2 Metabolic Syndrome

To Be or Not to Be?

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INTRODUCTION

Two separate statements published in the autumn of 2005 expressed diametrically opposed views as to the clinical utility of "diagnosing" the metabolic syndrome (MetS). On the one hand (1), the American Heart Association (AHA) and the National Heart, Lung, and Blood Institute (NHLBI) firmly endorsed the need to establish such a diagnostic category, and, with some minor modifications, utilized the approach outlined by the report of the Adult Treatment Panel III (ATP III) (2). On the other hand, the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) simultaneously issued a joint statement sharply critical of the notion of the clinical utility of making a "diagnosis" of the MetS (3).

One difficulty in coming to grips with this budding controversy is that multiple approaches to diagnosing the MetS now exist, and although the name may be the same, and the components quite similar, the conceptual constructs underlying the multiple definitions are quite different. Consequently, one goal of this chapter will be to examine the implications of the biological/philosophical basis of the various definitions of the MetS.

Published versions of the MetS also differ considerably as to their view of the association between the various criteria proposed to make this diagnosis. Thus, it seems important to examine the relationship between the common components of the various

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definitions of the MetS, as well as their link to cardiovascular disease (CVD). For example, is there a biological connection that links the individual diagnostic criteria of the MetS to each other, and, if so, is the relationship hierarchical in nature? Conversely, are the individual components simply CVD risk factors that have no physiological relationship with each other (i.e., they cluster together for no discernible reason)? A discussion of these issues is the second goal of this chapter.

Finally, there is much more unanimity concerning the relationship between the individual components and specific clinical syndromes than there is as to whether it is useful to make a diagnosis of the MetS, or the best way to accomplish that goal. For example, there is little or no argument as how to diagnose type 2 diabetes or essential hypertension. Thus, the third goal of this chapter is to examine the concept that there is clinical utility in making a diagnosis of the MetS. Specifically, does a diagnosis of the MetS provide more clinical information concerning CVD risk than the presence of any one of its components? More important, is it possible that failure to make a diagnosis of the MetS in patients with known CVD risks results in less effective therapeutic efforts?

Finally, it would be disingenuous if I did not make known the fact that I have published previous articles (4–6) indicating my skepticism as to either the pedagogical or clinical utility of making a diagnosis of the MetS. Consequently, since the readers have been forewarned, they should be forearmed.

IT'S A BIRD! IT'S A PLANE! IT'S THE METABOLIC SYNDROME!

The World Health Organization (WHO) was the first major organization to propose a set of clinical criteria for the MetS, formalized and published (7) in a 1998 document entitled, "Definition, Diagnosis and Classification of Diabetes Mellitus and its Complications." The primary purpose of this report was to update the classification and diagnostic criteria of diabetes mellitus. In this context, the WHO Consultation Group designated the MetS as a special classification for individuals with, or with the potential for developing, type 2 diabetes: manifested by having impaired glucose tolerance (IGT), impaired fasting glucose (IFG), or insulin resistance by hyperinsulinemic, euglycemic clamp. The Consultation Group felt that once these individuals developed certain "CVD risk components" they became a unique entity and qualified as having the MetS. Aside from glucose tolerance status and/or insulin resistance, risk components deemed useful to identify individuals with the MetS included obesity, dyslipidemia, hypertension, and microalbuminuria. It was the view of the WHO Consultation Group that each component conveyed increased CVD risk, but as a combination became more "powerful." Therefore, the primary goal of recognizing an individual as having the MetS was to identify persons at heightened risk for CVD. Secondarily, by design, the diagnosis also helped identify individuals with high risk for diabetes if they did not already have it. Table 2.1 displays the criteria proposed by the WHO by which to make a diagnosis of the MetS.

The ATP III, representing the National Cholesterol Education Program (NCEP), published their initial definition of the MetS in 2001 (2). As indicated in the ATP III document, its primary purpose was somewhat different from that of the WHO report in that its focus was not on diabetes, but instead to update clinical guidelines for cholesterol testing and management. In addition, a major thrust of this third report by the

Table 2.1
WHO Definition of the Metabolic Syndrome

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

Plus any two of the following:
- Waist:hip ratio >0.9 in men, >0.85 in women; and/or BMI >30 kg/m^2
- Triglycerides ≥1.7 mmol/L (150 mg/dL); and/or HDL-C <0.9 mmol/L (35 mg/dL) in men, <1.0 mmol/L (39 mg/dL) in women
- Blood pressure ≥140/90 mmHg (revised from ≥160/90)
- Microalbuminuria (urinary albumin excretion rate ≥20 μg/min or albumin:creatinine ratio ≥30 mg/g)

NCEP was to "focus on primary prevention in persons with multiple risk factors." With these goals in mind, the ATP III introduced the MetS as "multiple, interrelated factors that raise CVD risk." The panel believed that the MetS increased CVD risk at any given low-density lipoprotein cholesterol (LDL-C) concentration, and should be a secondary target of therapy in cholesterol management. Similar to the WHO, the ATP III goal for establishing criteria for the MetS was to identify individuals at special risk for CVD, and to institute intensified lifestyle changes to mitigate these risks. In contrast to the WHO, the ATP III did not consider direct evidence of insulin resistance necessary to make a diagnosis of the MetS.

Although both the WHO and ATP III considered the MetS as conveying high risk for CVD, they viewed the underlying concept of the MetS somewhat differently. The WHO introduced the MetS in the context of classifying diabetes mellitus and impaired glucose regulation. They believed that having the MetS syndrome elevated the CVD risk profile of individuals who had diabetes, or who were at risk for diabetes, and that these individuals should be classified separately. This point of view has the potential of resulting in two separate diagnostic categories of patients with type 2 diabetes: those with, or without, the MetS. The ATP III agreed that having the MetS enhanced CVD risk, but in keeping with their organizational focus, they viewed the MetS, not in terms of diabetes, but as a special risk factor for CVD that was additive to other known risk factors. However, the fundamental goal of the two organizations was similar: a more effective way to prevent CVD in high-risk individuals.

The ATP III criteria for diagnosing the MetS appear in Table 2.2, and although there are many similarities, fundamental differences exist between the WHO and ATP III definitions. The most prominent difference is that the ATP III does not identify any one essential criterion, but proposes that an individual meeting any three of the five criteria

Table 2.2
ATP III Definition of the Metabolic Syndrome

Any three of the following:	
• Fasting glucose	≥6.1 mmol/L (110 mg/dL)
• Waist circumference	
○ Men	>102 cm (40 in)
○ Women	>88 cm (35 in)
• Triglycerides	≥1.7 mmol/L (150 mg/dL)
• HDL-C	
○ Men	<1.036 mmol/L (40 mg/dL)
○ Women	<1.295 mmol/L (50 mg/dL)
• Blood pressure	≥130/85 mmHg

in Table 2.2 has the MetS. Thus, not only is the presence of insulin resistance no longer required to make a diagnosis of the MetS, a person can be identified as having the ATP III version without any evidence of abnormal glucose tolerance. The two definitions also contain minor differences in the actual values needed to have an "abnormal" plasma triglyceride (TG) or high-density lipoprotein cholesterol (HDL-C) concentration or blood pressure. However, there are two more substantive differences between the two organizations in that the ATP III no longer lists microalbuminuria as one of the possible diagnostic criteria, and abdominal obesity, as assessed by measuring waist circumference (WC), is the only acceptable index of excess adiposity.

