

Expert Commentary

The Metabolic Syndrome: Perhaps an Etiologic Mystery but Far From a Myth -- Where Does the International Diabetes Federation Stand?

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Setting the Scene: The American Diabetes Association/European Association for the Study of Diabetes Shot Across the Bow of the Metabolic Syndrome

Although the underlying cause of the metabolic syndrome remains controversial, the ultimate importance of the syndrome is that it helps identify individuals at high risk for cardiovascular disease (CVD) and type 2 diabetes.^[1] This is clearly a major benefit of its widespread recognition and acceptance. Nevertheless, a recent position paper jointly sponsored by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)^[2,3] has questioned the existence and utility of the metabolic syndrome. Kahn and colleagues,^[2,3] on behalf of these organizations, have suggested that the time has come for a critical appraisal of the metabolic syndrome. They claim that there is confusion about the syndrome. If this is so, then they have further added to this confusion with a long and tortuous exposé of its supposed problems. Their article, we believe, indicates a number of misconceptions and inconsistencies that we would like to address. Many of the issues that they raise have been covered in the recent International Diabetes Federation (IDF) Consensus,^[4] which they barely quote.

We recognize the importance of debate; however, the appearance of this initiative on behalf of 2 of the world's leading regional diabetes organizations raises questions of motive and timing. Are the criticisms part of a "turf protection" scenario^[5] or do they have a valid scientific basis?

In recent years, there has been increasing interest in the metabolic syndrome by the American Heart Association, the American College of Cardiology, the International Atherosclerosis Society, and other specialist groups in diabetes, insulin resistance, hypertension, and cardiology worldwide, effectively removing it from the province of pure diabetes. Thus, far from the metabolic syndrome being an offshoot of type 2 diabetes, one could consider that type 2 diabetes is but one of several manifestations of the metabolic syndrome.^[1]

The ADA/EASD position paper^[2,3] was released in a burst of publicity, and the issue received considerable media exposure. The authors of the ADA/EASD statement direct their main criticisms at earlier definitions, namely, those of the World Health Organization (WHO)^[6] and the National Cholesterol Education Program Adult Treatment Panel III (ATP III).^[7] Some investigators in the diabetes field, after embracing the concept wholeheartedly for about 15 years, are having "second thoughts" about the metabolic syndrome, not unreasonable in a rapidly changing field, providing that there are cogent arguments to do so. Several of the authors of the statement have been vigorous proponents of the metabolic syndrome. As recently as 2 years ago, Zachary Bloomgarden, MD,^[8] reported on a presentation by Professor Ferrannini, one of the ADA/EASD paper authors, at the Endocrine Society's 85th Annual Meeting:

Glycemic abnormality predicts hypertension and increased blood pressure predicts glycemic abnormality, with hyperinsulinemia an important additional predictive factor, Ferrannini noted, further suggesting the usefulness of the concept of metabolic syndrome. He concluded that 'the syndrome itself is atherogenic,' but suggested that insulin resistance causes atherosclerosis via the 'intermediate phenotypes' of increased blood pressure, dyslipidemia, and abnormal glycemia, suggesting that therapy not be primarily directed at insulin resistance. The metabolic syndrome exists, and he asserted, 'It predicts itself so it's not just an innocent cluster.' Whether it is directly atherogenic is not clearly established, and whether it can be prevented is an important therapeutic question.

Unfortunately, the joint ADA/EASD statement^[2,3] was published before the detailed report of the IDF Consensus report on the metabolic syndrome appeared in print.^[9] Nevertheless, the key features of the IDF report were available and summarized on the IDF Web site. It is noteworthy that 2 of the main authors of the ADA/EASD statement were on or represented on the IDF group and signed up to their conclusions.^[4] In this commentary, we respond to the ADA/EASD statement in the light of deliberations of the IDF panel.

