome for men and women in the WHO were 27% and 19% NCEP, 25.9%, 23.4%; NCEP revised, 32.2% and 28.5%; IDF, 35.9% and 34.1%, respectively. In men the likelihood of CV mortality was 2.09 (95% CI 1.59–2.76), 1.74 (95% CI 1.31–2.3), 1.72 (95% CI 1.31–2.26), and 1.5 (95% CI 1.15–1.99) for WHO, NCEP, NCEP revised, and IDF metabolic syndrome, respectively; the corresponding values in women were weaker: 1.60 (95% CI 1.01–2.51), 1.39 (95% CI 0.89–2.18), 1.09 (95% CI 0.7–1.69), 1.53 (95% CI 0.99–2.39), respectively. Individual components were predictive of CV mortality in men and women with similar orders of magnitude (e.g., for blood pressure, HR was 2.3 for men, for triglyceride HR was 1.68).

Sattar reported on two studies in the elderly in Britain.[169] One was the PROSPER study which randomized 4,812 nondiabetic individuals, age 70–82 years, to placebo or 40 mg pravastatin and followed them for 3.2 years; there were 774 incident cases of CV events and 287 of diabetes. The NCEP–ATP III criteria of metabolic syndrome did not predict CV events [HR 1.07 (95% CI 0.86–1.32)] nor did BMI > 30 g/m^2, triglyceride levels > 1.69 mmol/l, fasting glucose > 6.1 mmol/l, or blood pressure > 130/80 (adjusted for confounders including treatment allocation). Positive predictors included age, male sex, prior CV disease, and low HDL cholesterol. A second study of 2,737 men, age 60–79, reported in the same paper, showed similar negative findings. In contrast, both studies showed that metabolic syndrome was a robust predictor of diabetes [HR 4.41 (95% CI 3.33–5.84) and 7.47 (95% CI 4.90–11.46), respectively]; however, the FPG was a nearly 4-fold better predictor [HR 18.0 (95% CI 13.9–24.5)]. Fasting plasma glucose and waist as dichotomized variables did not predict CV disease. Overall, metabolic syndrome was of no benefit in CV disease risk stratification for the elderly.

Similarly, Gami's meta-analysis of 37 studies representing 172,572 middle age individuals without CV disease reported only a modest effect of metabolic syndrome in predicting CV risk with a HR of 1.49 (95% CI 1.37–1.61).[170] Gami concluded that metabolic syndrome did not enhance risk prediction beyond that of the Framingham algorithm.

The prospective Framingham Heart Offspring Study[161] followed 3323 individuals for 8 years and showed a more positive relationship of metabolic syndrome and CV disease. Of the 2649 with neither diabetes nor CV at baseline, there was a higher prevalence rate of NCEP–ATP III in men than women (26.8% vs 16.1%). Men had an age-adjusted HR of 2.88 (95% CI 1.96–4.16) for CV disease and 2.59 (95% CI 1.62–3.98) for CHD disease which was higher than that for women [HR 2.2 (95% CI 1.31–3.88) and 1.54 (95% CI 0.68–3.5)]. The population-attributable risk was 34 and 29% in men and 16 and 8% in women for CV disease and CHD, respectively, thus accounting for nearly a third of new CV disease cases in 8 years.

Does the Metabolic Syndrome Predict CV Disease in Diabetic Populations?

The evidence is mixed and suggests that metabolic syndrome does not uniquely predict incident CV disease or mortality over and above its components.

Three studies show a positive predictive value of the metabolic syndrome.[171–173] Bonora[171] studied over 900 individuals with diabetes and found that > 90% had the metabolic syndrome by the WHO criteria. Baseline CV disease was more common in patients with the metabolic syndrome than without (32.9% vs 17.8%); among a group without CV disease at baseline, metabolic syndrome was an independent predictor of incident CV disease with an OR of almost 5-fold over 4.5 years and 2-fold for prevalent CV disease. Guzder[172] reported that in new onset type 2 diabetes, metabolic syndrome by ATP III criteria was present in 82% and predicted 2- and

4-fold increases in incident and prevalent CV disease. Tong[173] reported on 4350 Chinese individuals followed for 7.1 years and found that metabolic syndrome by ATP III criteria (but not IDF criteria) predicted a 2.5-fold increase in CHD. This study also noted that micro- and macroalbuminuria, hypertension, and HDL cholesterol were all significant predictors of CV disease. The frequency of metabolic syndrome by NCEP–ATP III or IDF was 65%.