The International Diabetes Federation (IDF) is the most recent group to propose criteria with which to diagnose the MetS, and Table 2.3 lists the specific components they have chosen for this purpose (8). The IDF definition is similar to that of the WHO in that they have identified one essential criterion with which to make a diagnosis of the MetS. However, in contrast to the need to demonstrate the presence of glucose intoler-

Table 2.3
IDF Definition of the Metabolic Syndrome

In order for a person to be diagnosed with the metabolic syndrome, he or she must have:

- **Central obesity** (defined as a waist circumference ≥94 cm for Europid men and ≥80 cm for Europid women, with ethnicity-specific values for other groups)

plus any two of the following four factors:

1. Raised TG level: ≥150 mg/dL (i.7 mmol/L), or specific treatment for this abnormality.
2. Reduced HDL cholesterol: <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.
3. Raised blood pressure: systolic BP ≥130 or diastolic BP ≥85 mmHg, or treatment of previously diagnosed hypertension.
4. Raised fasting glucose (FPG) ≥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.

ance and/or insulin resistance, the diagnostic criterion that must be fulfilled is abdominal obesity as determined by measuring WC.

Inspection of Tables 2.1–2.3 demonstrates that the individual components of the various definitions of the MetS do not differ a great deal, but the superficial similarities should not serve to obscure fundamental differences among them. The most obvious difference is a conceptual one, involving the pathophysiological relationship between the individual diagnostic criteria. Thus, in the case of the ATP III version, the five criteria represent separate, but apparently equal CVD risks, and an abnormality in any three of them suffices to make a diagnosis of the MetS. In contrast, a diagnosis of the MetS with either the WHO or IDF version relies on a hierarchal ordering of the criteria, and in both instances, one essential ingredient must be satisfied: glucose intolerance and/or insulin resistance in the case of the WHO, whereas an abnormal WC must be present to satisfy IDF criteria for the MetS.

The second substantive difference involves the role of excess adiposity in the diagnosis of the MetS, specifically the clinical utility of assessing overall obesity, as measured by body mass index (BMI), versus abdominal obesity, quantified by WC or the ratio of waist/hip girth (WHR). Thus, excess adiposity, one of several supplemental criteria in the WHO definition, measured as either BMI or WHR, remains a criterion with the ATP III definition, but can only be met by having an abnormal WC, whereas in the IDF version WC has become the essential criterion with which to diagnose the MetS. The implication of these two fundamental areas of disparity among the various definitions of the MetS deserves careful consideration.

WHAT IS THE RELATIONSHIP AMONG THE METABOLIC SYNDROME DIAGNOSTIC CRITERIA: CASUAL OR CAUSAL?

In its recent statement, the AHA/NHLBI (1) indicates that the most widely recognized of the metabolic risk factors underlying the MetS are an "atherogenic dyslipidemia, elevated blood pressure, and elevated plasma glucose." They further point out that "individuals with these characteristics commonly manifest a prothrombotic and proinflammatory state." Although acknowledging that these changes represent "a grouping of ASCVD risk factors," the cluster identified "probably has more than one cause." This point of view is different from that expressed by either the WHO (7) or IDF (8) versions of the MetS, in that the former considers evidence of insulin resistance essential to make this diagnosis, whereas the IDF states that an increase in WC is the necessary ingredient.

It is difficult to disagree with the conclusion of the AHA/NHLBI that the cluster of abnormalities that make up the MetS "probably has more than one cause." In fact it is obvious that there are multiple examples of why this is the case. For example, Ahrens and associates (9) indicated that there were at least two divergent causes of increase in plasma triglyceride (TG) concentration: one related to the amount of carbohydrate ingested (CHO-induced lipemia) and the other to the quantity of fat consumed (fat-induced lipemia). However, they further pointed out that CHO-induced lipemia was by far the most common finding.

Returning to the AHA/NHLBI version of the MetS, do the authors believe that their "grouping of ASCVD risk factors" is coincidental? Alternatively, is it possible that a *common* physiological event greatly increases the likelihood that an individual will

develop the changes that make up their definition of the MetS? The proposed answer to this rhetorical question is that the abnormalities that comprise all three versions of the MetS do not "cluster" together by accident, and that a defect in insulin action plays a fundamental role in the development of the CVD risk factors that comprise all versions of the MetS. The evidence in support of the formulation follows.

Glucose Intolerance

The prevalence of some degree of abnormal glucose tolerance and/or type 2 diabetes—one of the criteria in all three definitions of the MetS—is the abnormality most closely related to insulin resistance. Indeed, more than 60 years ago, in 1939, Himsworth and Kerr (10) challenged the conventional wisdom that "all cases of human diabetes could be explained by deficiency of insulin." Instead, they suggested 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, in 1949, Himsworth concluded by indicating 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" (11).

The prescience of Himsworth's observations is borne out by the fact that we now know that resistance to insulin-mediated glucose disposal is present in the great majority of individuals with type 2 diabetes (12–16). It is also clear that insulin resistance (or hyperinsulinemia as a surrogate estimate of insulin resistance) is a powerful and independent predictor of the development of type 2 diabetes (17–21). Finally, the greater the degree of insulin resistance, the higher the plasma insulin response to oral glucose is in individuals with normal oral glucose tolerance (22). Parenthetically, although insulin resistance was highly predictive of the magnitude of hyperglycemia following a glucose load in glucose-tolerant individuals, there was no relationship between excess adiposity and glucose response in these same individuals. Thus, there is an enormous amount of evidence documenting a very close relationship between insulin resistance and abnormal elevations in plasma glucose concentrations.

Finally, it should be emphasized that nondiabetic individuals with relatively minor degrees of glucose tolerance also have higher blood pressures, and the dyslipidemic changes—a high TG and a low HDL-C concentration—that comprise the remaining metabolic criteria of all three definitions of the MetS (23–26).

Dyslipidemia

It has been known for approximately 40 years that there is a highly significant relationship among insulin resistance, *compensatory* hyperinsulinemia, and hypertriglyceridemia (27,28). It is now apparent that the link between insulin resistance/hyperinsulinemia and dyslipidemia is a much broader one, and not limited to an increase in plasma TG concentrations. Thus, although the various definitions of the MetS have selected the combination of a high plasma TG and a low HDL-C concentration as diagnostic criteria, it is clear that these changes are also associated with a decrease in low-density lipoprotein (LDL) particle size (small, dense LDL) and the postprandial accumulation of TG-rich remnant lipoproteins (29). Not only are all of these changes

Table 2.4
Relationship Between Insulin Resistance and Plasma Triglyceride Concentration

A. Triglyceride concentration (69–546 mg/dL)*
IMGU → Insulin conc ($r = 0.74$) → VLDL-TG secretion rate ($r = 0.74$) → TG conc ($r = 0.88$)
B. Triglyceride concentration (33–174 mg/dL)**
IMGU → Insulin conc ($r = 0.81$) → VLDL-TG secretion rate ($r = 0.68$) → TG conc ($r = 0.87$)

*Based on data in ref. 28.
**Based on data in ref. 40.
IMGU = insulin-mediated glucose uptake as quantified by the insulin suppression test; VLDL = very low density lipoprotein; TG = triglyceride; conc = concentration.

significantly associated with insulin resistance/hyperinsulinemia (27–33), *each one* has been shown to increase the risk of CVD (34–39).