The Metabolic Syndrome: Setting the Scene

As co-chairmen of the recent IDF Consensus publication on a new global definition of the metabolic syndrome,^[4] we welcome the debate engendered by the ADA and EASD. However, one must view the situation in terms of the world health challenge. A cluster of key cardiovascular risk factors, namely, abdominal obesity, dyslipidemia, hyperglycemia, and hypertension, are now one of the major public health challenges worldwide.^[1] Although the association of several of these risk factors has been known for more than 80 years, the clustering received only limited attention until 1988,

when Dr. Gerald Reaven^[10] described syndrome X: insulin resistance, hyperglycemia, hypertension, low high-density lipoprotein (HDL) cholesterol, and raised very low-density lipoprotein (VLDL) triglycerides. Reaven^[10] actually omitted obesity from the cluster, but it is now recognized as an essential component -- especially abdominal (visceral) obesity.^[1,4] The syndrome is now widely recognized in cardiovascular, diabetes, and renal circles.

The Metabolic Syndrome -- Development of Concept and Definition

In the past few years, there has been a growing interest in the phenomenon of risk-factor clustering that increases the "global risk" for atherosclerotic CVD. One pattern of this clustering is exemplified by the metabolic syndrome, labeled as such because the CVD risk factors that make up this pattern appear to be of metabolic origin. This clustering of metabolic risk factors has perhaps been best articulated by several distinguished diabetes investigators,^[9-15] who noted that most people who exhibit this risk pattern also have insulin resistance. This constellation of CVD risk factors has been given a number of names, such as deadly quartet, syndrome X, and insulin resistance syndrome.^[16]

Just as the metabolic syndrome has borne a variety of names, numerous definitions have surfaced since the first attempt to standardize criteria by WHO in 1998. WHO proposed a more descriptive "definition" (or clinical criteria) for the metabolic syndrome.^[7] Its purpose was to give utility in clinical practice to what was increasingly recognized by the scientific community as a multidimensional risk factor for both CVD and type 2 diabetes. We agree with Kahn and colleagues^[2,3] on the ambiguity of the various definitions, but they result from the healthy process of evolution in relation to clinical utility. Therefore, criticism of the WHO and ATP III definitions as being inconsistent ignores the fact that ATP III was developed to improve on the earlier WHO definition and to make it more clinically useful.^[8] This is, of course, part of the normal pattern of development in any rapidly evolving field.

With obesity prevalence rising worldwide,^[17] it has become evident that a particular pattern of risk factors is common in overweight and obese individuals, particularly those with central adiposity. The latter may be a major driving force behind the metabolic syndrome.^[1] This view has led to some controversy as to whether insulin resistance or visceral obesity is the major cause of the metabolic syndrome.^[1] The fact that obesity is probably the major cause of insulin resistance in the general population complicates this debate. Regardless of the precise metabolic pathways involved, both central obesity and insulin resistance are common risk conditions underlying the metabolic syndrome.^[1,13]

The Metabolic Syndrome: The Cardiovascular Interests

The concept of the metabolic syndrome has attracted much interest in the cardiovascular field. Cardiologists have recognized that the clustering of metabolic risk factors (metabolic syndrome) is a pattern of risk increasingly observed in persons exhibiting CVD. Although the metabolic syndrome does not encompass all CVD risk factors, it nonetheless appears to be a dominant picture of risk in a large portion of the population with CVD. For this reason, the National Cholesterol Education Program ATP III introduced the metabolic syndrome as a coequal partner of elevated low-density lipoprotein (LDL) as a risk factor for CVD.^[8] Underlying this initiative was the recognition of the need for clinicians to identify and deal with the risk factors emerging from the dramatic rise in the prevalence of obesity in the United States.

ATP III further simplified the clinical criteria developed by WHO in order to make the concept of the metabolic syndrome "user-friendly" for clinicians. This move saw enhanced worldwide interest in the metabolic syndrome by providing both clinicians and epidemiologists with simple measures that can be used in both research and clinical settings. Moreover, cardiologists have been particularly receptive to incorporating the syndrome into their prevention strategies. In the United States, the American Heart Association has joined the National Heart, Lung, and Blood Institute to better delineate considerations of diagnosis and clinical management of the syndrome in their educational programs.^[14,15]

Contemporaneously, there has been a strong movement among cardiovascular investigators to emphasize *global risk* that includes a summation of the CVD risk factors, including type 2 diabetes. The Framingham Heart Study took the lead in developing algorithms that incorporate all of the risk factors for the assessment of absolute risk, ie, the likelihood of developing cardiovascular events over a defined period of time (eg, 10-year risk).^[16] Other investigators^[17,18] have proposed modified risk-assessment tools that use similar risk-factor sets, but which are not necessarily identical to those of Framingham.

