Erratum

Reaven GM. The metabolic syndrome: is this diagnosis necessary? Am J Clin Nutr 2006;83:1237–47.

In Table 6 (page 1243), the references cited should read from 83 through 101, rather than from 82 through 100.

Erratum

Hallberg L, Hulthen L. Prediction of dietary iron absorption: an algorithm for calculating absorption and bioavailability of dietary iron. Am J Clin Nutr 2000;71:1147–60.

The correct equation for adjusting for iron status (Equation *11*) should be as follows:

$$\text{Iron absorption (mg)} = \text{iron absorption (alg mg)} \times (23/\text{SF})^{0.94049} \quad (1)$$

Additionally, the correct equation for calculating the expected iron absorption ration set when calcium is present (Equation *5*) should read as follows:

$$0.4081 + (0.5919/1 + 10^{-[2.022-\log(\text{Ca}+1)]\times 2.919}) \quad (2)$$

Erratum

Bischoff-Ferrari HA, Giovannucci E, Willett WC, Dietrich T, Dawson-Hughes B. Estimation of optimal serum concentrations of 25-hydroxyvitamin D for multiple health outcomes. Am J Clin Nutr 2006;84:18–28.

A sentence in the abstract begins "An intake for all adults of ≥1000 IU (40 μg) vitamin D...." The value for vitamin D should be 25 μg, not 40 μg.

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The metabolic syndrome: is this diagnosis necessary?[1,2]

Gerald M Reaven

ABSTRACT

Values of insulin-mediated glucose disposal vary continuously throughout a population of apparently healthy persons, and a difference of ≥600% exists between the most insulin-sensitive and the most insulin-resistant persons. Approximately 50% of this variability can be attributed to differences in adiposity (25%) and fitness (25%), with the remaining 50% likely of genetic origin. The more insulin-resistant a person, the more likely that he or she will develop some degree of glucose intolerance, high triacylglycerol and low HDL concentrations, essential hypertension, and procoagulant and proinflammatory states, all of which increase the risk of cardiovascular disease (CVD). To identify persons at greater CVD risk because of these abnormalities, the World Health Organization, the Adult Treatment Panel III, and the International Diabetes Federation created a new diagnostic category, the metabolic syndrome. Although the components of the 3 versions of the metabolic syndrome are similar, the specific values for those components that define an abnormality are somewhat different, and the manner in which the abnormalities are used to make a positive diagnosis varies dramatically from version to version. This review will summarize the similarities in and differences between the 3 versions of the metabolic syndrome, point out that the clustering of components that make up all 3 definitions of the metabolic syndrome is not accidental and occurs only in insulin-resistant persons, develop the argument that diagnosing the metabolic syndrome in a person has neither pedagogical nor clinical utility, and suggest that the clinical emphasis should be on treating effectively any CVD risk factor that is present. *Am J Clin Nutr* 2006;83:1237–47.

KEY WORDS Metabolic syndrome, insulin resistance, cardiovascular disease

INTRODUCTION

In today's climate of full disclosure, I should state at the beginning that I have published several articles (1–4) critical of the effort to create a diagnostic category of the metabolic syndrome, and that I believe that this effort has little clinical or pedagogic utility and even can do more harm than good. Although the 3 published versions of the metabolic syndrome are conceptually different (5–8), the reservation expressed above applies to all of these definitions. If there is anything useful to be accomplished by creating such a diagnostic category, I believe that the approach of the World Health Organization (WHO) was the most rational effort (5), and the recent version (8) of the International Diabetes Federation (IDF) was the most dangerous.

Although a major focus of the review will be on the physiologic and clinical utility of making a diagnosis of metabolic syndrome, it is equally important to differentiate between the metabolic syndrome and a construct that (1) might be best designated as insulin resistance syndrome. In the former instance, the goal is to develop criteria by which to "diagnose" the metabolic syndrome, and, in the latter instance, the goal is to increase the understanding of the relation between resistance to insulin-mediated glucose uptake (IMGU) and a variety of related abnormalities and clinical syndromes. Although the 2 notions are frequently considered interchangeable, the concepts are quite different, and this review is focused entirely on the metabolic syndrome.

THE MANY FACES OF THE METABOLIC SYNDROME

In a document whose primary purpose was to update the classification and diagnostic criteria of diabetes mellitus, the WHO was the first organization to outline clinical criteria (**Table 1**) for diagnosing the metabolic syndrome (5). In this context, the WHO designated the metabolic syndrome as a special classification for persons with the potential for diabetes (manifested as having impaired glucose tolerance, impaired fasting glucose, or insulin resistance by hyperinsulinemic euglycemic clamp). The WHO felt that, once these persons developed certain cardiovascular disease (CVD) risk components, those components combined into a unique clinical entity, and the patients should be considered to have the metabolic syndrome. Aside from glucose tolerance status and insulin resistance, risk components deemed useful in identifying persons with metabolic syndrome included central obesity, dyslipidemia, hypertension, and microalbuminuria. The WHO stated that each component conveyed greater CVD risk but that, when combined, the components became more "powerful." Therefore, the reason for diagnosing the metabolic syndrome was to identity persons at undue risk of CVD.