Plasma TG Concentration

The schema outlined in Table 2.4 is based on the results in two published studies (28,40). Table 2.4A depicts the relationship among insulin resistance, plasma insulin response, hepatic very-low-density (VLDL)–TG synthesis and secretion, and plasma TG concentrations in nondiabetic individuals (28) whose baseline plasma TG concentrations range from 69 to 546 mg/dL, whereas Table 2.4B describes the same relationships in individuals with plasma TG concentrations <175 mg/dL (40). These findings provide the experimental basis for the conclusion that the major cause of elevated plasma TG concentration in nondiabetic individuals is an increase in hepatic VLDL-TG secretion rate, secondary to insulin resistance and the resultant hyperinsulinemia.

Although there is widespread agreement as to the validity of the relationships (outlined above), controversy remains concerning the causal relationships among insulin resistance, compensatory hyperinsulinemia, hepatic VLDL-TG secretion, and plasma TG concentration. One view is that resistance to insulin regulation in muscle and adipose tissue leads to higher ambient levels of both insulin and FFA, and these two changes stimulate hepatic VLDL-TG secretion, leading to the increase in plasma TG concentration in insulin-resistant individuals (27,28,40,41). Alternatively, it is argued that hypertriglyceridemia occurs in insulin-resistant, nondiabetic individuals because the normal ability of insulin to inhibit hepatic VLDL-TG secretion is diminished (42). Irrespective of which of these alternatives is correct, there is no disagreement with the conclusion that hypertriglyceridemia is a characteristic finding in insulin-resistant individuals.

Postprandial Lipemia

The higher the fasting TG concentration, the greater will be the postprandial accumulation of TG-rich lipoproteins (VLDL, chylomicron remnants, and VLDL remnants) in nondiabetic individuals (43). In addition to the relationship between fasting TG concentration and postprandial lipemia, the daylong increase in TG-rich lipoproteins in nondiabetic individuals is significantly correlated with the magnitude of their insulin resistance/compensatory hyperinsulinemia (32,33,44). Although the postprandial

elevation of TG-rich lipoproteins is related to the fasting TG concentration, it can also be demonstrated that postprandial lipemia is enhanced when insulin resistant/hyperinsulinemic individuals are matched for degree of fasting hypertriglyceridemia with an insulin-sensitive population (45). These observations suggest that increases in postprandial lipemia are highly correlated to insulin resistance, directly by decreasing the removal from plasma of TG-rich lipoproteins by mechanisms not clearly defined, and indirectly by virtue of the role played by insulin resistance and compensatory hyperinsulinemia in stimulating hepatic VLDL-TG secretion and increasing fasting plasma TG concentration.

HDL Cholesterol

Increases in plasma VLDL-TG concentration are usually associated with low HDL-C concentrations, and it appears that insulin resistance/compensatory hyperinsulinemia are independently associated with both of these changes (30). In part, this is likely due to the transfer, catalyzed by cholesteryl ester transfer protein, of cholesterol from HDL to VLDL (46); the higher the VLDL pool size, the greater the transfer rate from HDL to VLDL, and the lower the ensuing HDL-C concentration. There is also evidence that the fractional catabolic rate (FCR) of apoprotein A-I is increased in patients with primary hypertriglyceridemia (47), hypertension (48), and type 2 diabetes (49). In type 2 diabetes, it has been shown that the greater the degree of hyperinsulinemia, the lower the HDL-C concentration (49). It has also been demonstrated in nondiabetic individuals that the higher the apoprotein A-I FCR, the lower the HDL-C concentration (50), and that these changes are associated with increases in plasma insulin concentrations. Thus, it is likely that insulin resistance and hyperinsulinemia contribute to a low HDL-C concentration indirectly by being responsible for the increase in VLDL pool size, and directly by increasing the FCR of apoprotein A-I.

LDL Particle Diameter

Analysis of LDL particle size distribution (35) has identified multiple distinct LDL subclasses, and it appears that LDL in most individuals can be characterized by either a predominance of larger LDL (diameter > 255 Å, pattern A) or of smaller LDL (<255 Å, pattern B). Individuals with pattern B have higher plasma TG and lower HDL-C concentrations. Not surprisingly, healthy volunteers with small, dense LDL particles (pattern B) are relatively insulin resistant, glucose intolerant, hyperinsulinemic, hypertensive, and hypertriglyceridemic, with decreases in HDL-C concentration (31).

Atherogenic Lipoproteins and Insulin Resistance

In summary, the lipoprotein abnormalities that are part of all three definitions of the MetS are more likely to occur in insulin resistant/hyperinsulinemic individuals. However, not all individuals with these abnormalities are insulin resistant. A high fasting plasma TG concentration and hyperchylomicronemia can occur (9,43) in individuals who have a fundamental defect in the catabolism of TG-rich lipoproteins (fat-induced lipemia). Similarly, a low HDL-C concentration can exist as a familial defect in lipoprotein metabolism (51), independent of any change in insulin sensitivity. Furthermore, not all insulin-resistant individuals will develop the atherogenic lipoprotein profile associated with the defect in insulin action. On the other hand, if the question becomes what fundamental physiological abnormality can account for the atherogenic lipoprotein profile

discussed above that occurs in combination with an elevated plasma glucose concentration and blood pressure, the sole contender is insulin resistance/hyperinsulinemia.

Blood Pressure

The blood pressure criteria suggested by the WHO for diagnosing the MetS have been lowered by both the ATP III and the IDF. However, since the objective basis of the values chosen by either organization is not clear, it is difficult to know which set of blood pressure criteria will be more useful. More importantly, the blood pressure link between insulin resistance on one hand, and CVD on the other, is more complicated than that of any of the criteria selected by the ATP III and the WHO. However, the following three sets of observations provide strong evidence linking insulin resistance/hyperinsulinemia to essential hypertension. First, patients with essential hypertension, as a group, are insulin resistant and hyperinsulinemic (52–54). Second, normotensive first-degree relatives of patients with essential hypertension are relatively insulin resistant and hyperinsulinemic as compared to a matched control group without a family history of hypertension (55–57). Finally, hyperinsulinemia, as a surrogate estimate of insulin resistance, has been shown in population-based studies to predict the eventual development of essential hypertension (58–61). These data provide substantial support that insulin resistance/hyperinsulinemia plays a role in the pathogenesis of essential hypertension.

On the other hand, since probably no more than 50% of patients with essential hypertension are insulin resistant (62), it is obvious that patients can have an elevated blood pressure and not be insulin resistant/hyperinsulinemic. However, although only approximately half the patients with essential hypertension are likely to be insulin resistant/hyperinsulinemic, this subset has the other components of the various definitions of the MetS that render them at greatest CVD risk. For example, patients with essential hypertension and electrocardiographic evidence of myocardial ischemia are insulin resistant, somewhat glucose intolerant, and hyperinsulinemic, with a high TG and low HDL-C as compared to either a normotensive control group or patients with essential hypertension whose electrocardiograms are entirely normal (63). The link between the dyslipidemia present in insulin resistant/hyperinsulinemic patients with essential hypertension and CVD is consistent with findings from the Copenhagen Male Study (64), in which 2,906 participants were divided into three groups based on their fasting plasma TG and HDL-C concentrations. Men whose plasma TG and HDL-C concentrations were in the upper third or lower third, respectively, of the whole population, were assigned to the high TG–low HDL-C group, whereas a low TG–high HDL-C group was composed of those individuals whose plasma TG and HDL-C concentrations were in the lower third and upper third, respectively, of the study population for these two lipid measurements. The intermediate group consisted of those participants whose lipid values did not qualify them for either of the two extreme groups. The results of this prospective study indicated that CVD risk was not increased in patients with hypertension in the absence of a high TG and low HDL-C, and that the group at greatest risk was those with a high blood pressure and a high TG and low HDL-C.