The Pharmaceutical Industry: Innocent Bystanders?

In the debate on the relevance of the metabolic syndrome, there have been claims that the pharmaceutical industry invented the syndrome to boost their own profits.^[19] The editorial accompanying the ADA/EASD statement on its publication in *Diabetologia* noted the recommendation in the IDF report that the thiazolidinediones be used, highlighting only one of a number of agents suggested, which included metformin, acarbose, orlistat, and new compounds, such as incretin mimetics, dipeptidyl peptidase IV inhibitors, protein tyrosine phosphatase 1B inhibitors, and the endocannabinoid receptor blocking agents. The history of development of knowledge about the syndrome discussed here and elsewhere^[1] does not provide any support for that claim. Certainly, one result of the interest generated in the metabolic syndrome in cardiovascular and diabetes circles is that the pharmaceutical industry is responding with research initiatives to develop drugs that target several or all of the components of the metabolic syndrome. These drugs are in an early stage of development, but some promising leads have been forthcoming.^[20] Indeed, IDF, like many others, strongly recommends the use of lifestyle modification as the first line of treatment. Should appropriate

drugs be developed, then of course they should be used if they benefit people by preventing or delaying the development of CVD and diabetes.

The 2005 IDF Global Definition of the Metabolic Syndrome

In 2005, the IDF set forth modified clinical criteria for the metabolic syndrome.^[4,9] These are designed for global application in clinical practice and represent modifications of the WHO and ATP III definitions. The IDF definition has a greater emphasis on abdominal (visceral) obesity as the core feature of the syndrome, making it an essential requirement for diagnosis. The other variables employed by ATP III are unmodified. The other simple clinical measures employed by ATP III are modified only slightly; and when they are present in persons with abdominal obesity, the syndrome is defined. The IDF took an important step forward by defining abdominal obesity for different ethnic populations defined by waist circumference measurements based on epidemiologic data from various ethnic populations.^[21,22] This extension adds universality and worldwide applicability to the concept of the metabolic syndrome. The claim by Kahn and colleagues^[2,3] that there is no basis for these ethnic-specific cutoffs displays an alarming lack of awareness of the literature -- and of the outside world!

Addressing the Issues Raised by the Joint ADA/EASD Statement

The authors of the ADA/EASD statement have raised a number of specific questions^[2,3] that we address:

- The clarity of the existing definition and whether it is justifiable to employ the term "syndrome" to the clustering of metabolic risk factors;
- Whether the metabolic syndrome is a valid indicator of cardiovascular risk;
- Whether there is enough known about the pathogenesis of the syndrome to justify including it in clinical practice;
- Whether the WHO and ATP III criteria are the best ways to identify the syndrome in clinical practice; and
- Whether cardiovascular prevention requires anything more than treatment of the individual risk factors.

1. The Clarity of the Existing Definition and Whether It Is Justifiable to Employ the Term Syndrome to the Clustering of Metabolic Risk Factors

Nomenclature. The ADA/EASD group seems confused about the definition of a syndrome. A well-accepted definition is: "The group or recognizable pattern of symptoms or abnormalities that indicate a particular trait or disease."^[23] The clustering of metabolic abnormalities that have provoked this debate appear to be fundamentally related to obesity and insulin resistance, but, because no firm underlying cause has been identified, clearly it fits the accepted definition of a syndrome and not a disease state.

We admit freely that the clustering of metabolic risk factors has posed a problem in nomenclature. A variety of terms have been suggested, as described above. More recently, dysmetabolic syndrome,^[24] hypertriglyceridemic waist,^[13] cardiometabolic syndrome,^[25] or simply cardiometabolic risk have been added to the burgeoning variations of nomenclature. It is likely that the competition and disagreements about naming will continue! However, Kahn and colleagues^[2,3] ask whether the clustering represents a syndrome. If a syndrome represents a clustering of disease-related conditions, then certainly the term is appropriate. The term syndrome has long been used in the diabetes field (eg, syndrome X, insulin resistance syndrome, and the metabolic syndrome),^[9, 26-28] and is increasingly employed by the cardiovascular field. Therefore, to challenge its usage after many years of widespread acceptance appears to be a retrograde maneuver to say the least.