The Adult Treatment Panel III (ATP III) released its definition of the metabolic syndrome in 2001 (6). The goal of the ATP III was somewhat different from that of the WHO, in that the ATP III was focused less on type 2 diabetes and more on CVD risk. Within that context, an additional aim was to "focus on primary prevention in persons with multiple risk factors." To address this second aim, the ATP III considered the metabolic syndrome to

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TABLE 1
World Health Organization definition of the metabolic syndrome[1]

The patient must have 1 of the following:
- Diabetes mellitus
  - Fasting plasma glucose ≥ 7 mmol/L (126 mg/dL) or 2-h postglucose load ≥ 11.1 mmol/L (200 mg/dL)
- Impaired glucose tolerance
  - Fasting plasma glucose < 7 mmol/L (126 mg/dL) and 2-h postglucose load ≥ 7.8 mmol/L (140 mg/dL) and < 11.1 mmol/L (200 mg/dL)
- Impaired fasting glucose
  - Fasting plasma glucose ≥ 6.1 mmol/L (110 mg/dL) and < 7 mmol/L (126 mg/dL) and (if measured) 2-h postglucose load < 7.8 mmol/L (140 mg/dL)
- Insulin resistance
  - Glucose uptake below lowest quartile for background population under investigation under hyperinsulinemic, euglycemic conditions

Plus any 2 of the following:
- Waist-to-hip ratio > 0.9 in men, > 0.85 in women; BMI > 30; or both
- Triacylglycerols ≥ 1.7 mmol/L (150 mg/dL); HDL cholesterol < 0.9 mmol/L (35 mg/dL) in men, < 1.0 mmol/L (39 mg/dL) in women; or both
- Blood pressure ≥ 140/90 mm Hg (revised from ≥ 160/90 mm Hg)
- Microalbuminuria (urinary albumin excretion rate ≥ 20 μg/min or albumin-to-creatinine ratio ≥ 30 mg/g)

[1] Adapted from reference 5.

represent "multiple, interrelated factors that raise CVD risk" and stated that the root causes were overweight or obesity, physical inactivity, and genetic factors. The specific factors considered important were abdominal obesity, atherogenic dyslipidemia, high blood pressure, glucose intolerance, and prothrombotic and proinflammatory states. The panel believed that the syndrome increased CVD risk at any given LDL-cholesterol concentration and that it should be a secondary target of therapy in cholesterol management. The ATP III definition of the metabolic syndrome is shown in **Table 2**.

The most recent version of the metabolic syndrome was the result of a consensus conference organized by the IDF that involved 21 participants invited from Europe, North and South American, Asia, Africa, and Australia. After the meeting, this group published the IDF's new worldwide definition of the metabolic syndrome, which laid out a "consensus on a 'platinum standard' definition, which highlights additional metabolic criteria which should be measured in all research conducted in this field from this point onwards" (7). The components that make up the diagnostic criteria for the IDF version of the the metabolic syndrome are seen in **Table 3**.

TABLE 2
Adult Treatment Panel III definition of the metabolic syndrome[1]

Any 3 of following:
- Fasting glucose ≥ 6.1 mmol/L (110 mg/dL)
- Waist circumference
  - Men: > 102 cm (40 in)
  - Women: > 88 cm (35 in)
- Triacylglycerols ≥ 1.7 mmol/L (150 mg/dL)
- HDL cholesterol
  - Men: < 1.036 mmol/L (40 mg/dL)
  - Women: < 1.295 mmol/L (50 mg/dL)
- Blood pressure ≥ 130/85 mm Hg

[1] Adapted from reference 6.

TABLE 3
International Diabetes Federation definition of the metabolic syndrome[1]

In order for a person to have a diagnosis of metabolic syndrome, he or she must have
- Central obesity (defined as a waist circumference ≥ 94 cm for European men and ≥ 80 cm for European women, with ethnicity-specific values for other groups

Plus any 2 of the following 4 factors:
- High triacylglycerol concentration: ≥ 150 mg/dL (1. 7 mmol/L), or specific treatment for this abnormality
- Low HDL-cholesterol concentration: < 40 mg/dL (1.03 mmol/L) in males and <50 mg/dL (1.29 mmol/L) in females), or specific treatment for this lipid abnormality
- High blood pressure (BP): systolic BP ≥ 130 mm Hg or diastolic BP ≥ 85 mm Hg, or treatment of previously diagnosed hypertension
- High fasting plasma glucose (FPG) concentration ≥ 100 mg/dL (5.6 mmol/L), or previously diagnosed type 2 diabetes. If FPG is above the values stated above, an oral-glucose-tolerance test is strongly recommended but is not necessary to define presence of the syndrome.

[1] Adapted from reference 7.

It is apparent from a comparison of Tables 1, 2, and 3 that only minor differences exist between the specific components that make up the 3 versions of the metabolic syndrome. Furthermore, the versions share one major characteristic—neither the individual components selected to serve as criteria nor the specific cutoffs are the result of prospective studies. Instead, they represent the collective wisdom or prejudices (or both) of "experts" selected by whoever was organizing the "consensus" conference. The appropriateness of this process is not the focus of this chapter, but it seems necessary to address this issue here.

Of greater pedagogic and clinical importance are 2 fundamental differences between the 3 diagnostic schemes. One major point of departure is the manner in which the various criteria are organized. The ATP III criteria are not distinguished qualitatively from each other, and a combination of any 3 of the 5 criteria is viewed as having the same adverse effect as any other group of 3 abnormalities. I assume this decision is based on the thought expressed in a recent joint statement from the American Heart Association and the National Heart, Lung, and Blood Institute that there is no common "cause" of the metabolic syndrome (8). This important issue will be discussed below, but at this point suffice it to say that both the WHO and the IDF take a different approach, in that they insist that one essential criterion be met. The similarity between the 2 positions ends at this point, with the WHO requiring that there be evidence of insulin resistance but the IDF's fundamental criterion for a diagnosis of metabolic syndrome is an ethnicity-adjusted degree of abdominal obesity.

