

The Metabolic Syndrome: Time for a Critical Appraisal

Joint statement from the American Diabetes Association and the European Association for the Study of Diabetes

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The term “metabolic syndrome” refers to a clustering of specific cardiovascular disease (CVD) risk factors whose underlying pathophysiology is thought to be related to insulin resistance. Since the term is widely used in research and clinical practice, we undertook an extensive review of the literature in relation to the syndrome’s definition, underlying pathogenesis, and association with CVD and to the goals and impact of treatment. While there is no question that certain CVD risk factors are prone to cluster, we found that the metabolic syndrome has been imprecisely defined, there is a lack of certainty regarding its pathogenesis, and there is considerable doubt regarding its value as a CVD risk marker. Our analysis indicates that too much critically important information is missing to warrant its designation as a “syndrome.” Until much needed research is completed, clinicians should evaluate and treat all CVD risk factors without regard to whether a patient meets the criteria for diagnosis of the “metabolic syndrome.”

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For most of the 20th century, cardiovascular disease (CVD) was identified as the major cause of morbidity and mortality in the developed world. During this period there was considerable effort to understand the underlying biology of the disease and to identify the contributing risk factors. As risk factors were identified, it became apparent that more than one were often present in the same individual. Toward the end of the century, the clustering of CVD risk factors

was first described, most notably the simultaneous presence of obesity, type 2 diabetes, hyperlipidemia, and hypertension (1–3). Although insulin resistance (i.e., resistance to insulin-stimulated glucose uptake) as a feature of type 2 diabetes was first described many years earlier (4), hyperinsulinemia was also found to be a key feature of type 2 diabetes (5,6), as well as hyperlipidemia (7–9), obesity (10–13), and hypertension (12–14). In addition, a cluster of heart disease risk factors

seemed clearly related to type 2 diabetes (15).

This risk factor clustering, and its association with insulin resistance, led investigators to propose the existence of a unique pathophysiological condition, called the “metabolic” (1–3) or “insulin resistance” (11) syndrome. This concept was unified and extended with the landmark publication of Reaven’s 1988 Banting Medal award lecture (16). Reaven postulated that insulin resistance and its compensatory hyperinsulinemia predisposed patients to hypertension, hyperlipidemia, and diabetes and thus was the underlying cause of much CVD. Although obesity was not included in Reaven’s primary list of disorders caused by insulin resistance, he acknowledged that it, too, was correlated with insulin resistance or hyperinsulinemia, and that the obvious “treatment” for what he termed “syndrome X” was weight maintenance (or weight loss) and physical activity.

Reaven’s seminal paper was followed by many studies documenting the clustering of CVD risk factors and their relationship to insulin resistance (17–25). Indeed, since Reaven’s publication in 1988, a recent Medline search for articles using the key words “syndrome X” or “insulin resistance syndrome” or “metabolic syndrome” (conducted 28.01.2005) identified 4,646 citations, with 3,948 studies performed on human subjects.

The term “metabolic syndrome” has now taken hold in the medical literature. It has been defined and institutionalized, principally by the World Health Organization (WHO) (26) and the Third Report of the National Cholesterol Education Program’s Adult Treatment Panel (ATP III) (27,28), albeit with different definitions. In addition, other organizations have developed similar, but again not identical, definitions (29,30). The fact that a version of the metabolic syndrome has its own ICD-9 code (277.7) also suggests that it is well thought out (31,32).

In this review we examine the evi-

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Abbreviations: ATP III, Third Report of the National Cholesterol Education Program’s Adult Treatment Panel; CHD, coronary heart disease; CRP, C-reactive protein; CVD, cardiovascular disease; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; IMT, intimal-medial thickness; WHO, World Health Organization.

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dence for its definition and underlying pathogenesis, as well as analyzing the evidence for its association with CVD. We also discuss the evidence for the goals and impact of treatment. We mainly focused our review on papers addressing the metabolic syndrome as defined by ATP III, the definition that appears to be used most often in the literature. Because the ATP III and WHO definitions are sometimes used almost interchangeably or compared with one another, we also examined the literature that used the WHO criteria.

For two reasons, we did not consider papers whose focus was on the ability of the metabolic syndrome to predict diabetes. First, ample data show that the presence of the metabolic syndrome is effective in predicting the future risk of diabetes. That association, however, is probably due to the fact that the definition of the syndrome includes glucose intolerance, i.e., impaired fasting glucose (IFG) or impaired glucose tolerance (IGT), themselves powerful predictors of future diabetes. Second, the practical use of diagnosing metabolic syndrome has not centered on its power to predict diabetes, but rather on its being a multivariate risk factor for CVD.

This review argues that the metabolic syndrome is not nearly as well defined and characterized as often assumed, and that the notion that it is a useful marker of CVD risk above and beyond the risk associated with its individual components is uncertain. In addition, although certain CVD risk factors undoubtedly occur together more often than expected by chance, the underlying pathophysiology of the syndrome is unclear. Moreover, the list of risk factors comprising the cluster is not grounded by well-defined criteria. Therefore, this manuscript is intended as a cautionary reminder to practitioners, and as an urgent call for further research. Our analysis addresses three key questions related to the metabolic syndrome: 1) How clear is the existing definition of the metabolic syndrome for diagnostic purposes?

A) How useful is the syndrome definition in predicting CVD risk? Do the individual components of the syndrome convey "risk" differently from the syndrome as a whole?

B) Is the cluster of symptoms associated with the syndrome the result of a common underlying pathological process?

Table 1—Definitions of the metabolic syndrome

ATP III definition (27,28)
Any three or more of the following criteria:
1) Waist circumference >102 cm in men and >88 cm in women
2) Serum triglycerides \geq 1.7 mmol/l
3) Blood pressure \geq 130/85 mmHg
4) HDL cholesterol <1.0 mmol/l in men and <1.3 mmol/l in women
5) Serum glucose \geq 6.1 mmol/l (\geq 5.6 mmol/l may be applicable)
WHO definition (26)
Diabetes, IFG, IGT, or insulin resistance (assessed by clamp studies) and at least two of the following criteria:
1) Waist-to-hip ratio >0.90 in men or >0.85 in women
2) Serum triglycerides \geq 1.7 mmol/l or HDL cholesterol <0.9 mmol/l in men and <1.0 mmol/l in women
3) Blood pressure \geq 140/90 mmHg
4) Urinary albumin excretion rate >20 μ g/min or albumin-to-creatinine ratio \geq 30 mg/g

2) Does the treatment of the metabolic syndrome differ from the treatment of its individual components?

3) What additional work should be done to improve our current knowledge of the metabolic syndrome?