In summary, (1) insulin resistant/hyperinsulinemic individuals are more likely to develop essential hypertension; (2) hypertension is a well-recognized CVD risk factor; and (3) patients with essential hypertension *and* a high TG and a low HDL-C are at

greatest CVD risk. Patients with essential hypertension are more likely to be insulin resistant/hyperinsulinemic with a high TG and low HDL-C concentration than they are to have type 2 diabetes, IGT, or IFG. Since clinicians will not be performing clamp studies, a dyslipidemic patient with essential hypertension frequently may not qualify for the metabolic syndrome by WHO criteria. Fortunately, failure to accomplish the goal for which these criteria were introduced (i.e., identifying insulin-resistant individuals at greatest CVD risk) should not prevent any thoughtful clinician from treating both the elevated blood pressure and the accompanying dyslipidemia in an effective manner.

Insulin Resistance and Procoagulant and Proinflammatory Factors

All three definitions of the MetS comment on the fact that the cluster of components that make up the diagnostic category are also associated with a procoagulant and/or proinflammatory state. Although measures of the latter changes have not been elevated to become diagnostic criteria, there is no doubt that both of these changes are closely associated with insulin resistance. The association between insulin resistance/hyperinsulinemia, elevated concentrations of plasminogen activator inhibitor-1 (PAI-1), and CVD have been known for some time (65–67). Of greater relevance to this review are the data in Table 2.5 showing that PAI-1 concentration in a group of apparently healthy individuals was significantly correlated with the degree of insulin resistance (as quantified by SSPG concentration during the insulin suppression test), and fasting

Table 2.5
Simple and Partial Correlations Among PAI-1 and Other Relevant Variables in Normotensive Volunteers

	Simple Correlation		*Partial Correlation*	
Variable	*R*	*P*	*R*	*p*
Age (years)	–0.42	0.02	—	—
BMI (kg/m≤)	0.39	0.03	—	—
Waist/hip (WHR)	0.15	0.49	–0.004	0.98
MAP (mmHg)	–0.06	0.77	–0.06	0.76
SSPG (mg/dL)	0.62	<0.001	0.56	<0.001
Fasting plasma insulin (μU/mL)	0.65	<0.001	0.58	<0.001
Triglyceride (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

Partial correlations were calculated after adjustment for age and BMI.

MAP = mean arterial pressure; WHR = waist to hip ratio; SSPG = the steady-state plasma glucose concentration (SSPG) during the last 30 min of a 180-min infusion of octreotide (0.27 μg/m^2/min), insulin (32 mU/m^2/min), and glucose (267 mg/m^2/min).

Since the steady-state plasma insulin concentrations are comparable in all individuals, and the glucose infusion rate is identical, the resultant SSPG concentration provides a direct measure of the ability of insulin to mediate the disposal of a given glucose load (i.e., the higher the SSPG, the more insulin resistant the individual).

Source: Reprinted from ref. 67 with permission of the journal and the authors.

plasma insulin, TG, and HDL-C concentrations (67). Thus, variations in PAI-1 concentrations cluster with insulin resistance/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 (CRP), but there is a much longer history of a relationship between an increase in white blood count (WBC) and heart disease. Indeed, data from the Women's Health Initiative Observational Study suggest that a high WBC was comparable in magnitude as a predictor of CVD risk to increases in CRP concentration (68). Evidence published several years ago (69) of a relationship between WBC and insulin resistance/compensatory hyperinsulinemia indicated that the WBC in apparently healthy individuals was significantly correlated with degree of insulin resistance ($r = 0.50$, $p > 0.001$), the magnitude ($p < 0.001$) of the plasma glucose ($r = 0.48$) and insulin responses ($r = 0.50$) to an oral glucose challenge, and higher TG ($r = 0.37$) and lower HDL-C ($r = -0.38$) concentrations ($p > 0.005$).

These observations provide evidence that the additional CVD risk factors considered to be present in patients diagnosed as having the MetS are significantly related to both insulin resistance/hyperinsulinemia as well as the other components of the MetS. As such, they provide additional evidence indicating that insulin resistance/hyperinsulinemia offers the only coherent explanation to account for how all of these individual variables cluster together in apparently healthy individuals, and increase the risk of CVD.

EXCESS ADIPOSITY, INSULIN RESISTANCE, CVD, AND THE METS

The use of an index of excess adiposity as a criterion with which to diagnose the MetS is qualitatively different from any of the other components listed in Tables 2.1–2.3. Dyslipidemia (a high TG and low HDL-C concentration), hyperglycemia, and hypertension are independent factors that directly increase risk of CVD (34,36,37,70,71). The relationship between excess adiposity and CVD risk is not the same. At the simplest level, there are substantial numbers of overweight/obese individuals who do not display the components used to make a diagnosis of the MetS (72,73). Being overweight/obese simply increases the probability that an individual will become glucose intolerant, dyslipidemic, and hypertensive, and the linchpin between excess adiposity and the remaining components of the various definitions of the MetS is largely a consequence of the adverse effect of being overweight/obese on insulin sensitivity (72–74). This point of view is consistent with the results of the recent study of Ninomiya et al. (75), showing that abdominal obesity, as defined by the ATP III, was the only one of their five variables not statistically associated with the development of either CVD or stroke in an analysis of the NHANES III data. The authors suggested that this finding "may reflect an indirect effect of high WC through other components of the syndrome." Consequently, this section will examine the relationship between excess adiposity, insulin resistance, and the diagnosis of the MetS.

Obesity and Insulin-Mediated Glucose Uptake (IMGU)

The most insightful study of the relationship between obesity and IMGU is the report from the European Group for the Study of Insulin Resistance (76). Based on the results

of euglycemic, hyperinsulinemic clamp studies in 1,146 nondiabetic, normotensive volunteers, these investigators concluded that only ~25% of the obese volunteers were insulin resistant by the criteria they used. Parenthetically, these authors also pointed out that differences in WC were unrelated to insulin sensitivity after adjustments for age, gender, and BMI.

We have published results similar to those of the European Group for the Study of Insulin Resistance, finding that the differences in degree of obesity account for approximately one-third of the variability of IMGU in apparently healthy individuals (72,73). Furthermore, these estimates did not take into account that overweight individuals tend to be more sedentary, and the more physically fit an individual, the more insulin sensitive (77). Indeed, in a bi-ethnic study involving nondiabetic Pima Indians and individuals of European ancestry, it was shown that differences in degree of physical fitness are approximately as powerful as variations in adiposity in modulation of IMGU (78). Thus, the heavier an individual the more likely they are to be insulin resistant, but although differences in adiposity are an important modulator of insulin action, it is only *one* of the variables determining whether an individual is sufficiently insulin resistant to develop an adverse clinical outcome.