Definition. The ADA/EASD group^[2,3] states that the metabolic syndrome is imprecisely defined. In the manner in which the definition has been arrived at, their confusion is again apparent. The IDF first lists several features of the syndrome, which include abdominal body fat distribution, insulin resistance, atherogenic dyslipidemia (elevated triglyceride, low HDL, small LDL particles, and elevated apolipoprotein B), elevated blood pressure, a proinflammatory state, and a prothrombotic state.^[6] There is a general agreement in both the cardiovascular and diabetes fields that these are general features of the metabolic syndrome.^[4,6,7] A simple definition would be "a clustering of closely related risk factors for cardiovascular disease and diabetes."

But we suspect that when Kahn and colleagues^[2,3] state that the syndrome is imprecisely defined, they mean that *diagnostic criteria* are not adequately defined to apply them in clinical practice. On that basis, would they argue that the definition of diabetes mellitus, as defined by the ADA as a fasting blood glucose concentration of 126 mg/dL (7.0 mmol/L) or higher, or its random glucose criterion^[29] is any more precise? Let's see what they say about the ADA's recent definition of "prediabetes."^[24] Is this more precise? (See below for further discussion.)

For a condition such as the metabolic syndrome in which there is a clustering of risk factors, precise clinical criteria are difficult to propose. For this reason, ATP III took 2 steps in its effort to achieve clinical utility. First, it restricted the clinical diagnosis to simple clinical measures: waist circumference, fasting triglycerides, HDL cholesterol, blood pressure, and fasting glucose. This ensured that clinicians almost anywhere in the world can readily identify affected individuals. In addition, it used thresholds for each of these measures that had already been defined by expert panels.^[8] The IDF employed the same approach by maintaining ATP III thresholds for all measures except waist circumference.^[4] For this parameter, thresholds were modified according to ethnic population, which similarly had been established for these populations by expert panels based on published data.^[21,22]

Thresholds by necessity are arbitrary, but in the ATP III^[7] and IDF clinical definitions,^[4] their use has the virtue of simplicity. By analogy, because cholesterol, blood pressure, glucose, and other risk factors are continuously related to CVD and diabetes risk, there is no compelling reason to identify specific thresholds for any of these other than for utility. This is exemplified by the actions of the ADA itself, in that expert panels of the ADA periodically modify their thresholds for the definition of diabetes.^[29] The same reasoning can be applied to the definition of the metabolic syndrome. Therefore, as the current thresholds employed for clinical diagnosis are based on contemporary recommendations of accepted expert panels, Kahn and colleagues^[2,3] are stretching credibility with the claim that the current clinical definition of the metabolic syndrome is imprecise.

Indeed, it is ironic that the ADA/EASD experts^[2,3] question the definition of the metabolic syndrome, considering the recent stance of the ADA on *prediabetes*. Despite the ADA's attraction to this term, prediabetes is not a new term. It was introduced in the context of classification in the 1965 WHO Report on Diabetes Mellitus.^[30] The WHO report stated,^[30] "This is a term that can be used retrospectively when reviewing a case," and that the term should be used for the period of time from conception to the diagnosis of an episode of diabetes. "However," the report continued, "prediabetes should exclude impairment of glucose tolerance by definition."

The WHO statement is mutually exclusive of the recommended ADA usage. Yet, according to the ADA, prediabetes is a simplifying diagnosis that can be applied to people who have either impaired glucose tolerance or impaired fasting glucose. By labeling people with prediabetes, the ADA implies that they will eventually develop diabetes, but, in reality, progression to diabetes is by no means certain. So it is inappropriate to use the term when there is only a 50% chance of developing diabetes in the next 10 years. It also excludes others with as great a risk of developing diabetes, eg, those with a first-degree family history of the disorder. Moreover, it could be argued that using the term prediabetes in clinical practice creates a medical condition out of a risk factor for diabetes -- with all the accompanying psychosocial stress that this implies.