Clarity of the existing definition

Table 1 shows the ATP III and WHO definitions of the metabolic syndrome. These definitions raise three important issues. First, some of the criteria used for defining the syndrome are ambiguous or incomplete (26–28). For example, it is unclear whether the blood pressure definition is systolic pressure \geq 130 mmHg and diastolic \geq 85 mmHg or whether it is either \geq 130 mmHg or >85 mmHg. It is also not defined whether a patient with hypertension who is now normotensive meets the blood pressure criterion, nor is it specified how blood pressure should be measured, e.g., supine, sitting, mean of two measurements. Given that there is no widespread agreement on the method for measuring waist circumference, it is also unclear how that factor should be determined. Does a patient previously diagnosed with IFG, but who now has normal glucose levels because of modest weight loss, meet the ATP III glucose criteria?

Such ambiguities affect the sensitivity

and specificity of the diagnosis and have undoubtedly led some physicians to diagnose the metabolic syndrome in patients who would not be labeled as such by other providers. The impact of a false-positive or a false-negative diagnosis has not been reported.

Second, it is apparent that the definitions of the syndrome differ in the criteria listed. For example, microalbuminuria is listed in the WHO criteria but not in the ATP III; insulin resistance (as measured under hyperinsulinemic-euglycemic conditions) is relevant for WHO but not for ATP III. And while only an elevated fasting plasma glucose value is considered important in the ATP III definition, the WHO criteria recognize any measure whatsoever of insulin resistance. Although it would promote better understanding of the justification for the criteria selected, no review of the clinical evidence for inclusion or exclusion criteria for either of the two definitions of the syndrome has been published to date.

Third and finally, the originally stated rationale for the criteria is that the syndrome components are associated with insulin resistance (26,27). But, as discussed below, there is considerable doubt whether all patients with the metabolic syndrome are indeed insulin resistant. More recently, a review of the ATP III definition (28) broadened the etiological basis for the syndrome from insulin resistance alone to include "obesity and disorders of adipose tissue," as well as a "constellation of independent factors that indicate specific components of the metabolic syndrome." However, it remains unclear why some factors associated with the latter two categories of abnormalities have not been included in the definition.

The fact that there are cut points for the various risk factors implies that values above the specified thresholds are associated with excess risk, yet the rationale for the specific cut points, as opposed to higher or lower values, has never been delineated. Laaka et al. (33), in a study conducted in men with the metabolic syndrome, showed that CVD and overall mortality was more consistently increased using a waist circumference criterion of 102 cm rather than 94 cm. Other investigators (34) found that reducing the threshold for IFG from 6.1 to 5.6 mmol/l did not materially change the hazard ratio (HR) for risk of coronary heart disease (CHD), though it did increase the number

of individuals identified. Other components of the syndrome show a continuous relationship with CVD risk (35). Although the thresholds defining the syndrome are generally derived from other well-established guidelines, we found no study that systematically examined the impact of all the metabolic syndrome thresholds on the risk of CVD, nor did we find a study that sought to optimize the positive predictive value of the definition by changing the cut points of the risk factors.

Some of the criteria (e.g., waist circumference, HDL) have sex-specific cut points, implying that the relationship between the risk factor level and outcomes differs between the sexes. However, we found no evidence that warrants establishing the sex-specific cut points used in the criteria as they relate to CVD risk. It is, for example, not known whether the same intra-abdominal fat mass carries a different risk in men than in women. An analogous argument can be made regarding whether cut points should vary according to race and ethnic groups.

There is ample evidence to show that CVD risk is a function of the criteria cited in the definitions of the metabolic syndrome, but it is unjustified to assume that the optimal predictive power would be obtained by arbitrary dichotomies. Risk is a progressive function of, for example, hyperglycemia and hypertension and cannot simply be regarded as present or absent, depending on whether thresholds are exceeded or not.

Although the WHO and ATP III definitions generally identify the same individuals, important differences have been found (36,37). Ford and Giles (36) showed that in the NHANES (National Health And Nutrition Examination Survey), a representative sample of the adult U.S. population, about the same proportions were identified as having the syndrome by the WHO or ATP III criteria (25.1 vs. 23.9%, respectively). However, ~15–20% of individuals were classified as having the syndrome by one definition but not the other, with equal discordance. Meigs et al. (37) determined the prevalence of the syndrome, defined by ATP III or WHO criteria, in a population of non-Hispanic whites and Mexican-American subjects in San Antonio and in subjects participating in the Framingham Offspring Study. Although the syndrome was common in these populations (affect-

ing 20–30%), more Mexican-American men were classified as having the syndrome using the WHO definition, whereas the ATP III criteria classified more Mexican-American women. Depending on the sex and ethnicity of the populations, the prevalence of metabolic syndrome varied up to 24% between the two definitions.

The question of how to define a syndrome (i.e., what factors comprise the syndrome) rests in large part on the purpose of the construct. A syndrome can be defined on the basis of its ability to predict (a) future adverse event(s). Such a definition implies that the risk associated with having the syndrome is greater than the sum of its parts, and that the factors included have greater predictive power than do other combinations. Alternatively, if the syndrome purports to identify factors related to a unifying pathological process (e.g., insulin resistance/hyperinsulinemia), then the definition should include all the factors clearly associated with that underlying pathophysiology, such that there is little ambiguity regarding the etiology of the clustering. If the etiology is unclear, it becomes much more difficult to decide what factors to include in the definition, since the word “cluster” itself can be ambiguous.

In the case of the metabolic syndrome, the existing definition attempts to bridge both constructs and, as will be pointed out in the following two sections, does not succeed very well with either.

Relationship between CVD risk and the metabolic syndrome

Many studies have shown that patients diagnosed with the metabolic syndrome, by either the ATP III or WHO definition (or by their modifications), have more prevalent CVD or are at greater risk of developing it (33,38–50). In these studies, the increased CVD risk in patients with the syndrome ranged from 30 to 400%; this wide variation is probably due to the population studied, the precise definition of the syndrome adopted, and the length of follow-up.