WC versus BMI as Predictors of IMGU

Measurements of BMI and WC in approximately 15,000 participants in the National Health and Nutrition Examination Survey (NHANES) indicated that the correlation coefficient between the two indexes of obesity was greater than 0.9 irrespective of the age, gender, and ethnicity of groups evaluated (79). Given this degree of correlation between BMI and WC, it is not immediately obvious why WC is considered to be a more useful index of metabolic abnormality associated with excess adiposity than is BMI. It is even less clear why it is considered to be the essential diagnostic criterion in the IDF version of the MetS (Table 2.3).

Figure 2.1 displays the results of a study in which IMGU was quantified with the Insulin Suppression Test (IST) in 208 apparently healthy individuals, and the relationship between these values and measurements of BMI and WC determined (80). The IST (12,13,16,22,28,30–32,40,44,53,54,56,63,67,69,72,73,77) is based on determining the steady-state plasma glucose (SSPG) and insulin (SSPI) concentrations during the last 30 minutes of a 180-minute infusion of octreotide (0.27 $\mu g/m^2/min$), insulin (32 $mU/m^2/min$), and glucose (267 $mg/m^2/min$). Since the SSPI concentrations are comparable in all individuals, and the glucose infusion rate is identical, the resultant SSPG concentration provides a direct measure of the ability of insulin to mediate the uptake of a given glucose load (IMGU); that is, the higher the SSPG, the more insulin resistant the individual. The results in men (upper two panels) and women (lower two panels) are shown separately. The fact that the correlation coefficient relationships (*r*-values) between the two indexes of obesity and the SSPG concentration are essentially identical was not surprising in light of the NHANES data (79). However, it was surprising, and of considerable interest, to find that the magnitude of the correlation between the two indexes of adiposity and the measure of IMGU was much greater in men (*r*-value ~0.7) than in women (*r*-value ~0.5). Consistent with the results of the NHANES study described above, BMI and WC were also highly correlated (*r*-value = 0.9). Since there is substantial evidence that the relationship between IMGU and overall obesity (BMI)

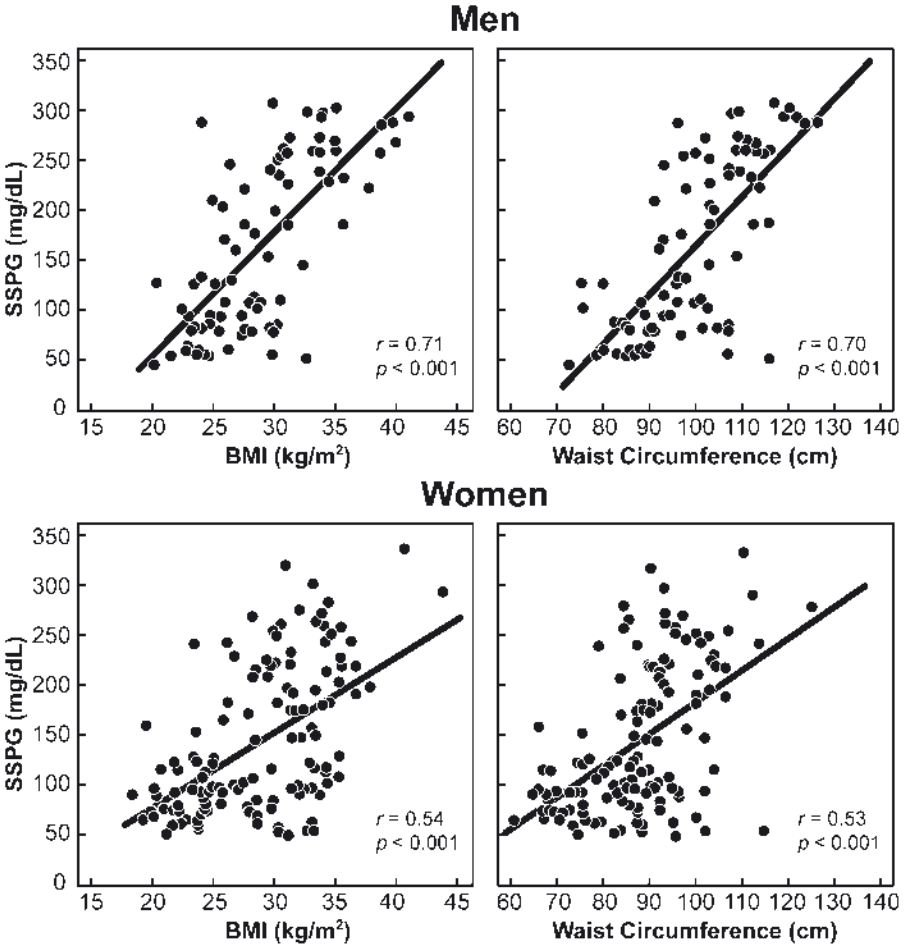

Figure 2.1. Relationship between degree of insulin resistance (SSPG concentration*) and BMI or waist circumference in 208 apparently healthy volunteers. (Reprinted from ref. 80 with permission of the journal and the authors.)
*SSPG = the steady-state plasma glucose concentration (SSPG) during the last 30 min of a 180-min infusion of octreotide (0.27 μg/m^2/min), insulin (32 mU/m^2/min), and glucose (267 mg/m^2/min). Since the steady-state plasma insulin concentrations are comparable in all individuals, and the glucose infusion rate is identical, the resultant SSPG concentration provides a direct measure of the ability of insulin to mediate the disposal of a given glucose load (i.e., the higher the SSPG, the more insulin resistant the individual).

is no different from that between IMGU and abdominal obesity (WC), it seems that either index of adiposity is equally predictive of differences in insulin action.

Relationship Among Adiposity, Insulin Resistance, and CVD Risk

Rates of IMGU vary by more than sixfold in apparently healthy individuals, and the distribution of these values is continuous (81). Consequently, there is no objective way to select cut points that define individuals as being either insulin resistant or insulin sensitive. Obviously, this complicates any discussion of the relationship among excess

Table 2.6
Distribution of Body Mass Index (kg/m^2) According to Degree of Insulin Resistance (number and percent)

BMI (kg/m^2)	*Most Insulin-Sensitive Third*	*Intermediate Third*	*Most Insulin-Resistant Third*
<25.0	109 (70%)	75 (48%)	24 (15%)
25.0–29.9	39 (25%)	54 (35%)	75 (48%)
30.0–34.9	7 (5%)	26 (17%)	56 (36%)
Total	155	155	155

Source: Reprinted from ref. 85 with permission of the journal and the authors.

adiposity, insulin resistance, and CVD. However, there are prospective studies that can serve as the basis for a more or less reasonable approach to address this issue. For example, if the magnitude of the insulin response to oral glucose is used as a surrogate marker of insulin resistance, 25% of an apparently healthy population with the highest insulin concentrations is at statistically significant increased risk to develop CVD (82). Based on the results of two studies in which the IST (a specific measure of IMGU) was used at baseline, the third of the population with the greatest defect in IMGU (the highest SSPG concentrations) was at significantly greater risk to develop CVD (83,84). Thus, for the purposes of this discussion, the third of the population at large with the highest SSPG concentrations will be operationally defined as being insulin resistant (IR), and those with SSPG concentrations in the lower third will be considered to be insulin sensitive (IS).