Surely, this is the same argument that they use to demolish the metabolic syndrome! The ADA justification is that warning individuals that they have prediabetes is a wake-up call for the need for lifestyle changes. ADA panelists decided that adding the term prediabetes to the medical vocabulary is justified for preventive purposes even though it increases the number of persons with a "medical condition" by millions. Now, can anyone explain to us how this ADA stance is different from the rationale for identifying persons with the metabolic syndrome who are at increased risk for CVD and type 2 diabetes in the years ahead?

2. Is There Enough Known About Pathogenesis of the Syndrome to Justify Including It in Clinical Practice?

Several underlying factors appear to contribute to the development of the metabolic syndrome.^[1] The ADA/EASD statement acknowledges that the clustering of these CVD risk factors may imply a common underlying etiology. This in itself may be a good justification for using the concept of a syndrome. There are, however, more disputes about how they interact than about what they are. These factors interact in complex ways that are not entirely understood and are reviewed in detail elsewhere.^[1] Kahn and colleagues^[2,3] nonetheless asked whether the metabolic syndrome should be elevated to a medical condition when the causation is incompletely understood. Do they have knowledge that we do not have about the precise etiology of type 1 and/or type 2 diabetes? Although the same thing could be said of many other medical conditions, the IDF report has outlined in some detail the factors contributing to the development of the metabolic syndrome.^[4] These can be briefly reviewed.

The primary underlying causes of the metabolic syndrome were identified as central obesity and insulin resistance. Central obesity almost certainly is a major cause of insulin resistance.^[1] Because of the strong connection between central obesity and the risk factors of the metabolic syndrome, the IDF Consensus identified an increase in waist circumference as a necessary component of the clinical diagnosis of the metabolic syndrome.^[4] Some individuals or ethnic groups may be unusually insulin-resistant and develop the metabolic syndrome despite levels of abdominal obesity below diagnostic thresholds, but such persons are relatively uncommon, less than 5% in the recent Australian national survey (Shaw J, et al., unpublished).

In recent years, much has been learned about how excess body fat contributes to the metabolic syndrome. The role of excess circulating free fatty acids derived from adipose tissue in the causation of insulin resistance in muscle and the liver has been known for many years.^[1] More recent research has documented the production of a large number of other adipokines that seemingly promote the risk factors of the metabolic syndrome.^[31-33] These include inflammatory cytokines (eg, tumor necrosis factor-alpha and interleukin [IL]-6), plasminogen activator inhibitor-1, leptin, adiponectin, and angiotensinogen, among others. The release of the "protective" adiponectin by adipose tissue is reduced in obese persons. It seems clear that adipose tissue metabolism is central to the development of the metabolic syndrome.^[1] Nonetheless, there are several modifying factors that affect the expression of the syndrome. Some of these include advancing age with loss of muscle mass, physical inactivity, endocrine dysfunction, and genetic factors that modify the

response to underlying risk factors. Regardless, the complexity of the pathogenesis of the metabolic syndrome does not justify eliminating it as a higher risk condition for CVD and type 2 diabetes, just as the lack of knowledge on the pathogenesis of type 2 diabetes does not rule it out as a disease state!

3. Is the Metabolic Syndrome a Valid Indicator of Cardiovascular Risk?

Predicting Risk for Cardiovascular Disease. The 2 major clinical outcomes of the metabolic syndrome are CVD and type 2 diabetes.^[1] The relative risk for CVD varies somewhat among different reports. However, as a general rule, the risk from the metabolic syndrome for major CVD events is approximately twice as high as for those without the syndrome.^[1] For type 2 diabetes, the metabolic syndrome confers an approximate 5-fold greater risk.^[1] Finally, type 2 diabetes itself is accompanied by increased risk for CVD, and most of this increased risk is conferred by the concomitant risk factors of the metabolic syndrome. In other words, type 2 diabetes alone, independent of the metabolic syndrome, carries much less risk for CVD than when the metabolic syndrome is concomitantly present.^[34]

It cannot be overemphasized that the metabolic syndrome is not an *absolute risk predictor*. This misconception has seemingly led the ADA/EASD experts to question whether the metabolic syndrome has clinical utility as a risk predictor. To predict absolute risk for individuals, sometimes called *global risk*, it is necessary to include all of the risk factors related to the outcome. For CVD, these include age, sex, total cholesterol, HDL cholesterol, triglyceride, blood pressure, body mass index, glucose status, tobacco usage, and family history, depending on the risk-assessment algorithm employed.^[35-37] The metabolic syndrome is an incomplete predictor of absolute risk, and to question it for this reason represents a significant misunderstanding of its use in clinical practice.