The other major difference between the 3 definitions of the metabolic syndrome has to do with the role of excess adiposity. The WHO considers it to be an ancillary criteria (Table 1) and can be satisfied by either a certain level of overall obesity, as assessed by body mass index (BMI), or an excessive waist-to-hip ratio, as an index of abdominal obesity. For the ATP III, excess adiposity is one of the 5 equally important criteria that can be used to diagnose metabolic syndrome (Table 2), but in this case can only be met by exceeding a sex-specific value of waist circumference (WC). The status of WC has been further elevated in the IDF version of the metabolic syndrome (Table 3), and it is now the one

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criterion that must be fulfilled for a diagnosis of the metabolic syndrome.

DOES THE METABOLIC SYNDROME HAVE A COMMON "CAUSE"?

When the components that make up the 3 versions of the metabolic syndrome are compared, it is paradoxical to see how similar they are and how disparate are the ways in which they are used to diagnose metabolic syndrome. In the case of the WHO, abnormal values for blood pressure, urinary albumin excretion, and triacylglycerol and HDL-cholesterol concentrations will determine whether an insulin-resistant person has or does not have metabolic syndrome. In the case of the IDF definition, even if a person displayed all of these abnormalities and had type 2 diabetes in addition, he or she would not have the metabolic syndrome if the WC was not large enough. The ATP III version of the metabolic syndrome is the most democratic; there is no hierarchical relation between the 5 components, and any combination of 3 will do. The lack on the part of the ATP III of assigning any priority to the 5 components of the metabolic may be a reflection of the panel's view that the cluster of abnormalities "probably has more than one cause" (6, 8). It is difficult to disagree with the conclusion that the related abnormalities that make up all 3 versions of metabolic have more than one cause. For example, it is obvious there are many potential reasons for elevated blood pressures. At the same time, one must ask whether the fact that any of the criteria used to diagnose the metabolic syndrome may develop for more than one reason means that there cannot be a *common* physiologic event that greatly increases the likelihood that a person will undergo the changes that can lead to a diagnosis of metabolic syndrome. I propose that the answer to this rhetorical question should be "no," and, moreover, that the clustering of abnormalities that make up all 3 versions of the metabolic syndrome does not evolve accidentally, and that a defect in insulin action plays a fundamental role in the development of the CVD risk factors that make up all versions of the metabolic syndrome.

Glucose intolerance

The prevalence of some degree of abnormal glucose tolerance or type 2 diabetes (or both)—one of the criteria in all 3 definitions of the metabolic syndrome—is the abnormality most closely related to insulin resistance. Indeed, > 60 y ago, Himsworth and Kerr (9) challenged the conventional wisdom that "all cases of human diabetes could be explained by deficiency of insulin," proposed that "a state of diabetes might result from inefficient action of insulin as well as from a lack of insulin," and stated, "the diminished ability of the tissues to utilize glucose is referable either to a deficiency of insulin or to insensitivity to insulin, although it is possible that both factors may operate simultaneously." In the same vein, Himsworth (10) suggested in 1949 that "we should accustom ourselves to the idea that a primary deficiency of insulin is only one, and then not the commonest, cause of the diabetes syndrome." It is now appreciated that insulin resistance is a common characteristic of patients with type 2 diabetes (11–16) and that insulin resistance (or hyperinsulinemia as a surrogate estimate of insulin resistance) is a powerful and independent predictor of type 2 diabetes (17–21). Finally, the greater the degree of insulin resistance, the higher the plasma glucose response to oral glucose in persons with normal oral glucose tolerance (22). Thus, an enormous amount of evidence documents a very close relation between insulin resistance and abnormal elevations in plasma glucose concentrations.

TABLE 4
Relation between insulin resistance and plasma triacylglycerol concentrations[1]

	Relation
Triacylglycerol	
69–546 mg/dL[2]	IMGU → insulin concentration ($r = 0.74$) → VLDL-triacylglycerol secretion rate ($r = 0.74$) → triacylglycerol concentration ($r = 0.88$)
33–174 mg/dL[3]	IMGU → insulin concentration ($r = 0.81$) → VLDL-triacylglycerol secretion rate ($r = 0.68$) → triacylglycerol concentration ($r = 0.87$)

[1] IMGU, insulin-mediated glucose uptake.
[2] Based on data from reference 28.
[3] Based on data from reference 40.

Finally, it should be emphasized that nondiabetic persons with relatively minor degrees of glucose intolerance also have higher blood pressures and the dyslipidemic changes—high triacylglycerol and low HDL-cholesterol concentrations—that make up the remaining metabolic criteria of all 3 definitions of the metabolic syndrome (23–26)

Dyslipidemia

It has been known for > 30 y that there is a highly significant relation between insulin resistance, compensatory hyperinsulinemia, and hypertriglyceridemia (27, 28). It is now apparent that the link between insulin resistance or hyperinsulinemia and dyslipidemia is a much broader one, which is not limited to an increase in plasma triacylglycerol concentrations. Thus, although the various definitions of metabolic syndrome have selected the combination of high plasma triacylglycerol and low HDL-cholesterol concentrations as a diagnostic criterion, it is clear that these changes are also associated with a decrease in LDL particle size (small, dense LDL) and the postprandial accumulation of triacylglycerol-rich remnant lipoproteins (29). Not only are all of these changes significantly associated with insulin resistance or hyperinsulinemia (27–33), but each one has also been shown to increase the risk of CVD (34–39).