Prevalence of Insulin Resistance as a Function of BMI

The results shown in Table 2.6 come from a study of 465 apparently healthy individuals, divided into tertiles of IMGU based on their BMI (85). Although the majority of normal-weight individuals (BMI < 25.0 kg/m^2) are in the most IS third (70%), 30% of the most IS individuals are either overweight/obese. Furthermore, approximately two-thirds of those in the IR third were either normal weight or overweight, and only approximately one-third of the most IR individuals were actually obese (BMI 30–35 kg/m^2). These data provide further evidence that, in general, the heavier the individuals, the more likely they are to be insulin resistant, but that obesity does not necessarily equal insulin resistance.

Interaction Among BMI, Insulin Action, and CVD Risk Factors

Figure 2.2 illustrates the results of applying the operational definitions of IR and IS to 314 healthy, nondiabetic individuals (72). Each panel displays the best-fit line describing the relationship among BMI and a series of CVD risk factors following the separation of the population into thirds on the basis of their SSPG concentration. Results in the two left panels indicate that the greater the BMI, the higher the total (upper left) and LDL-C (lower left) concentrations, but that these relationship do not vary as a function of degree of insulin resistance. In contrast, results in the middle panels of Figure 2.2 demonstrate that the relationship between BMI and plasma (upper middle) and HDL-C (lower middle) concentrations are quite different in IR as compared to IS

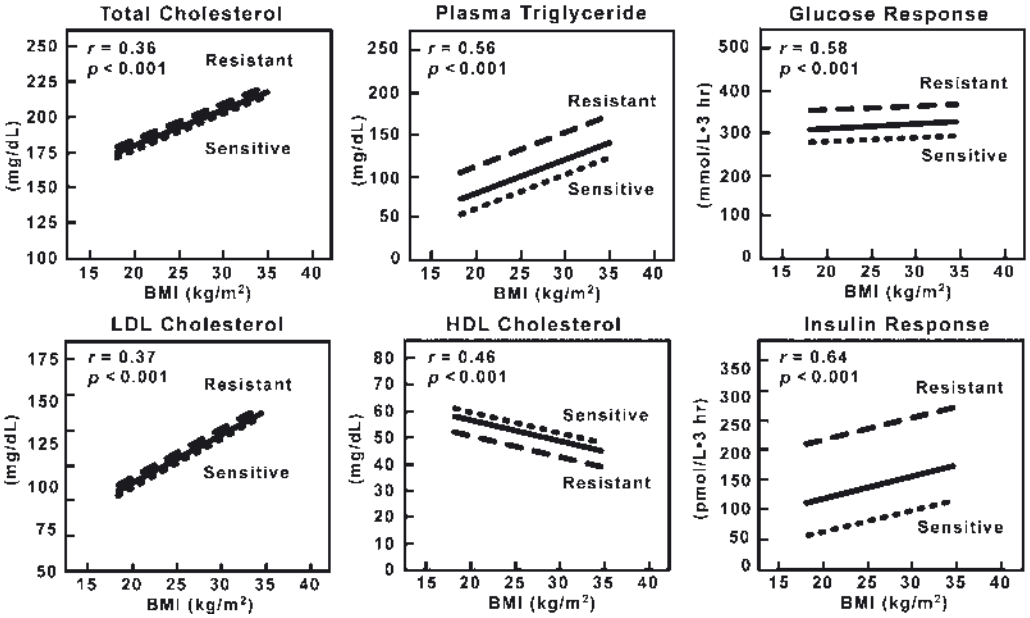

Figure 2.2. Relationship between BMI and SSPG* tertile and several cardiovascular disease risk factors. (Reprinted from ref. 72 with permission of the journal and the authors.)
*SSPG = the steady-state plasma glucose (SSPG) concentration during the last 30 min of a 180-min infusion of octreotide (0.27 μg/m^2/min), insulin (32 mU/m^2/min), and glucose (267 mg/m^2/min). Since the steady-state plasma insulin concentrations are comparable in all individuals, and the glucose infusion rate is identical, the resultant SSPG concentration provides a direct measure of the ability of insulin to mediate the disposal of a given glucose load (i.e., the higher the SSPG, the more insulin resistant the individual).

individuals; at any given BMI, the plasma concentrations of TG are higher and HDL-C lower in IR as compared to IS individuals. Finally, the results in the right panels of Figure 2.2 highlight the untoward impact of being insulin resistant on the total integrated plasma glucose (upper right) and insulin (lower right) responses to a 75 g oral glucose challenge. In addition to documenting the enormous impact that being insulin resistant has on the plasma insulin response to oral glucose, the results in Figure 2.2 also emphasize that the plasma glucose response to oral glucose is relatively well maintained despite increasing degrees of both obesity and insulin resistance. These latter comparisons emphasize the extraordinary ability of compensatory hyperinsulinemia to prevent gross decompensation of glucose homeostasis in insulin-resistant individuals.

Obesity Does Not Necessarily Translate into Increased CVD Risk

If insulin resistance/hyperinsulinemia increases CVD risk at any given BMI, and not all overweight/obese persons are insulin resistant, it seems clear that excess adiposity, per se, does not necessarily increase CVD risk. One way to look at this issue is to evaluate CVD risk factors in obese individuals selected to be either insulin resistant (IR) or insulin sensitive (IS) with the IST as defined above. The results in Figure 2.3 compare daylong glucose, insulin, and free fatty acid (FFA) concentrations in response to breakfast and lunch in 20 IR and 18 IS obese individuals, matched for age, gender, BMI, and WC (86). In addition to having daylong increase in plasma glucose, insulin,

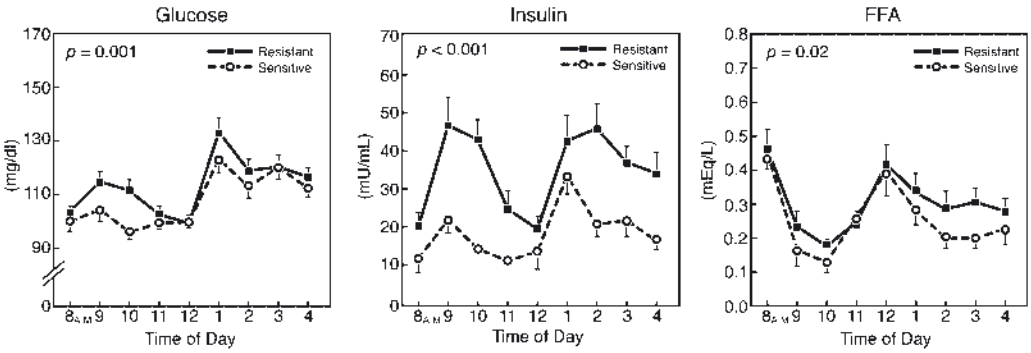

Figure 2.3. Comparison of daylong plasma glucose, insulin, and free fatty acid (FFA) concentrations in insulin-resistant and insulin-sensitive obese individuals. Test meals were consumed at 8 A.M. and noon, and blood drawn before and at hourly intervals after the meals. (Reprinted from ref. 86 with permission of the journal and the authors.)

and FFA concentrations, the C-reactive protein concentrations were also significantly higher in the IR subjects (0.39 ± 0.08 vs. 0.12 ± 0.03 mg/dL, $p < 0.005$).