There are three notable exceptions to the large body of evidence documenting the adverse impact of the metabolic syndrome. One is a study by Bruno et al. (51) conducted in 1,565 elderly diabetic subjects from the Italian town of Casale Monferrato, who were followed for a median of 8 years. At baseline, the prevalence of

the metabolic syndrome was 76%, and those with the syndrome had HRs for all-cause and CVD mortality that were no different from those of subjects without the syndrome. With frank diabetes of long duration, the incremental risk attributable, for example, to raised triglycerides or low HDL, is likely to be “swamped” by the presence of diabetes itself (48). The fact that subjects were, on average, much older (mean age at baseline: 69 years) than in virtually all other studies, and that hypertension was highly prevalent in the cohort may have masked the detrimental effects of the syndrome. Another study was conducted in nondiabetic American Indians (52) and showed a nonsignificant HR for risk of CVD in those with the syndrome. The small number of events that occurred during the follow-up period, as well as several other factors reviewed by the authors, could have contributed to their borderline results. Finally, the presence of the metabolic syndrome in a cohort of women with suspected CVD who had no angiographically significant coronary artery disease did not result in an increased 4-year risk of CVD, whereas the presence of the syndrome resulted in significantly higher risk in those who were angiographically positive (53).

Three studies have examined whether the difference in prevalence between the two definitions affects the predictive power for subsequent development of CVD (33,37,49). Two of these found the ATP III definition to be a slightly better predictor of all-cause and cardiovascular mortality (49) or CHD (37), whereas one (33) showed that the WHO definition more consistently predicted CVD and all-cause mortality. The fact that all three studies made modifications to one or both of the definitions, and that they included populations with dissimilar baseline characteristics, precludes drawing any conclusion as to which definition is superior.

Nonetheless, individuals with metabolic syndrome, however defined, have a much higher CVD risk than subjects without the syndrome. This conclusion is not surprising, since the individual components of the syndrome have long been known to be major cardiovascular risk factors (54–59). Thus when they occur simultaneously, it is logical that adverse outcomes should be more likely (60–62).

ATP III uses the term metabolic syndrome to imply that certain risk factors are associated with each other, and that

insulin resistance is the primary cause (27,28). They identify six components of the metabolic syndrome as “underlying,” “major,” and “emerging” CVD risk factors (28). However, some risk factors associated with insulin resistance in each of those categories are not included in the definition of the syndrome. For example, physical inactivity is omitted as an underlying risk factor, while obesity is included. Family history, sex, and age are major CVD risk factors that do not enter into the definition, but hypertension is included. Some emerging risk factors associated with insulin resistance, e.g., certain proinflammatory and prothrombotic markers, are not included, but elevated triglycerides and glucose intolerance are. Interestingly, although the latter four were designated “metabolic risk factors” and a “component of the metabolic syndrome,” only elevated triglycerides and glucose intolerance are included in the official list of components (28). The lack of any standardized methodology or rationale for how the definition was constructed, or can be modified, hampers its optimization and utility.

It is not known whether the substitution or addition of any other well-known, conventional CVD risk factor(s) would improve the predictive value of the syndrome. In studies demonstrating that metabolic syndrome was associated with higher CVD risk (33,38–50), this excess risk remained after adjustment for other conventional risk factors. This would suggest that if other risk factors are included in the definition, the predictive value of the syndrome may improve. However, we found no study that examined the impact of substituting another CVD risk factor for one already included in the definition. The issue of whether the risk factors act synergistically has also not been analyzed.

Conversely, there are many studies suggesting that relatively new indexes related to both insulin resistance and CVD may also be useful predictive tools (or useful additions to the syndrome definition). Since it is now well accepted that inflammation plays a major role in atherogenesis (63), it is not surprising that markers of inflammation might be used to predict CVD events. One such marker, C-reactive protein (CRP), has been studied in great detail, and has been found to be an independent CVD risk factor (64–68) and an independent marker of insulin resistance (69–72). Three large popula-

tion studies examined the relationship between CRP, the metabolic syndrome, and incident cardiovascular events (68,73,74). In all three, CRP was a strong independent predictor of events, and its predictive value was equal to that of the metabolic syndrome. In the two studies (68,73) that dichotomized CRP levels (above and below 3.0 mg/dl), the age-adjusted relative risk of future events was no different in subjects with high CRP but without the metabolic syndrome than it was in subjects with low CRP and with the metabolic syndrome. However, in subjects with high CRP levels plus the metabolic syndrome, the relative risk of events virtually doubled from that found with either parameter alone, indicating that CRP might be a valuable addition to the definition of the syndrome.

Rutter et al. (74) also found that CRP and the metabolic syndrome were independent risk factors, but in contrast to the two other reports, combining CRP and metabolic syndrome did not improve the predictive value of either used alone. Reilly et al. (75) also found that CRP did not add significantly to the metabolic syndrome, but their study did not include CVD outcomes. It is unclear why some studies show great value when CRP is added, while others do not. The discrepant results have not, however, deterred some investigators from advocating that CRP be included in the definition of the metabolic syndrome (76).

There is also an association between other markers of inflammation and insulin resistance/hyperinsulinemia (70,72), as well as inflammation and obesity (77–79), leading some investigators to conclude that inflammation is integrally related to the components of the metabolic syndrome (76,77,80). CRP is also strongly associated with adipose-derived cytokines including interleukin-6 and tumor necrosis factor α (81), and is more likely to be elevated in obese insulin-resistant, but not obese insulin-sensitive, subjects (71). Because obesity (particularly in the visceral compartment) is associated with insulin resistance, and these adipose-derived inflammatory markers have been linked to dyslipidemia, hypertension, and insulin action (70,72), there is a heightened interest in markers from adipose tissue that are predictive of CVD (81).

One such marker is adiponectin. It is now well established that there is a strong

and consistent inverse association between adiponectin and both insulin resistance and inflammation (70,82,83). In addition, adiponectin is also inversely associated with other CVD risk factors such as blood pressure, LDL cholesterol, and triglycerides (84,85). Moreover, several studies have shown adiponectin to be a strong (inverse) independent risk factor for CVD (86–89).

Several other molecules have also been found to be closely associated with insulin resistance, metabolic syndrome risk factors, and the risk of CVD. These include plasminogen activator inhibitor (90–92) and fibrinogen (91–94).

All told, therefore, many candidate markers could be included in the metabolic syndrome. In combination with other markers related to CVD and insulin resistance, more research may lead to a clearer understanding of the etiology of the syndrome and hence to a definition that has strong (or stronger) CVD predictive value.

Some investigators have compared the predictive value of the metabolic syndrome with that of the Framingham risk prediction model. For example, a recent post hoc analysis of the placebo-treated groups in the 4S (Scandinavian Simvastatin Survival Study) and AFCAPS/TexCAPS (Air Force/Texas Coronary Atherosclerosis Prevention Study) trials (47) showed that the increased event rate in subjects with the metabolic syndrome remained significant after adjustment for the Framingham 10-year risk score (which uses both dichotomized and continuous variables), suggesting that the syndrome carries risk not captured by Framingham risk scoring. It should be noted, however, that this analysis omitted diabetes (or any other measure of glucose intolerance) from the metabolic syndrome definition, thereby requiring patients to meet three of the remaining four factors to qualify and removing what may be a critical criterion from the definition. This modification may have biased their findings. Also, they dichotomized the Framingham score (i.e., >20% risk vs. \leq 20%), so a precise determination of the predictive ability of Framingham versus metabolic syndrome could not be determined.