Plasma triacylglycerol concentrations

The relations outlined in **Table 4** are based on the results of 2 published studies (28, 40). Table 4 depicts the relation among insulin resistance, plasma insulin response, hepatic VLDL-triacylglycerol synthesis and secretion, and plasma triacylglycerol concentrations in nondiabetic persons (28) whose baseline plasma triacylglycerol concentrations range from 69 to 546 mg/dL; the table also describes the same relations in persons with plasma triacylglycerol concentrations < 175 mg/dL (40). Implicit in these findings is the view that the major cause of elevated plasma triacylglycerol concentrations in nondiabetic persons is an increase in hepatic VLDL-triacylglycerol secretion rate, secondary to insulin resistance and the resultant hyperinsulinemia. These data provide a quantitative estimate of the close relation between insulin resistance, compensatory hyperinsulinemia, hepatic VLDL-triacylglycerol secretion, and plasma triacylglycerol concentrations in apparently healthy persons.

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Postprandial lipemia

The higher is the fasting triacylglycerol concentration, the greater will be the postprandial accumulation of triacylglycerol-rich lipoproteins (ie, VLDL, chylomicron remnants, and VLDL remnants) in nondiabetic persons (41). Both the relation between fasting triacylglycerol concentration and postprandial lipemia and the daylong increases in triacylglycerol-rich lipoproteins in nondiabetic persons are significantly correlated with the magnitude of the insulin resistance and compensatory hyperinsulinemia (32, 33, 42). Although the postprandial elevation of triacylglycerol-rich lipoproteins is related to the fasting triacylglycerol concentration, postprandial lipemia is also enhanced when insulin-resistant or hyperinsulinemic persons are matched by degree of fasting hypertriglyceridemia with persons from an insulin-sensitive population (43).

HDL cholesterol

Increases in plasma VLDL-triacylglycerol concentration are usually associated with low HDL-cholesterol concentrations, and it appears that insulin resistance and compensatory hyperinsulinemia are independently associated with both of these changes (30). Low HDL-cholesterol concentrations in insulin-resistant or hyperinsulinemic persons are partly due to the transfer, which is catalyzed by cholesteryl ester transfer protein, of cholesterol from HDL to VLDL (44); the higher the VLDL pool size, the greater the transfer rate from HDL to VLDL and the lower the resulting HDL-cholesterol concentration. The fractional catabolic rate of apoprotein A-I is increased in patients with primary hypertriglyceridemia (45), hypertension (46), and type 2 diabetes (47). In type 2 diabetes, it has been shown that the greater the degree of hyperinsulinemia, the lower the HDL-cholesterol concentration (47). Evidence also exists that, in nondiabetic persons, the higher the fractional catabolic rate of apoprotein A-I, the lower the HDL-cholesterol concentration (48), and that these changes are associated with increases in plasma insulin concentrations

LDL particle diameter

Analysis of LDL particle size distribution (35) has identified multiple distinct LDL subclasses, and it appears that LDL particles in most persons can be characterized by a predominance of larger LDL (diameter: $>$ 255 Å; pattern A) or smaller LDL (diameter: $<$ 255 Å; pattern B). Persons with pattern B LDL have higher plasma triacylglycerol and lower HDL-cholesterol concentrations than do persons with pattern A LDL. Not surprisingly, healthy volunteers with small, dense LDL particles (pattern B) are relatively insulin resistant, glucose intolerant, hyperinsulinemic, hypertensive, and hypertriglyceridemic, and they have low HDL-cholesterol concentrations (31).

Atherogenic lipoproteins and insulin resistance

The evidence discussed above provides strong support for the conclusion that the lipoprotein abnormalities that are part of all 3 definitions of the metabolic syndrome are more likely to occur together and are significantly associated with insulin resistance and compensatory hyperinsulinemia. However, not all persons with these abnormalities are insulin resistant. A high fasting plasma triacylglycerol concentration and hyperchylomicronemia can occur in persons who have a primary defect in the catabolism of triacylglycerol-rich lipoproteins (ie, fat-induced lipemia; 49). Furthermore, not all insulin-resistant persons will develop the atherogenic lipoprotein profile associated with the defect in insulin action. On the other hand, insulin resistance or hyperinsulinemia is the only physiologic abnormality that can lead to the clustering of abnormalities that includes the atherogenic lipoprotein profile discussed above, as well as increases in plasma glucose concentration and blood pressure.

Blood pressure

The relation between insulin resistance, elevated blood pressure, and CVD is more complicated than that of any of the other components that make up the various definition of metabolic syndrome. There is substantial evidence for the following 3 findings linking insulin resistance and hyperinsulinemia to essential hypertension. First, patients with essential hypertension, as a group, are insulin resistant and hyperinsulinemic (50–52). Second, normotensive first-degree relatives of patients with essential hypertension are more insulin resistant and hyperinsulinemic than are matched control subjects without a family history of hypertension (53–55). Third, hyperinsulinemia, as a surrogate estimate of insulin resistance, has been shown in population-based studies to predict the eventual development of essential hypertension (56–59).