WC IS NOT THE SAME AS VISCERAL OBESITY

Based on the experimental data summarized in the previous section, it can be concluded that measurements of BMI and WC are highly correlated, and associated with a specific measure of IMGU to an identical degree, and that CVD risk factors are increased primarily in those overweight/obese individuals who are also insulin resistant. It is apparent that this formulation is at odds with the views of the ATP III (1,2) and IDF (8) that abdominal obesity is the ultimate villain. A possible explanation for this discrepant view of the central role (pun intended) of abdominal obesity in the genesis of insulin resistance and its consequences is that measurements of WC provide only a surrogate estimate of visceral obesity, and it is visceral obesity that is responsible for the manifestations of the MetS that increase CVD.

Visceral Obesity and Insulin Resistance

Table 2.7 presents the results of 19 studies (22 comparisons) attempting to define the relative magnitude of the relationship between IMGU and various estimates of adiposity, including visceral obesity (VF), in nondiabetic subjects (87–105). The studies are listed in chronological order, and several inclusion criteria were used to construct the table. In the first place, imaging techniques had to be used to determine the magnitude of the various fat depots. Second, IMGU had to be quantified with specific methods, and studies using surrogate estimates were not included. In addition, the actual experimental data had to be available prior to the use of arbitrary "adjustments" or multiple regression analysis. For example, following an "adjustment" for the relationship between differences in total body fat and IMGU, it is not clear how much one learns from now discerning a relationship between IMGU and VF. Finally, the omission of any study that satisfied these two simple criteria was inadvertent, and no information was deliberately excluded. However, given the number of studies included, and the diversity in the experimental populations represented, it is unlikely that the inclusion

of additional reports would substantially alter the interpretation of these data. It should also be realized that space constraints prohibit a thoughtful discussion of possible differences in the imaging techniques used in individual studies, and the same considerations apply to the specific methods used to quantify IMGU. Finally, given the diversity of the participants enrolled in these studies, as well as the differences in experimental techniques used, it will not be possible to discuss each one thoroughly. Instead, an effort will be made to draw the general conclusions that seem to be both consistent with the data and most relevant to the issue at hand.

First, perhaps the simplest conclusion to be drawn from the results in Table 2.7 is that correlation coefficients (*r*-values) between visceral fat (VF) and IMGU are usually less than 0.6 and certainly no greater than the *r*-value between IMGU and either BMI or WC seen in Figure 2.1. Indeed, *r*-values between IMGU and VF varied from 0.4 to 0.6 in 17 of the 22 measurements in Table 2.7, with differences in VF accounting for approximately 25% of the variability in IMGU in most instances.

Second, although the relationship between BMI and IMGU was analyzed in only four studies (89,97,101,103), the correlation coefficients were comparable in these instances to the values between VF and IMGU. More comparisons were made between the relationships of IMGU with VF as contrasted to total fat (TF), and it appears that either estimate of adiposity provided *r*-values of similar magnitude. If anything, the

Table 2.7
Correlation Coefficients (*r*-values) Between IMGU and Body Fat Distribution

Ref No.	*Population*	*VF*	*SF*	*TF*	*BMI*
87	39 men	–0.51	–0.62	–0.61	
88	60 subjects	–0.50	–0.50	–0.57	
89	26 OB subjects	–0.56		–0.54	–0.55
90	54 subjects	–0.52	–0.61	–0.58	
91	20 S. Asian men	–0.59	–0.54	–0.56	
92	47 men	–0.61	–0.53		
93	27 postM women	–0.39	–0.43	–0.30	
94	44 OB postM women	–0.40	–0.17		
95	68 Cau children	–0.59	–0.70	–0.68	
	51 AA children	–0.43	–0.47	–0.52	
96	55 postM women	–0.49	–0.43		
97	48 subjects	–0.58	–0.41		–0.52
98	24 subjects	–0.55	–0.47	–0.61	
99	89 Ob males	–0.41			
100	40 Ob preM women	–0.34	–0.06		
101	174 subjects	–0.69	–0.57		–0.63
102	32 Hispanic children	–0.44	–0.46	–0.46	
103	39 men	–0.71			–0.56
104	44 AA men	–0.57	–0.57		
	35 AA women	–0.50	–0.67		
105	11 Thai women	–0.60	–0.47	–0.38	
	11 Thai men	–0.54	–0.45	–0.80	

IMGU = measurement of insulin-mediated glucose uptake; OB = obese; postM = postmenopausal; Cau = Caucasian; AA = African American; preM = premenopausal.

relationship of TF with IMGU was somewhat greater in 8 of the 12 comparisons (87,88,90,95,98,102,105).

However, the emphasis in the studies listed in Table 2.7 was a comparison of the relationship between IMGU and subcutaneous abdominal fat (SF) with that between IMGU and VF. As before, the magnitude of the relationship with IMGU was reasonably comparable with either fat depot, but in this case there were two examples in which the values were quite discrepant (94,100). In both of these, the study population consisted of obese women, and whether this accounts for the somewhat discrepant results cannot be determined. On the other hand, in the remaining 17 available comparisons, the *r*-values between IMGU with VF or SF did not vary a great deal, being somewhat higher with VF 8 times (91,92,96–98,101,105), higher with SF 7 times (87,90,93,95,102,104), and identical on two occasions (88,104).

Given the information in Table 2.7, it is not easy to understand the basis for the conventional wisdom that visceral obesity has a uniquely adverse effect on IMGU. One of the explanations may be the widespread use of multiple regression analysis to decide which variable is an *independent* predictor of an outcome, in this case IMGU. Although this approach can provide useful information, it is well recognized that it presents problems when very closely related variables are entered into the model being used. Since all measures of adiposity are highly correlated, there is no clear biological significance of the results of a multivariate analysis indicating that only one of them is an independent predictor of IMGU. However, it is clear from the data in Table 2.7 that there is hardly overwhelming experimental support for the notion of a uniquely close relationship between VF and IMGU, in contrast to the relationship among IMGU and BMI, WC, SF, or TF. Indeed, this conclusion should not be too surprising in view of the results of a study showing that "independent of age and sex, the combination of BMI and WC explained a greater variance in nonabdominal, abdominal, subcutaneous and visceral fat than either BMI or WC alone" (106).

Visceral Fat and Adverse Clinical Outcomes

Although the data presented in Figure 2.2 and Table 2.7 do not identify a uniquely close relationship between either WC or VF and IMGU, measurements of abdominal obesity might still be the most effective way to identify individuals at increased risk of developing clinical syndromes related to insulin resistance. For example, many studies have been published emphasizing the relationship between abdominal obesity in general, or VF specifically, as predicting the development of the clinical syndromes related to insulin resistance (107–112). On the other hand, there are also publications that come to a somewhat different conclusion. For example, in Pima Indians, increases in visceral obesity did not correlate with decreases in IMGU (113), and BMI was the estimate of adiposity with the highest hazard ratio in the prediction of type 2 diabetes (114). Furthermore, adding WC to this study's model did not improve its predictive ability. In a prospective study of Mexican Americans (115), Haffner and colleagues reported somewhat similar results, illustrating that those individuals with the highest baseline plasma glucose and insulin values were most likely to develop type 2 diabetes, independently of differences in age, BMI, or central obesity. In addition, a prospective study in a predominantly Caucasian population concluded that ''both overall and abdominal adiposity strongly and independently predict risk of type 2 diabetes" (116). It has also been shown in studies of several ethnic groups that BMI is more strongly associated with blood

pressure than is abdominal obesity (117–119). Finally, 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 when adjusted for differences in BMI and abdominal obesity (120). In this latter instance, it was concluded that all three variables (insulin concentration, abdominal girth, and BMI) contributed to the adverse consequences related to insulin resistance. Thus, although WC may be a powerful predictor of clinical outcomes linked to insulin resistance, there is also considerable evidence that overall obesity, as estimated by BMI, not only contributes to insulin resistance, but also increases the likelihood that an individual will develop the clinical syndromes associated with the defect in insulin action.