In contrast, Wilson et al. (95), using data from Framingham, found no advantage in risk assessment above the Framingham algorithm (i.e., age, sex, smoking, blood pressure, total chole-

terol, diabetes, HDL cholesterol) when some of the unique metabolic syndrome factors (obesity, triglycerides) were added or substituted. Further, when taking an elevated blood glucose level out of the metabolic syndrome definition, the 10-year risk for CHD did not achieve the threshold for ATP III's CHD risk equivalent (27), suggesting that glucose intolerance is a critical component contributing to the predictive power of the syndrome. Additional evidence for the greater predictive value of the Framingham scoring system has been provided by Stern et al. (96) in a study of the Hispanic and non-Hispanic whites who participated in the San Antonio Heart Study ($n = 2,570$) and were free of diabetes and CVD at baseline and followed for 7–8 years. Their analysis showed that the Framingham score had significantly higher sensitivity for predicting events than the presence of the metabolic syndrome, and when used in combination, the predictive value did not improve. In a multivariate analysis for predicting CVD, using a model that incorporated the Framingham equation and the metabolic syndrome, the former had an HR of 7.9 (95% CI 5.3–11.7) compared with 1.5 (1.0–2.2) for the latter, confirming the superiority of the Framingham equation. Expressed differently, they found that the metabolic syndrome predicts CVD with a sensitivity of 55% and a false-positive rate of 22%, whereas the Framingham risk score had a significantly higher sensitivity (69%) when the false-positive rate was held to 22%. In another study that compared receiver operating characteristic curves (which denote the effectiveness of an assay or test), the metabolic syndrome provided identical risk prediction to that achieved by the Framingham score (34).

In the studies reviewed so far, a person was diagnosed with the metabolic syndrome if he or she had any three or more of the five criteria (Table 1). (To meet the WHO definition, three of five possible criteria must be present, one of which is mandatory.) Thus, there are 16 possible combinations that will meet the ATP III definition of the syndrome and 11 for the WHO definition. Do all these combinations portend the same CVD risk?

This question has not yet been answered, and may never be, since an extremely large population that includes sufficient numbers of people with each combination of criteria would have to be

followed for many years. There are studies, however, that partially address this issue. Malik et al. (48) reported that, compared with individuals with no risk factors, those with one to two syndrome factors had an HR of 2.1 for CHD mortality and 3.5 if they had the full syndrome (i.e., three to five risk factors). Other investigators (34,73,97) also found that the risk for CVD increased with the number of factors present.

Other studies, using multivariate analysis, have shown that the individual risk factors comprising the syndrome each carried a different odds ratio for predicting prevalent CHD, incident CHD, or CVD mortality. In addition to hyperglycemia, low HDL cholesterol and hypertension usually conferred a significantly greater risk compared with the presence of obesity or high triglycerides (44,49), although McNeill et al. (34) found that only an elevated blood pressure and low HDL cholesterol were significantly associated with CHD. Golden et al. (98) assessed carotid intimal-medial thickness (IMT) related to 57 combinations of six factors related to insulin resistance. In their analysis, 29 of the 57 groupings were associated with excess carotid IMT. The difference in excess IMT between individuals with two, three, or four factors was minimal, but those with five or six factors showed an appreciable increase in excess IMT. Hypertension and hypertriglyceridemia were the two factors that most contributed to the excess IMT. Taken together, these studies suggest that not all combinations that lead to the diagnosis of the syndrome convey equal risk, although the actual hierarchy of risk predictability for each of the syndrome combinations remains unknown.

The studies also illustrate another likely shortcoming of the current approach to diagnosing the syndrome. Both the ATP III and WHO definitions weigh each risk component equally, yet it is clear that some risk factors included in the definition have greater CVD predictive importance than others. This fact is highlighted in other algorithms used to predict CVD risk using regression coefficients to assign different weights to risk factors (95,99), and it is apparent from studies that examined the risk of CVD in persons with one or two components of the syndrome versus three or more (97). For example, the disproportionate impact of glucose intolerance

(IFG/IGT/diabetes) in the syndrome definition was demonstrated by Malik et al. (48) in their study on NHANES II participants. They observed that diabetes alone conveyed a much greater risk of CHD (HR = 5), CVD (3.6), or overall mortality (2.1) than the presence of the metabolic syndrome (3.5, 2.7, and 1.5, respectively) according to definitions that included subjects with and without IFG/IGT/diabetes. Adding preexisting CVD to diabetes was an even more powerful predictor of mortality (11.3, 7.9, and 2.9, respectively) over the 13-year follow-up period. Similarly, Stern et al. (100) showed that, among patients with prevalent CVD, the excess risk for all-cause and CVD mortality associated with the metabolic syndrome was entirely driven by the inclusion of diabetes in the definition, and once diabetes was controlled for, the presence of the metabolic syndrome no longer conferred excess risk. Finally, Hunt et al. (49) also showed that the presence of IFG (>6.1 mmol/l) alone was a stronger predictor of CVD or all-cause mortality in a general population than either the syndrome as a whole or any of its individual components. These reports raise the question of why glucose intolerance (particularly diabetes) is included in the definition of the metabolic syndrome, since it appears to account for most, if not all, of the CVD predictive value.

Since the metabolic syndrome does not include all known CVD risk factors, it should convey risk independently of other conventional risk factors (e.g., LDL, age, smoking, family history); however, the proportion of the global CVD risk captured by the syndrome is unknown. It would be invaluable to know, from a list of all known CVD risk factors, the hierarchy of combinations with the highest predictive value. Then, a true comparison between the metabolic syndrome, other models using different risk factors (72,73), or perhaps some new combination would tell us what is the best CVD predictive model.