The prime purpose of absolute risk prediction is to identify persons whose 10-year risk for CVD is high enough to justify introducing drug therapy for risk reduction. The most important drugs for this purpose currently are cholesterol-lowering drugs and low-dose aspirin. The metabolic syndrome does not serve as a tool to define absolute risk for decisions about preventive drug therapy. The clinical utility of the syndrome for risk assessment lies in its ability to readily identify individuals who are at a relatively high, long-term risk for *both* CVD and diabetes. All such individuals should undergo absolute risk assessment to determine whether they are candidates for preventive drug therapies. But once found to have the metabolic syndrome, they deserve more intensive intervention with lifestyle approaches. This distinction between different forms of risk and their significance is blurred by the authors of the ADA/EASD statement.^[2,3]

Is the Risk the Sum of the Parts? Kahn and colleagues^[2,3] are not alone in asking whether the risk accompanying the metabolic syndrome is "greater than the sum of its parts." There are 3 answers to this question.

First, statistical epidemiologists differ as to whether multiple risk-factor conditions best fit an additive model or a multiplicative (synergistic) model. If the latter holds, then the risk that is associated with multiple risk factors is greater than the sum of the individual risk factors. If the former is true, the risk equates to the sum of that conveyed by the individual risk factors. A sizable body of experts favors the multiplicative model. Included among these are the Framingham Heart Study investigators.^[38] If this model holds, then the risk accompanying the metabolic syndrome is indeed greater than the sum of its parts.

Second, the metabolic syndrome contains risk factors that are not commonly identified in clinical practice, eg, prothrombotic state and proinflammatory states.^[1] Even if the appropriate model is an additive one, the risk is greater than its readily identifiable parts.

Finally, some of the so-called "independent" risk factors, eg, blood pressure and HDL cholesterol, subsume some of the risk contained in the "hidden" risk factors of the metabolic syndrome. Thus, it cannot be assumed that all of the risk accompanying the metabolic syndrome can be reversed by lowering blood pressure and raising HDL levels, the so-called independent risk factors associated with the syndrome.

Kahn and colleagues^[2,3] suggest that C-reactive protein could be a "valuable" addition to the definition of the syndrome. This requires the research that both they and the IDF call for. However, the more "sophisticated" the definition becomes, the more it loses the primary objective of supplying a simple clinical tool to define those at greatest risk, particularly in poor developing nations where the metabolic syndrome is on an exponential rise.

4. Does Cardiovascular Prevention Require Anything More Than Treatment of the Individual Risk Factors?

Clinical trials reveal that blood pressure-lowering drugs reduce risk less than predicted from epidemiologic studies, and to date, there are no robust clinical trials to document that HDL-raising therapies will significantly reduce the risk for CVD. Thus, the prescription of Kahn and colleagues^[2,3] to just treat the independent risk factors of the metabolic syndrome does not ensure the degree of risk reduction that is implied. In addition, their arguments neglect the fact that the summation of the individual CVD risk factors account for only 50% of cardiovascular risk, and current therapies reduce risk by only 50%. This means that there is a 50% "residual risk" that cannot be explained by the risk factors. If we are to cut into the additional CVD risk, we need to affect other factors. The metabolic syndrome is one of the components of residual risk, and is the best additional target to the standard risk factors. The big question for the future is whether pharmacologic therapy will be found to target the metabolic syndrome specifically. In the meantime, however, we know that lifestyle modification will improve the many components of the syndrome.