IS THERE CLINICAL UTILITY IN DIAGNOSING THE METS?

Although the specific approaches to diagnose the MetS vary from version to version (Tables 2.1–2.3), the components listed in each of them are remarkably similar in that they are significantly associated with insulin resistance and increased CVD risk. It also seems reasonable that the more of these abnormalities that exist in an individual, the greater will be the risk of CVD. On the other hand, once the values of these measurements are known, how much clinical benefit is there in knowing whether the number of arbitrary criteria exceeded qualifies an individual as having the MetS? It seems to me that the answer to this rhetorical question is "not much," and the following brief examples explain the basis of my view.

All three versions of the MetS include type 2 diabetes as one of the diagnostic criteria. It is well recognized that patients with type 2 diabetes are at increased risk of CVD, and, in addition to being hyperglycemic, are often dyslipidemic, hypertensive, with a procoagulant and proinflammatory state. Furthermore, there are clinical guidelines (121) outlining the appropriate treatment paradigms for patients with type 2 diabetes. Once this diagnosis is made, the clinical problem is how best to control the hyperglycemia appropriately and effectively address all remaining CVD risk factors, not deciding whether the MetS is present.

Rather than continue to describe a series of situations that question the clinical utility of diagnosing the MetS, it might be more informative to explore the clinical implications of *not* identifying patients at increased CVD risk who *do not* meet the requisite diagnostic criteria. Perhaps the simplest way to address this issue is to consider how the same individual is classified by the three versions of the MetS. The patient in question is a man, of European ancestry, with a WC of 93 cm, with an elevated blood pressure (145/95 mm/Hg), associated with a high TG (155 mg/dL) and a low HDL-C (30 mg/dL) concentration. However, since his fasting plasma glucose concentration is only 103 mg/dL, he does not meet the diagnostic criteria for the MetS by WHO criteria unless his physician is willing to perform either an oral glucose tolerance test or a euglycemic, hyperinsulinemic clamp study. Should the lack of a positive diagnosis of the MetS adversely affect the treatment plan for this patient? Would it make any substantive difference in the treatment if the patient's fasting plasma glucose concentration had been 111 mg/dL? Alternatively, what if a second physician is willing to measure the patient's glucose level 120 minutes after a 75 g oral glucose challenge, and it turns out to be 145 mg/dL. The patient would now have the MetS. Would this additional

information make any substantive difference in the treatment program? I hope not! The patient has hypertension and the dyslipidemia characteristic of insulin resistance and there are well-established algorithms for treating both abnormalities. Parenthetically, approximately one-third of apparently healthy, insulin-resistant individuals have neither IFG nor IGT (122).

In contrast to the WHO version of the MetS, the patient described would meet ATP III criteria for this diagnosis, even if his fasting plasma glucose concentration was only 98 mg/dL. However, this would not be the case if his plasma TG concentration were 145 mg/dL, rather than 155 mg/dL. Is there any doubt that a hypertensive patient with a low HDL-C concentration is at increased CVD risk? Would use of ATP III criteria lead to a different treatment approach to a patient with hypertension and a low HDL-C concentration if his fasting plasma glucose and TG concentrations were 98 mg/dL and 145 mg/dL, as compared to 103 mg/dL and 155 mg/dL? If not, what is the clinical utility of making, or not making, this diagnosis?

Finally, since this patient did not meet the essential criterion of abdominal obesity (his WC was only 93 cm), he does not have the MetS by the IDF definition, and this is true despite the presence of hypertension (145/95 mmHg), a high TG (155 mg/dL) and low HDL-C (30 mg/dL) concentration, and IFG (103 mg/dL). Clearly, this prototypical patient is at considerable increased CVD risk, despite not having the IDF version of the MetS. Would his clinical status be any different if he now satisfied the essential criterion of abdominal obesity (WC = 95 cm)? Clearly, neither the CVD risk nor the appropriate therapeutic approach has changed because the abdominal girth has increased by 2 cm!

The values of WC needed to diagnose the MetS shown in Table 2.3 are specific for "Europids," and the IDF indicates that these values should vary with ethnicity. The requirement of ethnic-specific criteria for abdominal obesity raises additional questions concerning the clinical utility of the IDF criteria. As defined by the IDF, a normotensive man of Japanese ancestry will have the MetS if he has a WC of 88 cm, and moderately increased fasting plasma concentrations of glucose (103 mg/dL) and TG (155 mg/dL). In contrast, a Chinese man with the same WC will not have the IDF version of the MetS, even if he is hypertensive (145/95 mmHg), frankly diabetic (fasting plasma glucose concentration = 150 mg/dL), with a plasma TG concentration of 220 mg/dL. Is there any doubt that the Chinese patient is at greater CVD risk, even though he does not have the IDF version of the MetS?

The examples discussed above were chosen purposefully to question the clinical utility of making a diagnosis of the MetS, irrespective of what organization's definition is used. It is obvious that it would be possible to continue almost indefinitely to describe clinical findings in individuals who had the MetS by one or another of the three versions whose CVD risk was less than persons who did not meet the diagnostic criteria. The point of this exercise is to emphasize that the specific components of the various definitions of the MetS are CVD risk factors, and should be recognized as such, but there is not a great deal to be gained by deciding whether any particular combination of them merits diagnosis of the MetS. This point of view is consistent with recent findings based on the Framingham database (123), in which the authors used the ATP III criteria for the MetS, and concluded that "clusters of 3 traits do not substantially increase risk for outcomes over risk associated with clusters of 2 traits." They further pointed out that these findings are "consistent with the hypothesis that even a modest degree of risk

clustering reflects a global underlying insulin-resistant pathophysiology, and individual risk factors may contribute marginally to risk associated with the insulin-resistant phenotype."

CONCLUSION

The ability of insulin to simulate glucose disposal varies six- to eightfold in apparently healthy individuals (81). Approximately one-third of the most insulin-resistant of these individuals are at greatly increased risk to develop a number of abnormalities and clinical syndromes, only one of which is CVD (83,84). Approximately 50% of this extraordinary degree of variability in insulin action can be attributed to differences in degree of adiposity (25%) and level of physical fitness (25%), with the remaining 50% most likely related to genetic differences (78). Despite being composed of almost identical components, the three versions of the MetS differ profoundly in the philosophical basis underlying their approach to making a positive diagnosis. In this review, a number of issues have been raised that question the pedagogical utility of classifying an individual as having the MetS. Finally, it seems to me most reasonable to forget about making a clinical diagnosis of the MetS, irrespective of which version seems most appealing, and adhere to the following clinical advice from the joint report of the ADA and EASD (3):

- "Providers should avoid labeling patients with the term metabolic syndrome."
- "Adults with any major CVD risk factor should be evaluated for the presence of other CVD risk factors."
- "All CVD risk factors should be individually and aggressively treated."

If these goals are achieved, it will end (1) the need to make a diagnosis of the MetS; (2) the controversy over the best definition of the MetS; and (3) the confusion as to the clinical approach to patients who, although they are at increased CVD risk, do not qualify for a diagnosis of the MetS.

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