Another important question is the degree to which the presence of the syndrome in itself adds to CVD prediction beyond the contribution of the component risk factors. In other words, is the whole greater than the sum of its parts? If the syndrome conveyed no additional risk beyond its components, then clinicians would have little reason to treat cases of the syndrome rather than ad-

addressing each risk factor as it was identified. At least five studies address this issue. One is the study by Golden et al. (98) reviewed above, which examined all possible combinations of six factors related to insulin resistance. Individuals with any four-, five-, or six-component groupings had no greater excess IMT than the sum of the same factors taken separately. The cross-sectional studies by Alexander et al. (44) and Yarnell et al. (101) showed that the impact of the syndrome on CVD was greatly attenuated in a multivariate analysis by controlling for certain of its components, thereby suggesting that the whole is not greater than its parts. Also, in a prospective study of diabetic and nondiabetic subjects free of CVD and followed for an average of 11 years, the risk of incident CHD associated with the syndrome was no greater than that explained by the presence of its components (34). Finally, in the secondary analysis of the prospective WOSCOPS (West of Scotland Coronary Prevention Study), Satter et al. (73) showed that the metabolic syndrome was not a significant predictor of CHD when adjusted for its component factors in a multivariate model. Thus, these studies suggest that the syndrome itself conveys no greater information than the sum of its component risk factors.

In summary, if the metabolic syndrome is a multicomponent risk factor for CVD, the components of which may be more or less strongly linked with insulin resistance, neither the ATP III nor the WHO definitions consider the many other similarly related CVD risk factors, such as age, physical activity, or history of CVD events. Some of these and other risk factors are included in the Framingham algorithm (95), which has been shown to be in general a more powerful tool for predicting future CVD events. However, even the Framingham risk equation does not include important CVD risk factors (e.g., previous CVD events, family history), and has been shown to be much less useful than other risk equations in predicting future CVD events in people with diabetes (102–104). Other newly identified CVD risk factors have been shown to be strongly associated with insulin resistance and CVD, but it is unclear if they should be added to the syndrome and given equal or greater weight than the current components.

Because the criteria for the syndrome will capture individuals with frank dis-

ease (e.g., diabetes, hypertension, proteinuria, clinical CVD), as well as with far milder forms of the same conditions, it is likely that there is a risk gradient for CVD events among people with the syndrome. Thus, the definition will capture a spectrum of severities, and it is highly likely that a person who satisfies the diagnostic criteria with risk factor levels just over the cut point will have a much lower CVD risk than another individual with the same combination but higher risk factor levels. This problem stands in contrast to the Framingham (95) and UKPDS (U.K. Prospective Diabetes Study) (99) risk models, in which the spectrum of severities is weighted, so that it is clear who may be at greater or lesser risk.

Finally, people with diabetes and clinical CVD should be excluded from the definition of metabolic syndrome, since their inclusion provides no additional clinically useful information to guide treatment beyond current guidelines.

Does the syndrome reflect a single underlying pathological process?

When the concept of the syndrome was first proposed, insulin resistance and/or hyperinsulinemia were initially thought to be the primary etiological process, since most subjects with the syndrome had one or the other abnormality. Consistent with the primary adverse outcome of the metabolic syndrome (CVD), many studies (11,105–116), but not all (117–119), have shown that insulin resistance or hyperinsulinemia is a CVD risk factor. Although the reasons for the disparity in results have been debated elsewhere (120–122), it is important to note that the measurement of insulin itself, whether to determine the presence of insulin resistance or hyperinsulinemia, is fraught with errors and inconsistency (123,124) and that the methods used vary considerably from laboratory to laboratory. Thus, many subjects who are insulin resistant or hyperinsulinemic in one institution may not be classified as such when tested in another setting, because the measurement of insulin is not standardized. Moreover, insulin-mediated glucose disposal varies six- to eightfold in apparently healthy, nondiabetic men (125), absolute insulin concentrations vary widely (16,126), and there is no absolute criterion with which to classify individuals as being insulin resistant or insulin sensitive.

Very recently, however, Stern et al.

(35) analyzed the results of insulin clamp measurements in a large number of nondiabetic and diabetic subjects. An analysis of the distribution of insulin-mediated glucose disposal, as measured by the clamp, showed evidence of bimodality, and the optimal cut point classified 33% of nondiabetic subjects and 93% of diabetic subjects as insulin resistant. Some investigators have chosen a cut point based on the relationship between insulin resistance and the frequency of adverse outcomes; however, their sample sizes were very small (114,127).

Although many nondiabetic adult subjects with a wide range of age and body mass are hyperinsulinemic and insulin resistant (~50%), ~25% are insulin resistant but without hyperinsulinemia and the same proportion are hyperinsulinemic but without insulin resistance (126). The relationship between insulin resistance and hyperinsulinemia, reviewed in detail by Ferrannini and Balkau (126), is complex, and although both parameters will capture individuals with the metabolic syndrome, each makes an independent contribution to the clinical findings associated with the syndrome (128,129). Thus, hyperinsulinemia and insulin resistance each partially identify different groups of individuals, they each cluster with various CVD risk factors, and individuals with the metabolic syndrome may have either, both, or none of these “insulin-related” abnormalities.

Even though most people who have the metabolic syndrome are insulin resistant, as discussed earlier, this is probably due to the fact that almost all people with an elevated blood glucose value (the most prevalent characteristic among those with the syndrome) are insulin resistant. Conversely, many studies have shown that only a minority of nondiabetic individuals with insulin resistance (but who may have IFG or IGT) will have the metabolic syndrome. In a study of 260 nondiabetic, overweight/obese individuals, McLaughlin et al. (130) found that 78% of those with metabolic syndrome were insulin resistant, but only 48% with insulin resistance had metabolic syndrome. Liao et al. (131) reported that 39% of 74 overweight/obese nondiabetic adults were insulin resistant, and 31% with insulin resistance met ATP III criteria. Moreover, the ATP III–negative/insulin-resistant individuals had CVD risk factor profiles that were significantly worse than the ATP III–

negative/insulin-sensitive group, implying that many presumably high-risk individuals will not be identified by screening for metabolic syndrome. Also, they found that the sensitivity, specificity, and positive predictive value for predicting insulin resistance in nondiabetic individuals with three or more metabolic syndrome traits were 20, 92, and 50%, respectively, denoting poor clinical utility. Cheal et al. (132) determined that 16% of 443 healthy, nondiabetic subjects were insulin resistant and/or positive for metabolic syndrome, with a sensitivity, specificity, and positive predictive value for metabolic syndrome as predictor of insulin resistance of 46, 93, and 76%, respectively. This study also showed that very few of the possible three-, four-, or five-factor combinations occurred in the nondiabetic patients classified with the syndrome.

As noted above, most investigators use the phrase “insulin resistance” to describe the hallmark of the metabolic syndrome, even though insulin resistance or hyperinsulinemia may not be present in subjects with the syndrome. Furthermore, the extent to which an elevated risk of CVD is due to insulin resistance itself, versus isolated hyperinsulinemia, or versus some other related factor is still unclear. Some investigators turn to studies on the relationship of insulin resistance to the etiology of atherosclerosis (133–136) and to the underlying etiology of type 2 diabetes (137) as evidence that insulin resistance is the more important abnormality (138). Unfortunately, we could find no study that has compared insulin resistance, as measured by sensitive and specific methods (e.g., euglycemic insulin clamp), with fasting insulin levels to determine which variable is a better predictor of cardiovascular events in nondiabetic individuals.