In contrast, probably no more than 50% of patients with essential hypertension are insulin resistant (60). However, it is patients with essential hypertension who are insulin resistant or hyperinsulinemic who have the other components of the various definitions of metabolic syndrome and are therefore at greatest risk of CVD. For example, patients with essential hypertension and electrocardiographic evidence of myocardial ischemia are insulin resistant, somewhat glucose intolerant, and hyperinsulinemic and have high triacylglycerol and low HDL-cholesterol concentrations compared with a normotensive control group or patients with essential hypertension whose electrocardiograms are entirely normal (61). Direct evidence of the link between the dyslipidemia present in insulin-resistant or hyperinsulinemic patients with essential hypertension and CVD comes from the results of the Copenhagen Male Study (62), in which 2906 participants were divided into 3 groups according to their fasting plasma triacylglycerol and HDL-cholesterol concentrations. Men whose plasma triacylglycerol and HDL-cholesterol concentrations were in the upper or lower third, respectively, of the whole population, were assigned to the high-triacylglycerol–low-HDL-cholesterol group. At the other extreme, a low-triacylglycerol–high-HDL-cholesterol group was composed of those persons whose plasma triacylglycerol and HDL-cholesterol concentrations were in the lower and upper thirds, respectively, of the study population for these 2 lipid measurements. The intermediate group consisted of those participants whose lipid values did not qualify them for either of the 2 extreme groups. The results of this prospective study indicated that CVD risk was not increased in patients with hypertension in the absence of high triacylglycerol and low HDL-cholesterol concentrations, and the group at greatest risk was made up of those persons with high blood pressure and high triacylglycerol and low HDL-cholesterol concentrations.

In summary, insulin-resistant or hyperinsulinemic persons are more likely to develop essential hypertension, hypertension is a well-recognized CVD risk factor, and patients with essential hypertension *and* high triacylglycerol and low HDL-cholesterol concentrations are at greatest risk of CVD. If high blood pressure

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TABLE 5
Simple and partial correlations for PAI-1 in normotensive volunteers[1]

	Simple correlation		Partial correlation[2]	
Variable	*R*	*P*	*R*	*P*
Age (y)	−0.42	0.02	-	-
BMI (kg/m^2)	0.39	0.03	-	-
Waist-to-hip ratio	0.15	0.49	−0.004	0.98
MAP (mm Hg)	−0.06	0.77	−0.06	0.76
SSPG (mg/dL)[3]	0.62	<0.001	0.56	<0.001
Fasting plasma insulin (μU/mL)	0.65	<0.001	0.58	<0.001
Triacylglycerol (mg/dL)	0.32	0.07	0.39	<0.05
HDL cholesterol (mg/dL)	−0.69	<0.001	−0.65	<0.001
LDL cholesterol (mg/dL)	0.22	0.23	0.29	0.13

[1] PAI-1, plasminogen activator inhibitor-1; MAP, mean arterial pressure; SSPG, steady-state plasma glucose. Adapted from reference 65.
[2] Calculated after adjustment for age and BMI.
[3] The higher the value, the more insulin resistant the individual.

is one of the criteria for the metabolic syndrome, there is little doubt that its association with the other components can only be attributed to the concomitant presence of insulin resistance or hyperinsulinemia.

Insulin resistance and procoagulant and proinflammatory factors

Although measures of procoagulant or proinflammatory factors have not been elevated to the status of diagnostic criteria, definitions of the metabolic, all comment on their relation with the cluster of abnormalities that make up the definition. The association between insulin resistance and hyperinsulinemia, elevated concentrations of plasminogen activator inhibitor-1, and CVD have been known for some time (63, 64). Of greater relevance to this review are the data in **Table 5** showing that concentrations of plasminogen activator inhibitor-1 in a group of apparently healthy persons was significantly correlated with degree of insulin resistance (as quantified by steady-state plasma glucose concentrations during the insulin suppression test), and fasting plasma insulin, triacylglycerol, and HDL cholesterol concentrations (65). Thus, variations in concentrations of plasminogen activator inhibitor-1 cluster with insulin resistance or compensatory hyperinsulinemia, and the dyslipidemia characteristic of the defect in insulin action.

The proinflammatory factor currently attracting the most attention as indicating increased CVD risk is C-reactive protein, but there is a much longer history of a relation between an increase in white cell count and heart disease. Indeed, data from the Women's Health Initiative Observational Study suggest that a high white cell count was comparable in magnitude to increases in concentrations of C-reactive protein as a predictor of CVD risk (66). Evidence of a relation between white cell counts and insulin resistance or compensatory hyperinsulinemia was published several years ago (67); the evidence indicated that the higher the white cell count, the more insulin resistant a person ($r = 0.50$, $P > 0.001$), the greater ($P < 0.001$) the person's plasma glucose ($r = 0.48$) and insulin ($r = 0.50$) responses to an oral glucose challenge, the higher the person's triacylglycerol concentration ($r = 0.37$), and the lower the person's HDL-cholesterol concentration ($r = -0.38$, $P > 0.005$). However, there was no significant relation between the white cell count and either age or BMI.

The relations described in this section provide evidence that the additional CVD risk factors considered to be present in patients diagnosed as having metabolic syndrome are significantly related to both insulin resistance and hyperinsulinemia, as well as to the other components of the metabolic syndrome. These observations provide further support for the view that insulin resistance or hyperinsulinemia provides a coherent explanation for how all of these individual variables cluster together.

EXCESS ADIPOSITY, INSULIN RESISTANCE, AND THE METABOLIC SYNDROME

Evidence was marshaled in the preceding section that insulin resistance or hyperinsulinemia was the one factor that could explain the clustering of diagnostic criteria for the different versions of the metabolic syndrome. Implicit in this view is that the adiposity criteria that appear in all metabolic syndrome definitions are qualitatively different from any of the other components listed in Tables 1–3. Specifically, dyslipidemia (high triacylglycerol and low HDL-cholesterol concentrations), hyperglycemia, and hypertension are independent factors that directly increase the risk of CVD (34, 36, 68, 69), whereas the relation between excess adiposity and CVD risk is different. For example, substantial numbers of overweight or obese persons do not have the abnormalities outlined above (70, 71). The components of the metabolic syndrome occur more commonly in overweight or obese persons, but this relation is not due to obesity, per se, but rather to the fact that excess adiposity increases the likelihood that a person will be insulin resistant (70, 71). This point of view receives support from the results of the recent study of Ninomiya et al (72), which showed that abdominal obesity, as defined by the ATP III, was the only criterion not statistically associated with the development of either CVD or stroke in an analysis of the data from the third National Health and Nutrition Examination Survery (NHANES III). The authors suggested that this finding "may reflect an indirect effect of high WC through other components of the syndrome," and this formulation will be pursued below.