In contrast, three studies show that the metabolic syndrome has no clear predictive value for CV disease.[174–176] Studies by Sone[174] from Japan and Bruno[175] from Italy showed similar results in approximately 1550 patient each followed for 8.9 and 11 years, respectively. Sone's study in type 2 diabetes without baseline CV disease reported 51% with metabolic syndrome by WHO criteria and 45% with metabolic syndrome by ATP III criteria.[174] ATP III was not predictive of CV disease in men or women. WHO was predictive only in women. In men, other factors such as triglycerides or HDL cholesterol were better or equivalent. Bruno's study reported 75% with metabolic syndrome (WHO) but with no difference in mortality in patients with and without the metabolic syndrome (∼50% in each group) over 11 years.[175] As with Sone's study, metabolic syndrome with one or more components compared to zero components conferred an ∼2-fold increase in CV disease but the individual components were equally predictive. Finally, in 2007, Cull reported on the 10.3-year follow-up of 4,542 new onset type 2 diabetes patients in the UKPDS study.[176] Metabolic syndrome was determined in four ways resulting in different prevalence rates: by ATP III 61%, by WHO 38%, by IDF 54%, and by EGIR 24%. The HR for CV disease was 1.3, 1.45, 1.23, and 1.0, respectively. Metabolic syndrome did not predict microvascular disease. The positive predictive value for CV disease was poor and ranged from 18 to 20%. Furthermore, in 47% of individuals *without metabolic syndrome,* there was a 10-year estimated CV disease risk of > 20% and in 37% of those *with metabolic syndrome* there was a 10-year estimated CV disease risk of < 20%.

Despite positive reports, overall, the metabolic syndrome is a rather poor predictor of CV disease in type 2 diabetes.

Why Does Not the Metabolic Syndrome Predict CV Disease in Type 2 Diabetes?

There are several potential explanations for the lack of predictive power of the MS for CV disease in patients with diabetes.[176] The metabolic syndrome uses dichotomized variables while in fact these variables have a continuous relationship with CV disease (e.g., triglyceride and HDL). Not all the elements of the metabolic syndrome are equivalent in determining CV risk even though in the NCEP–ATP III criteria all are given equal weight. In fact, fasting plasma glucose of greater than 6.1 mmol/l is very strongly associated with CV disease risk.[177,178] Diabetes is a greater risk factor for mortality and CV disease than metabolic syndrome (HR 5 and 3.6 vs 3.5 and 2.7, respectively),[179] and the excess CV mortality in patients with known CV disease associated with metabolic syndrome is due mostly to diabetes; this excess disappears after controlling for diabetes.[180,181]

Does the Combination of Metabolic Syndrome and Insulin Resistance Predict CV Disease?

Although the elements do cluster, the metabolic syndrome does not improve the ability to identify a high CV risk cohort. In the current context, it is not clear whether this is because insulin resistance is not an antecedent CV risk factor or because metabolic syndrome does not capture insulin resistance. Another very real issue is that each component may have several causes besides insulin resistance. It is not clear if insulin resistance serves as an etiology for traditional or nontraditional CV disease risk factors.

Studies using the euglycemic insulin clamp (or FSIVGTT) showed that insulin resistance was present in only 33% of subjects with the metabolic syndrome[182,183] and its sensitivity varied from 20 to 66%. Thus, metabolic syndrome may have a low sensitivity for identifying insulin resistance.

Several population studies bear on this question. The 11-year follow-up report of the Framingham Heart Offspring Study analyzed the impact of insulin resistance (measured using HOMA-IR) on CV disease and diabetes in a subset of people with and without the metabolic syndrome.[184] Using ATP III criteria, approximately one quarter had metabolic syndrome (27.8%) and over half of these were insulin resistant, while in those without metabolic syndrome, 12.8% were insulin resistant. The study found that compared to those with neither the metabolic syndrome nor insulin resistance, metabolic syndrome alone or insulin resistance alone did not predict CV disease [HR 1.2 (95% CI 0.7–1.9)] and 1.3 (95% CI 0.9–1.19)] but both together doubled the risk [HR 2.3 (95% CI 1.7–3.1)] with a population-attributable risk for both men and women of 18% compared to neither metabolic syndrome nor insulin resistance (Figure 34.7). Thus, insulin resistance adds to the CV disease risk beyond just metabolic syndrome and confirms earlier reports that insulin resistance and metabolic syndrome are not identical but describe different subsets of population risk. In contrast, insulin resistance, metabolic syndrome, or both are increasingly predictive for diabetes.