Perhaps most important is the fact that the multitude of reports relating insulin resistance to any risk factor or CVD are all association studies. It may well be that there is a more basic defect that can result in insulin resistance and/or other CVD risk factors. The uncertainty surrounding the causative factor(s) that give rise to the syndrome has prompted many investigators to perform a “factor analysis” as an approach toward understanding the fundamental cause of the clustering. Factor analysis is a multivariate correlation method that seeks to explain the relation-

ship between a set of observed variables (in this case the clinical features of the metabolic syndrome) and a smaller set of unknown underlying variables (e.g., the etiology) termed “factors.” The factors ideally represent unique, independent domains that have not been directly measured but give rise to the observed variables. Thus an array of CVD risk variables, occurring more than would be expected by chance (25), may be related to one underlying factor, thereby supporting a single unifying etiology, or they may be related to two or more factors, suggesting a relationship between the underlying domains. Alternatively, more than one underlying factor suggests a more complex etiology, and often the analysis cannot account for all the variability, thereby providing additional evidence that more than one physiological process underlies the expression of the observed correlations.

Although factor analysis was developed some time ago (139–141), there is no standardized methodology and its use and interpretation is often problematic (142). Nonetheless, factor analysis is an intriguing exploratory, somewhat subjective and qualitative approach toward understanding the root cause(s) of the metabolic syndrome. The results of many of these studies are shown in Fig. 1.

As shown, all of the studies (24,33,38, 143–149) found that at least two and usually three to four factors underlie the overall correlation between risk variables, even though different factor analysis methods were used. Shen et al. (150), using “confirmatory factor analysis,” which provides some advantages and is complementary to exploratory factor analysis, proposed a correlated four-factor model that nicely depicts the major factors related to the syndrome (Fig. 2). Thus, it is clear that more than one distinct pathophysiological process underlies the clinical expression of the syndrome, but insulin resistance/hyperinsulinemia appears related in some fashion to most. Also, and equally important, all the factors can account for no more than about two-thirds of the total variance observed in the clustering, suggesting that the syndrome may be even more complex than that inferred by factor analyses. These studies, therefore, again call into question the appropriateness of implying that a handful of CVD risk factors have a common underlying pathophysiology.

To the extent that insulin resistance/

hyperinsulinemia is itself a cardiovascular risk factor, many investigators have sought to identify ways to better and more simply identify persons with insulin resistance apart from the diagnosis of the metabolic syndrome. Indeed, easier, simpler, and at least equally effective ways are now available to identify insulin-resistant subjects. Laws and Reaven (151) showed that a high triglyceride and low HDL cholesterol concentration is a strong indicator of insulin resistance, and when expressed as a ratio (130), the optimal cut points in overweight/obese individuals resulted in a sensitivity, specificity, and positive predictive value for insulin resistance of 64, 68, and 67%, respectively. The addition of extra measurements (i.e., blood glucose, blood pressure, BMI) was less sensitive (52%) but more specific (85%) in predicting insulin resistance. Thus, both the metabolic syndrome and this abbreviated index have only a moderate likelihood of identifying the person with insulin resistance. More recently, Stern et al. (35) collected euglycemic clamp (the gold standard for measuring insulin resistance) data from >2,000 lean and overweight/obese individuals and used a decision tree classification scheme to develop decision rules for identifying insulin-resistant individuals based on common clinical measurements. In their study, decision rules based on either homeostasis model assessment of insulin resistance and BMI or BMI and family history of diabetes had sensitivities and specificities in the range of 80%. Thus, if the aim is to identify insulin resistance in either lean or overweight/obese subjects, there are simpler ways to do so than by identifying those with the metabolic syndrome.

In summary, the attempt to define the metabolic syndrome as the result of a single (or even major) unifying pathophysiological process, e.g., insulin resistance, is problematic. Although insulin resistance or hyperinsulinemia is clearly an important feature of the syndrome, many other as yet unidentified factors are also important. Insulin resistance may simply be one of many abnormalities linked to a more fundamental, truly unifying pathophysiology. Moreover, the definition of the syndrome includes risk factors that are only weakly related to insulin resistance or hyperinsulinemia (e.g., blood pressure) and excludes others that are closely related (e.g., CRP, adiponectin). Finally, although many clinical values are signifi-

Study (Ref)	Population Characteristics	Number of Factors Identified	Description of Factor*	Unexplained Variance
Meigs et al (24)	Non-diabetic Framingham Offspring. N=2458	3	1. HII/R, ↓Gluc., obesity, ↑Tri, ↓HDL 2. HII/R, ↑Gluc., 3. BP	~37%
Gray et al (143)	Non-diabetic and diabetic American Indians N=4228	3	1. HII/R, ↑Gluc., obesity 2. BP 3. Dyslipidemia	~30%
Lempiainen et al (38)	Non-diabetic Finnish N=1069	4	1. HII/R, ↑Gluc., besity, ↑Tri 2. ↓HDL -C 3. BP 4. ↑Total -C	~47%
Lehto et al (144)	Diabetic Finish N=902	4	1. Obesity, gender 2. HII/R, obesity, ↑Tri 3. ↑Total -C 4. BP, age	Not available
Sakkinen et al (145)	Non-diabetic Americans N=32	4	1. BP 2. Obesity, HII/R 3. HII/R 4. ↑Total -C, ↑Tri	~30%
Maison et al (146)	Non-diabetic and diabetic UK population N=937	3	1. BP, obesity 2. HII/R, ↑Gluc. 3. Lipid	~30%
Lakka et al (33)	Non-diabetic Finnish men N=1209	4	1. "Metabolic Syndrome" (includes obesity, HII/R, ↑Tri.) 2. Inflammation/procoagulation, smoking 3. ↓HDL -C 4. ↓LDL-C, family history	~46%
Hanley et al (147)	Non-diabetic IRAS study participants N=1087	2	1. Obesity, HII/R, ↑Gluc. 2. BP	~46%
Wang et al (148)	Non-diabetic and diabetic Chinese N=1239	4	1. BP 2. Obesity, HII/R 3. HII/R 4. ↑Total -C, ↑Tri	~40%
Ford (149)	Non-diabetic and diabetic representative samples of U.S. males N=3410	3	** 1. ↑Tri, ↓HDL -C, HII/R, obesity 2. BP 3. Glucose, albuminuria	~40%

* For the purposes of this table, only those variables correlation >50% (i.e. "factor load") to each factor are tested.