5. Are the WHO and ATP III Criteria for the Syndrome the Best Way to Identify the Syndrome in Clinical Practice?

Kahn and colleagues,^[2,3] on behalf of the ADA and EASD, question whether the metabolic syndrome is clinically useful. Without doubt, because of the increased prevalence of the underlying causes of the metabolic syndrome (eg, obesity and sedentary lifestyles), the clustering of risk factors portends an enormous increase in CVD and type 2 diabetes worldwide.^[1] The fact that diabetes itself, when combined with the metabolic syndrome, is associated with greater CVD risk represents a great challenge for the management of patients with diabetes. At the same time, it also has significant public health implications for the prevention of CVD and type 2 diabetes. It is likely to provide a useful practical tool that reminds healthcare professionals of the metabolic consequences of obesity, and identifies individuals at risk for CVD and diabetes who are likely to benefit from (lifestyle) interventions. The clustering of CVD risk factors is a call to action for preventive medicine, as it is clearly not satisfactory just to treat the major risk factors once they have reached categorically increased levels. This would be a prescription for widespread use of drug therapy in primary prevention and would be a huge burden on economically developed societies, and an even greater burden on developing nations.

Few would disagree that it is better and more economical to detect the clustering at an earlier stage of development and to introduce lifestyle interventions to prevent progression to a more advanced risk. This is a task for both public health and clinical sectors of the healthcare system. An additional benefit of the new IDF criteria is that the initial screening test is simple and low-cost, ie, measurement of waist size.

Summary

The IDF, and clearly many other international groups, regard the metabolic syndrome as a viable and useful concept in clinical medicine. Debate is always welcomed as a stimulus to new understanding, but criticism should have a valid platform, something that is not always apparent in the ADA/EASD statement^[2,3] and the supporting editorial in *Diabetologia*.^[19] The IDF report does raise a series of questions that need more research.

The IDF's new clinically oriented definition of the metabolic syndrome^[4] is an important new approach that health professionals can employ to facilitate detection and intervention for risk reduction in one common pattern of multifactorial risk for both CVD and type 2 diabetes. Most important is the need to promote lifestyle interventions to reduce long-term risk. But at the same time, absolute risk assessment is required to assist clinicians in making decisions about drug therapies for prevention in higher risk patients. It is important to note that the American Heart Association and National Heart, Lung, and Blood Institute have just published a scientific statement on the metabolic syndrome that contains an updated ATP III classification.^[39] In the updated ATP III classification, increased waist circumference is not deemed a necessity if the 3 other risk-factor criteria are present. The ATP III definition also allows for the lower waist circumference risk thresholds, particularly for Asian Americans. This updated ATP III version and the new IDF criteria^[9] identify essentially the same individuals as having the metabolic syndrome.^[39] Thus, not only are ATP III and the IDF criteria virtually identical; their recommendations for clinical management are also identical.

The ADA/EASD attempt to disregard the metabolic syndrome will only confuse health professionals at all levels. The utility of the syndrome as a public health initiative has been put at risk by a statement that has come "out of the blue" and does not reflect the past intellectual and constructive contributions of some of its individual authors! Debate is always welcomed, but misconstrued criticism can only harm the initiatives of others in the CVD, diabetes, and other related fields who were making progress in raising awareness of patients toward risk-factor clustering. The ADA/EASD stance may also hinder research and fund-raising, baffle the public, and weaken its confidence in clinical scientists as well as delay treatment advances. This reflects a total lack of foresight and vision.

Perhaps the last words should be with Richard N. Fogoros, MD,^[5] writing as "Dr Rich" on a Web site:

Dr Rich suspects that what the ADA/EASD are doing here is engaging in turf protection. The concept of the metabolic syndrome has non-specialists paying a lot more attention to conditions related to diabetes (specifically, to insulin-resistance and related conditions) than they ever have in the past. Indeed, in recent years, non-diabetes-specialists are engaging numerous active clinical trials aimed at insulin-resistance conditions (i.e., metabolic syndrome.) One suspects that the relatively small ADA, viewing the recent efforts of the American Heart Association and American College of Cardiology in this regard, is beginning to feel like Netscape did in the mid-1990s when Microsoft decided to enter the browser business. This, of course, is pure speculation, but *something* must explain the otherwise nearly inexplicable effort to quash the metabolic syndrome.

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