Obesity and insulin-mediated glucose uptake

The European Group for the Study of Insulin Resistance analyzed the results of euglycemic, hyperinsulinemic clamp studies

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in 1146 nondiabetic, normotensive volunteers and found that only ≈25% of the obese volunteers were classified as being insulin-resistant according to the criteria used (73). These authors also pointed out that differences in WC were unrelated to insulin sensitivity after adjustment for age, sex, and BMI. Results similar to those of the European Group for the Study of Insulin Resistance have been published by investigators at Stanford University (70, 71); in those studies, differences in the degree of obesity accounted for approximately one-third of the variability of insulin-mediated glucose uptake (IMGU) in apparently healthy persons. Those studies did not take into consideration the fact that the more physically fit a person is, the more insulin sensitive he or she will be (74) or that differences in degree of physical fitness are approximately as powerful as differences in adiposity in modulation of IMGU (75). Thus, differences in adiposity modulate insulin action, but adiposity is only one of the variables determining whether a person is sufficiently insulin resistant to develop an adverse clinical outcome.

Waist circumference compared with body mass index as a predictor of insulin-mediated glucose uptake

Because BMI and WC are highly correlated, it is not obvious on an a priori basis that WC is a superior predictor of the adverse effects of excess adiposity, let alone that it is considered the essential diagnostic criterion in the IDF version of the metabolic syndrome. For example, measurements obtained from ≈15 000 participants in NHANES III indicated that the correlation coefficient between BMI and WC was > 0.9 irrespective of the age, sex, or ethnicity of groups evaluated (76). Given these findings, it was not surprising that the correlation coefficient between degree of adiposity and insulin resistance was the same ($r = 0.6$) in apparently healthy persons, irrespective of whether BMI or WC was used as the index of obesity (77). As in NHANES III, BMI and WC were also highly correlated ($r = 0.9$). Because the relation between IMGU and overall obesity (BMI) does not differ significantly from that between IMGU and abdominal obesity (WC), it seems that either index of adiposity is equally predictive of differences in insulin action.

Relation between adiposity, insulin resistance, and risk of cardiovascular disease

Rates of IMGU vary by >600% in apparently healthy persons, and, because the distribution of these values is continuous (78), there is no objective way to classify a person as insulin-resistant. However, prospective studies exist that can serve as the basis for an operational definition. With the use of the magnitude of the insulin response to oral glucose as a surrogate maker of insulin resistance, 25% of an apparently healthy population with the highest insulin concentrations is at a significantly greater risk of CVD (79). According to the results of 2 prospective studies in which the insulin suppression test was used to quantify IGMU at baseline (80, 81), the third of the population that was the most insulin resistant (ie, those with the highest steady-state plasma glucose concentrations) was at significantly greater risk of CVD than was the population third that was the most insulin sensitive (ie, those with the lowest steady-state plasma glucose concentrations). Thus, for the purposes of this discussion, the third of the population with the highest steady-state plasma glucose concentrations will be operationally defined as insulin-resistant, and the third with the lowest steady-state plasma glucose concentrations will be defined as insulin-sensitive.

Prevalence of insulin resistance as a function of body mass index

When 465 apparently healthy persons were divided into tertiles of IMGU according to their BMI (82), a large majority (≈66%) of the normal-weight persons (BMI: < 25.0) were in the most insulin-sensitive tertile, whereas the other third of the insulin-sensitive persons were either overweight or obese. Furthermore, approximately two-thirds of those in the insulin-resistant tertile were either normal-weight or overweight, and only about one-third of the most insulin-resistant persons were actually obese (BMI: 30–35). These data provide further evidence that, in general, the heavier the person, the more likely he or she is to be insulin resistant, but that obesity does not necessarily equal insulin resistance.

WHAT ABOUT VISCERAL OBESITY?

Evidence presented to this point has shown that measurements of BMI and WC are highly correlated, that they are associated with a specific measure of IMGU to an identical degree, and that not all overweight or obese persons are insulin resistant. These conclusions are at odds with the conventional wisdom that overweight or obesity is synonymous with insulin resistance and with the notion, codified by the ATP III (6) and the view of the IDF (7), that abdominal obesity is the source of all metabolic "evil." One possible explanation for this discrepant opinion of the importance of abdominal obesity in the genesis of insulin resistance and its consequences is the failure to take into consideration the importance of visceral obesity, and this issue will be addressed next.

Visceral obesity and insulin resistance

The results of 19 studies (22 comparisons; 83–101) that have quantified the magnitude of the relation between IMGU and various estimates of adiposity, including visceral obesity (or visceral fat, VF), in nondiabetic subjects are shown in **Table 6**. The studies are listed in chronological order, and the following inclusion criteria were used to construct the table: imaging techniques were used to quantify the various fat depots; IMGU had to be quantified with specific, not surrogate estimates; and the actual experimental data had to be available, before the use of arbitrary "adjustments" or multiple regression analysis. Space constraints prohibit a complete discussion of possible differences in both the imaging techniques used in individual studies and the specific methods used to quantify IMGU.