** Factor loadings for women (N=3458) were different: factor 1 had no lipid component; factor 3 had lipids, but no proteinuria

Symbols: HII/R=hyperinsulinemia and/or insulin resistance, BP=blood pressure, ↑Tri = elevated triglycerides, ↓HDL -C = decreased HDL cholesterol, ↓LDL -C = decreased LDL cholesterol, obesity = elevated BMI or increased waist hip ratio or increased waist circumference, ↑Gluc.= elevated fasting or 2hr-OGTT glucose

Figure 1—Results from analyses of CVD risk variables.

Table 2—Treating the metabolic syndrome

Characteristic	Patient A	Patient B	Patient C
Waist circumference (cm)	110	103	114
Triglycerides (mmol/l)	1.62	0.34	1.34
Systolic/diastolic blood pressure (mmHg)	170/95	135/90	125/80
HDL (mmol/l)	1.06	1.68	1.29
Fasting plasma glucose (mmol/l)	5.28	6.1	7.22
LDL (mmol/l)	4.65	1.81	1.94
Other	Patient smokes; taking no drugs	None; taking no drugs	Patient had previous MI 4 years ago; taking a β blocker and aspirin

All three patients are 50 years old, white males, with no symptoms of CVD and no family history of diabetes, CHD, or stroke. They present for a routine physical examination. Based on the findings above, what factor(s) should be treated and what is the goal of therapy?

cantly associated with insulin resistance/hyperinsulinemia, the strength of their association (which has not exceeded a correlation coefficient of 0.7 and is usually 0.3–0.6) is not particularly impressive.

Although the studies reviewed above question the hypothesis that insulin resistance/hyperinsulinemia is the major un-

derlying pathological process, it must be remembered that the clustering of CVD risk factors has been well documented, and thus it is likely (but not assured) that there is some underlying etiology. It may be that insulin resistance is simply a risk factor not unlike other metabolic syndrome components, and that the underlying etiology for some of the syndrome

factors is related to abnormalities in visceral adipose tissue (152) or an altered inflammatory state; other factors may be associated with the cluster because they relate indirectly to one of its components.

Treatment of patients who have the metabolic syndrome

When a person is identified as having the metabolic syndrome, it is not always clear what should be the treatment of choice or the goals of therapy. In a post hoc analysis of the 4S, Pyorala et al. (153) found that simvastatin reduced CVD events to the same degree in nondiabetic patients with or without the metabolic syndrome. We found no other controlled trial results examining the value of a specific pharmacological therapy on patients with the metabolic syndrome. It should again be

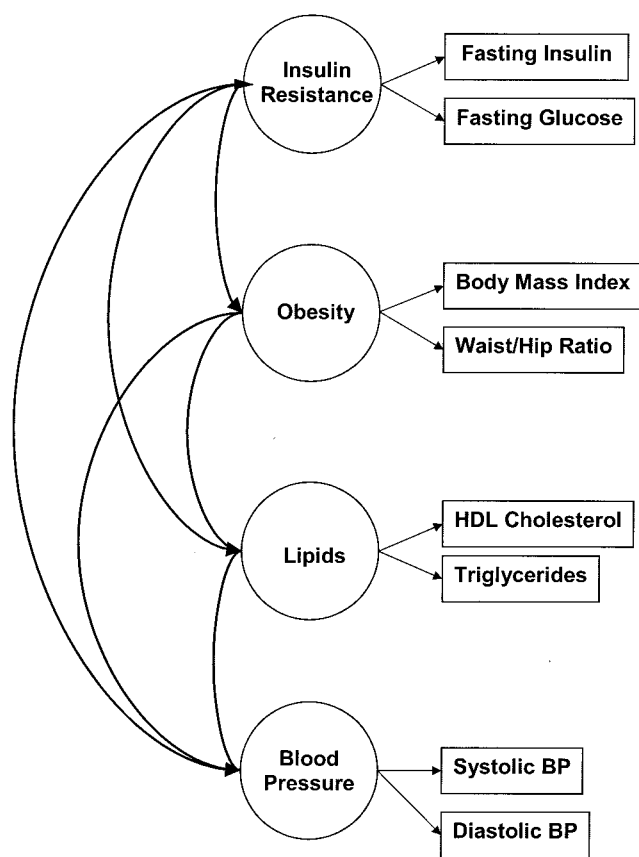


Figure 2—Factor structure of the metabolic syndrome. Adapted with permission from Shen et al. (150).

Table 3—Summary of concerns regarding the metabolic syndrome

- 1) Criteria are ambiguous or incomplete. Rationale for thresholds are ill defined.
- 2) Value of including diabetes in the definition is questionable.
- 3) Insulin resistance as the unifying etiology is uncertain.
- 4) No clear basis for including/excluding other CVD risk factors.
- 5) CVD risk value is variable and dependent on the specific risk factors present.
- 6) The CVD risk associated with the “syndrome” appears to be no greater than the sum of its parts.
- 7) Treatment of the syndrome is no different than the treatment for each of its components.
- 8) The medical value of diagnosing the syndrome is unclear.

remembered that the current definitions of the syndrome capture many people with frank disease (e.g., diabetes, hypertension, clinical CVD), as well as those who have milder conditions or “normal” values that, while qualifying them for the diagnosis of the syndrome, are not high enough to warrant specific therapy. Thus, it is important to distinguish the approach and value of treating various metabolic syndrome combinations. However, no studies have examined the value of tailoring the treatment algorithm to the particular combination of criteria that resulted in the diagnosis of the syndrome.

Many of the syndrome characteristics are acknowledged to be closely related to insulin resistance or hyperinsulinemia and their correlates. Yet at the same time it is unknown whether treating “insulin resistance” itself would be of value in preventing CVD in all, or a subset, of metabolic syndrome patients. Although some studies suggest that the newer insulin-sensitizing agents (i.e., thiazolidinediones) improve glycemic control, reduce CVD risk factors, and generally result in a beneficial CVD profile (154–161), at the time of writing no controlled studies have shown that thiazolidinediones reduce CVD events even in the setting of diabetes, although one major trial that will help address this issue will be reported shortly (i.e., the PROactive [Prospective Pioglitazone Clinical Trial in Macrovascular Events] study); studies using metformin are equivocal. Since thiazolidinediones affect a wide variety of parameters, even favorable trial results will not prove that reducing insulin resistance itself is the critical factor. Moreover, even if positive trial evidence were to emerge relatively soon, other important issues have been identified (162), such as how will insulin resistance be measured, what is the cut point to begin treatment, and is the target population only patients similar to those included in the trials? Thus, our knowledge base is such that we cannot yet contemplate drug treatment for insulin resistance, let alone the metabolic syndrome.