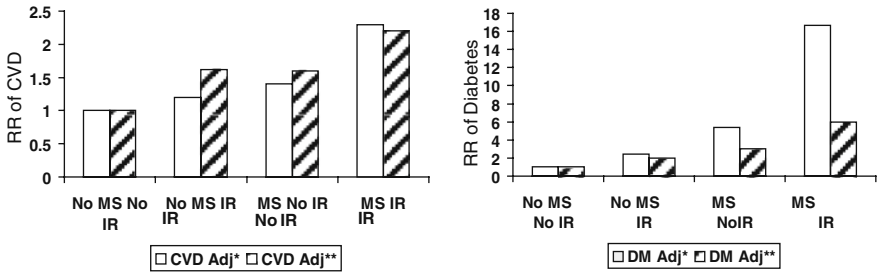

Fig. 34.7 Relative risk of incident CVD (*left panel*) or diabetes (*right panel*) and 8-year follow-up based on the presence of ATP III metabolic syndrome (MetS) or insulin resistance (IR) in the Framingham Heart Offspring Study. On both panels, *open bars* reflect data adjusted for age and sex. *Hatched bars* are adjusted for CV risks factors (*left panel*): age, sex, LDL cholesterol, and smoking and for diabetes risk factors (*right panel*): age, sex, family history of diabetes, BMI, and 2-h glucose during oral glucose tolerance testing. (modified from ref[184])

To conclude, although the metabolic syndrome may add to the prediction of CV risk, overall its magnitude is not as great as was once thought. Nevertheless, the metabolic syndrome is likely to be not more than the sum of its parts after adjusting for standard CV risk factors.

Summary: Insulin

Resistance and the Metabolic Syndrome: The Debate Continues

From its popular inception in 1988, the metabolic syndrome, aka the insulin resistance syndrome, was presented as a testable hypothesis. Initially, insulin resistance was hypothesized to be the physiological basis for the observed clustering of metabolic variables including diabetes, lipid abnormalities, blood pressure, increased cardiovascular disease, and central obesity. It captured the imagination of thousands of scientific investigators and the lay public as the incidence of obesity and diabetes increased to epidemic proportions. Although a great deal of scientifically exciting and valid knowledge has been generated to understand how the variables are related, there is still no unifying consensus that links them.

In 2001, this scientific hypothesis was used as the basis to create a simple clinical screening tool to prevent cardiovascular disease. The presence of three of five variables defined the ATP III metabolic syndrome which was given the stamp of approval by the American Heart Association. It was a novel approach to the old problem of cardiovascular risk and set off a worldwide frenzy of investigations resulting in hundreds of papers, reviews and chapters. It was formally legitimized by an International Classification of Diseases (ICD-9) code. Many competing definitions of the "metabolic syndrome" developed. In 2005, the American Diabetes Association and the European Association for the Study of Diabetes concluded that the metabolic syndrome was an emperor

with no clothes. A calculating look revealed that it did not provide sufficient predictive power for CV disease beyond conventional risk factors or the individual components of the metabolic syndrome. Although metabolic syndrome was strongly predictive of diabetes, the fasting plasma glucose was markedly better. The darling of two decades had lost favor.

In 2008, the Endocrine Society published a Clinical Practice Guideline for the Primary Prevention of CV disease or coronary heart disease.[185] Expert opinion recommended that the metabolic syndrome could be used to identify an early likelihood of developing CV disease. Since the variables of the metabolic syndrome are CV risk factors and do cluster, the presence of any one should raise awareness to determine 10 years' absolute risk for cardiovascular disease using the Framingham, PROCAM, or SCORE algorithms. Treatment should be initiated based on this with a focus on apoB-containing lipoproteins [LDL and VLDL cholesterol (triglyceride)], hypertension, increased blood glucose, enlarged waist, a prothrombotic, and a pro-inflammatory state. The guideline further advises that patients with metabolic risk initiate preventive measures with priority given to lifestyle modifications. The metabolic syndrome has risen again.

In the final analysis, what is needed is a way to identify individuals at high risk for cardiovascular disease who might benefit from prevention of the first CV event (primary prevention). Currently, the absolute prevalence rates of CV events are low, at ~2–3% and in a recent trial of primary prevention of CV disease, only 1 individual benefited out of 100 treated with a statin.[186] Given these data, most "healthy" individuals choose not to adhere to long-term preventive strategies, whether lifestyle or pharmacologic. It is obvious that the metabolic syndrome is not a robust marker and neither are the usual risk factors such as LDL cholesterol.

In order to identify individuals who are at risk before they have an event, future novel approaches might involve genomic analyses of CV risk. Another potential approach is to develop the concept of the vascular system phenotype or condition of the vascular using structural measures. This would enrich the target population for primary prevention of CV disease. With the advent of new technology such as ultrasound or CT, can we develop a better correlation between the structure of the vasculature and the risk for CV events? This would also identify a population enriched for risk of CV disease and an effective target for primary prevention. It is likely that these novel approaches would increase compliance, adherence, and cost-effectiveness of CV disease prevention.

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