Perhaps the simplest conclusion to be drawn from the results in Table 6 is that correlation coefficients (r values) between VF and IMGU are usually < 0.6, values that are no greater than the relation between IMGU and either BMI or WC, as shown previously (70, 71). Indeed, r values between IMGU and VF varied from 0.4 to 0.6 in 18 of the 21 measurements in **Table 7**, and differences in VF accounted for ≈25% of the variability in IMGU in most instances.

Second, although the relation between BMI and IMGU was analyzed in only 4 studies (85, 93, 97, 99), the correlation coefficients in those instances were comparable to the values for the relation between IMGU and VF. That relation was compared more often that was that between IMGU and total fat, but, when both fat depots were evaluated, it appeared that the 2 estimates of adiposity provided r values of similar magnitude. If anything, the relation of total fat and

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TABLE 6
Correlation coefficients (*r*) between insulin-mediated glucose uptake and body fat distribution[1]

Reference	Population	VF	SF	TF	BMI[2]
82	39 men	−0.51	−0.62	−0.61	
83	60 subjects	−0.50	−0.50	−0.57	
84	26 obese subjects	−0.56		−0.54	−0.55
85	54 subjects	−0.52	−0.61	−0.58	
86	20 South Asian men	−0.59	−0.54	−0.56	
87	47 men	−0.61	−0.53		
88	27 postmenopausal women	−0.39	−0.43	−0.30	
89	44 obese postmenopausal women	−0.40	−0.17		
90	68 white children	−0.59	−0.70	−0.68	
	51 African American children	−0.43	−0.47	−0.52	
91	55 postmenopausal women	−0.49	−0.43		
92	48 subjects	−0.58	−0.41		−0.52
93	24 subjects	−0.55	−0.47	−0.61	
94	89 obese males	−0.41			
95	40 obese premenopausal women	−0.34	−0.06		
96	174 subjects	−0.69	−0.57		−0.63
97	32 Hispanic children	−0.44	−0.46	−0.46	
98	39 men	−0.71			−0.56
99	44 African American men	−0.57	−0.57		
	35 African American women	−0.50	−0.67		
100	11 Thai women	−0.60	−0.47	−0.38	
	11 Thai men	−0.54	−0.45	−0.80	

[1] VF, visceral fat; SF, subcutaneous (abdominal) fat; TF, total fat.
[2] Measured as kg/m^2.

IMGU was somewhat greater in 8 of the 12 comparisons than was that of VF and IMGU (83, 84, 86, 91, 94, 98, 101).

The emphasis in the studies listed in Table 6 was a on comparison of the relation between IMGU and subcutaneous abdominal fat (SF) with the relation between IMGU and VF, and the magnitude of the 2 relations seems reasonably comparable. Although there are 2 examples in which the relation between IMGU and SF was quite different from that between IMGU and VF (89, 95), the *r* values in the remaining 17 available comparisons between IMGU and VF or SF did not vary a great deal: in 8 instances, they were somewhat higher with VF (87, 88, 92–94, 97, 101), in 7 instances, they were higher with SF (83, 86, 90, 91, 98, 100), and on 2 occasions, they were identical (84, 100).

The data in Table 6 do not show a uniquely close relation between VF and IMGU, which contrasts with the relation between insulin sensitivity and BMI, SF, or total fat. This conclusion should not be too surprising in view of a study whose results showed that, "independent of age and sex, the combination of BMI and WC explained a greater variance in nonabdominal, abdominal, subcutaneous, and visceral fat than [did] either BMI or WC alone" (102).

TABLE 7
"Diagnosing" the metabolic syndrome in 3 men of European ancestry[1]

Variable	Patient A (WHO)	Patient B (ATP)	Patient C (IDF)
Age (y)	54	54	54
Waist circumference (cm)	93	93	93
FPG (mg/dL)	107	103	187
Triacylglycerol (mg/dL)	197	157	197
HDL cholesterol (mg/dL)	30	45	30
Blood pressure (mm Hg)	145/95[2]	135/90	145/95
Metabolic syndrome	No	Yes	No

[1] FPG, fasting plasma glucose; WHO, World Health Organization; ATP, Adult Treatment Panel III; IDF, International Diabetes Federation.
[2] Systolic/diastolic (all such values).

Visceral fat and adverse clinical outcomes

Although the data presented in Table 6 do not identify a unique relation between either WC or VF and IMGU, abdominal obesity could still be particularly useful in identifying persons at increased risk of clinical syndromes related to insulin resistance, For example, there are many reports emphasizing the relation between IMGU and abdominal obesity in general or VF specifically as a predictor of the development of the clinical syndromes related to insulin resistance (103–108). At the same time, other studies have come to a somewhat different conclusion. For example, in Pima Indians, increases in visceral obesity did not correlate with decreases in IMGU (109), and BMI was the estimate of adiposity with the highest hazard ratio in the prediction of type 2 diabetes (110). Furthermore, adding WC to that study's model did not improve its predictive ability. Results of a prospective study of Mexican Americans (111) indicated that persons with the highest baseline plasma glucose and insulin values were most likely to develop type 2 diabetes, independent of differences in age, BMI, or central obesity. In addition, a prospective study in a predominantly white population concluded that "both overall and abdominal adiposity strongly and independently predict risk of type 2 diabetes″ (112). Moreover, studies in several ethnic groups have shown that BMI was as good as if not better than abdominal obesity as a predictor of high blood pressure and the dyslipidemia of insulin resistance (113–115). The clustering of dyslipidemia, hyperuricemia, diabetes, and hypertension described in both whites and African Americans was most strongly related to insulin concentration, although the magnitude decreased after adjustment for differences in BMI and

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abdominal obesity (116) In this latter instance, it was concluded that all 3 variables—insulin concentration, abdominal girth, and BMI—contributed to the adverse consequences of insulin resistance. Thus, although WC may be a powerful predictor of clinical outcomes linked to insulin resistance, considerable evidence also exists that overall obesity, as estimated by BMI, not only contributes to insulin resistance but also increases the likelihood that a person will develop the clinical syndromes associated with the defect in insulin action.