Other modifiers of insulin resistance include weight reduction and exercise, and they have been identified as key elements in the treatment of the metabolic syndrome (27,31,32). But they are also key elements in the treatment of all components of the syndrome when they occur in isolation (27,163,164). Clinicians,

therefore, should neither rely on, nor require a diagnosis of, metabolic syndrome to prescribe and encourage what is now a fundamental tenet of medicine—weight maintenance (or reduction), exercise, and a healthy meal plan.

The conundrum of treating the metabolic syndrome is illustrated in the case studies shown in Table 2. Patient A is obese and has severe hypertension; the likely treatment is lifestyle modification (exercise and weight loss) to include smoking cessation counseling, an antihypertensive drug, and aspirin. Patient B is obese, has prehypertension and prediabetes; his likely treatment is aggressive lifestyle modification and aspirin. Patient C is also obese, has diabetes and a history of acute myocardial infarction; his treatment would also be aggressive lifestyle modification with perhaps a glucose-lowering agent and aspirin.

Does it matter that only patient B has the metabolic syndrome (by ATP III criteria)? If that were immediately apparent, would the treatment change? Who will have the next CVD event, patient A, B, or C? We submit that at this time, the diagnosis of the metabolic syndrome itself, or the lack of it, adds virtually nothing to the treatment of one or more CVD risk factors in a given patient. If, however, it were known that insulin resistance causes CVD and there was a sensitive way to measure and treat it, or if we knew the relative risk of CVD among various configurations of risk factors, or if we knew that a combination of risk variables found at borderline disease levels elevates one’s CVD risk considerably, then knowing that a patient has the metabolic syndrome could also be useful. But at present, none of those criteria have been fulfilled.

These case studies also raise additional concerns. For patients with type 2 diabetes, a comprehensive set of evidence-based prevention services should be provided (e.g., regular eye and foot exams). In patients who are diagnosed with the metabolic syndrome and who also have diabetes, the importance and treatment of the diabetes may, in contrast to what might be expected, take a backseat relative to the syndrome, with patients or their doctors possibly neglecting or overlooking essential factors of diabetes management. Also, for patients who fail to meet the necessary number of criteria to diagnose the syndrome (e.g., only two of the factors are present), the absence of the

syndrome may divert attention away from addressing risk factors that are present.

Further research needed

In the preceding sections, we identified many unanswered questions related to the metabolic syndrome. Many are unresolved fundamental issues that raise considerable doubt about the construct itself.

All this should prompt an aggressive research agenda, and based on what is highlighted by this review as missing, should give pause to those in medical practice or in industry. Importantly, there have yet to be any controlled randomized trials, or systematic, prospective, longitudinal studies that carefully document the clinical value of treating a disease label now being given out to a huge number of our population.

At the very least, we suggest that the following is urgently needed:

- 1) A critical analysis of how the syndrome is defined. Are all risk factors equally important? Do some combinations (of two, three, or four factors) portend greater CVD risk than others?
- 2) A definition of the syndrome, in which variables have defined lower and upper cut points or that uses continuous variables in a multivariate score system (e.g., Framingham/UKPDS risk engine).
- 3) An evidence-based analysis assessing the rationale and value of adding (or replacing) other CVD risk factors (e.g., age, CRP, family history, a direct measure of insulin resistance) to the definition.
- 4) An assessment of CVD risk in subjects with combinations of intermediate phenotypes only (e.g., IFG/IGT, mildly elevated triglycerides, blood pressure 120–140 mmHg) and who have, or don’t have, insulin resistance or hyperinsulinemia.
- 5) An aggressive research agenda to identify the underlying cause(s) of the CVD risk factor clustering.

Conclusion

As a construct that denotes risk factor clustering, the metabolic syndrome has been a useful paradigm. That is, it draws attention to the fact that some CVD risk factors tend to cluster in patients so predisposed. The teaching point implied by the term, and explicitly stated by ATP III, is that the identification of one of the risk variables in a patient should prompt a search for others.

At the time these relationships were first documented, the advent of a phrase

to capture the prevalence of the clustering was likely a helpful reminder to clinicians, and certainly served to open a wide avenue of research into its etiology and impact. Now, however, it has taken on meaning and import greater than is justified by our current knowledge. Indeed, only recently the International Diabetes Federation developed yet a new definition, which suggests that the key element is central obesity (165). In their paper, however, no data were reviewed indicating the impact or benefit derived from their new definition.

As shown in this review (Table 3), there is much fundamental, clinically important, and critically missing information about the metabolic syndrome to warrant a more serious examination of whether medical science is doing any good by drawing attention to (166) and labeling millions of people with (36) a presumed disease that does not stand on firm ground. In particular, patients with diabetes or clinical CVD should be excluded from the case definition of metabolic syndrome, as they provide no additional understanding of risk or treatment recommendations that are otherwise not currently recommended.

Medical science usually defines a syndrome as an “aggregate of symptoms and signs associated with any morbid process, and constituting together the picture of the disease” (167). The specific signs and symptoms are usually caused by a unifying underlying pathology, and their combination confers a risk that is different from the sum of the parts. In almost every way—from the term itself, to the underlying pathophysiology, to the variables included or excluded, to the value of making the diagnosis, and finally to its treatment—the metabolic syndrome requires much more study before its designation as a “syndrome” is truly warranted and before its clinical utility is adequately defined. We hope this reappraisal gives pause to the growing use of the term, as well as stimulates urgently needed research.

Consequently, in addition to the research suggested above, our recommendations to clinicians are:

- 1) Adults with any major CVD risk factor should be evaluated for the presence of other CVD risk factors.
- 2) Patients with CVD risk variables above the cut point for normal should receive counseling for lifestyle modification, and

at cut points indicative of frank disease (e.g., blood pressure >140/90 mmHg, fasting plasma glucose \geq 7.0 mmol/l), treatment should correspond to established guidelines (27,163,168).

3) Providers should avoid labeling patients with the term “metabolic syndrome,” as this might create the impression that the metabolic syndrome denotes a greater risk than its components, or that it is more serious than other CVD risk factors, or that the underlying pathophysiology is clear.

4) All CVD risk factors should be individually and aggressively treated.

5) Until randomized controlled trials have been completed, there is no appropriate pharmacological treatment for the metabolic syndrome, nor should it be assumed that pharmacological therapy to reduce insulin resistance will be beneficial to patients with the metabolic syndrome.

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