METABOLIC SYNDROME: CLINICAL UTILITY OR FUTILITY?

The goal of diagnosing the metabolic syndrome is to identify persons at increased risk of CVD. Because each component that makes up the versions of the metabolic syndrome increases CVD risk (34, 36, 37, 62, 68, 69), it seems prudent to treat any of these abnormalities that are present. Furthermore, it would not be too surprising that the more abnormalities present in any given person, the greater would be his or her risk of CVD. The question can be raised, however, as to whether identifying a person as having metabolic syndrome necessarily indicates that he or she is at greater risk of CVD than is a person who may not qualify for that designation. This did not seem to be the case when the ATP III criteria were applied to the Framingham Study database (117); a recent report pointed out that persons meeting any 2 criteria were at no less risk than were those meeting 3 criteria. Indeed, it would be possible to describe a number of prototypic clinical situations in which a person with 1 or 2 abnormalities would be at greater risk of CVD than would a patient who met the metabolic syndrome diagnostic criteria. For example, a 54-y-old man of European ethnicity, with a WC of 93 cm and plasma glucose and triacylglycerol concentrations of 203 and 193 mg/dL, respectively, does not have the metabolic syndrome according to the IDF criteria. If that patient is compared with another European male, who meets the IDF criteria for the metabolic syndrome by virtue of having a WC of 94 cm and elevated plasma glucose (103 mg/dL) and triacylglycerol (155 mg/dL) concentrations, is there any doubt that the first patient, with frank type 2 diabetes and a greater degree of hypertriglyceridemia but without the metabolic syndrome, is at greater risk of CVD than is the second patient, who does have the metabolic syndrome?

Another confounding clinical issue relates to the fundamental philosophical differences between the 3 definitions of the metabolic syndrome. This dilemma is exemplified by the clinical data in Table 7, in which 3 different men of European ancestry are classified by the 3 different versions of the metabolic syndrome. If the WHO criteria are applied to patient A, the plasma glucose concentration is not high enough to meet the essential criterion of insulin resistance. Thus, unless an oral-glucose-tolerance test or a euglycemic clamp study is performed, this patient does not have metabolic syndrome according to the WHO criteria. At the same time, in light of his plasma triacylglycerol (197 mg/dL) and HDL-cholesterol (30 mg/dL) concentrations and his blood pressure (145/95), is there any doubt that he is at increased risk of CVD?

Patient B has the metabolic syndrome according to the ATP III diagnostic criteria because he exceeds the glucose, triacylglycerol, and blood pressure cutoffs. The modest elevations of plasma glucose and triacylglycerol concentrations, along with the minimal increase in blood pressure, may well place this person at greater risk of CVD. However, if his triacylglycerol concentration were 147 mg/dL instead of 157 mg/dL, and if his glucose concentration were 153 mg/d rather than 103 mg/dL, he would no longer have the metabolic syndrome but would be at much greater risk of CVD.

Patient C has type 2 diabetes and is at the greatest risk of CVD because he has the characteristic dyslipidemia of insulin resistance and is hypertensive, although his WC is not large enough to merit the diagnosis of metabolic syndrome. A diagnosis of type 2 diabetes is one of the components of all 3 definitions of the metabolic syndrome. However, irrespective of the version of the metabolic syndrome that is being used, it is possible to have type 2 diabetes and not have the metabolic syndrome. Patient C falls into that category. Once the diagnosis of type 2 diabetes has been made, clinical guidelines outlining treatment approaches to all of the abnormalities present in patients with type 2 diabetes are available (118). Do we need 2 diagnostic categories—type 2 diabetes patients with and without metabolic syndrome?

It is obvious that, by juggling the clinical findings in Table 7, it is possible to create an almost infinite number of scenarios in which persons who do not meet the diagnostic criteria for metabolic syndrome would be at greater risk of CVD than would those who do. Given this situation, it seems difficult to maintain that a diagnosis of metabolic syndrome provides unique clinical information.

CONCLUSION

IMGU varies by 600% to 800% in apparently healthy persons, and the third of this population that is the most insulin resistant is at a much greater risk of several abnormalities and clinical syndromes, including type 2 diabetes and CVD. Differences in degree of adiposity (25%) and level of physical fitness (25%) explain approximately half of the variability in insulin action, and the remaining 50% is most likely related to genetic differences. Although the 3 versions of the metabolic syndromecontain essentially identical components, they differ profoundly in the philosophical basis underlying their approach to a positive diagnosis. On the basis of the considerations discussed in this review, it is argued that there are multiple reasons to question the pedagogic utility of making diagnoses of metabolic syndrome. From a clinical standpoint, I subscribe to the guidelines outlined in the recent joint report from the American Diabetes Association and the European Association for the Study of Diabetes (119): *1*) providers should avoid labeling patients with the term *metabolic syndrome*; *2*) adults with any major CVD risk factor should be evaluated for the presence of other CVD risk factors; and *3*) all CVD risk factors should be individually and aggressively treated. If these goals are achieved, there is no longer a need for a diagnosis of metabolic syndrome, a controversy about the best definition of the metabolic syndrome, or any confusion as to the clinical approach to patients who, although they are at greater risk of CVD, do not qualify for a diagnosis of metabolic syndrome.

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