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# The Metabolic Syndrome: Management and inclusion into clinical practice

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## INTRODUCTION

In recent years, several organizations have proposed that the metabolic syndrome be introduced into clinical practice as a multidimensional risk condition for both atherosclerotic cardiovascular disease (ASCVD) and type-2 diabetes[1]. This proposal generally has been well received. Recently, however, Kahn et al[2] questioned whether evidence for the existence and characteristics of the metabolic syndrome is sufficiently developed to support its inclusion in clinical practice. Several critical issues were broached in their article. The present commentary will attempt to briefly respond to the issues raised.

## RISK FACTOES OF METABOLIC SYNDROME

Five risk factors of metabolic origin (atherogenic dyslipidemia, elevated blood pressure, elevated glucose, aprothrombotic state, and a pro inflammatory state) commonly cluster together [1]. This aggregation is frequently observed in clinical practice, and it has been convincingly documented in prospective studies by cluster analyses [3]. Risk factor clustering cannot be explained by chance occurrence alone. Thus, if the metabolic syndrome is defined as multiple risk factors that are metabolically interrelated, then the syndrome certainly exists.

## APPROPRIATENESS OF THE TERM "METABOLIC SYNDROME"

The commonly observed aggregation of metabolic risk factors has gone by several different names: syndrome X, insulin resistance syndrome, pre-diabetes, metabolic syndrome, dysmetabolic syndrome, plurimetabolic syndrome, cardio metabolic syndrome, dyslipidemic hypertension, hypertriglyceridemic waist, and deadly quartet[1,4,5,6,7,8]. No single term has been universally accepted, and terminology likely will continue to be a topic of some disagreement. Kahn et al have misgivings regarding whether the clustering of risk factors deserves the name "syndrome," although most investigators are accepting it[2]. Among the various names, "metabolic syndrome" is widely used and broadly accepted in both cardiovascular and diabetes fields. It is a general term and does not commit to a particular pathogenesis. Consequently, it is reasonable to employ the term because of precedent and common usage. The term appears to be at least as good as any of the alternatives.

## UNITY CAUSATION OF METABOLIC SYNDROME

For reasons not entirely clear, some investigators stipulate the need for a single causation for a pathological process to be termed a "syndrome"[3]. This requirement hardly seems warranted. In fact, metabolic syndrome, along with many other syndromes and diseases, is multifactorial in origin. The pathogenesis of the metabolic syndrome can be separated into underlying causes and factors. Two tightly intertwined conditions underlie the development of metabolic syndrome. These are obesity and insulin resistance[1]. Obesity causes insulin resistance, and conversely, inherent forms of insulin resistance modify adipose tissue responses to insulin and thereby recapitulate the obese state.

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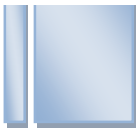


Mechanisms whereby each elicits metabolic risk factors are increasingly understood. For example, in obese subjects[9] and those with inherent insulin resistance[10], excess amounts of nonesterified fatty acids and a host of other adipokines are released into the circulation. These several factors cause ectopic lipid accumulation in liver and muscle and contribute to insulin resistance, dyslipedemia, pro thrombotic and pro inflammatory states.

When obesity occurs concomitantly with a genetic basis for insulin resistance, the metabolic syndrome is worsened. Finally, the metabolic syndrome is exacerbated by other factors: physical inactivity, advancing age, endocrine imbalance, genetic factors, and abnormalities in regulation of specific metabolic risk factors. Thus, metabolic syndrome, like most other chronic conditions (e.g. type-2 diabetes and hypertension), has a multifactorial causation; however, in fact, the pathogenesis of metabolic syndrome is better understood than that of many other recognized medical disorders. Certainly, a multifactorial etiology does not negate the syndrome's existence.

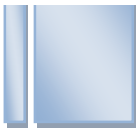
The exact mechanisms of the complex pathways of metabolic syndrome are not yet completely known. The pathophysiology is very complex and has been only partially elucidated. Most patients are old, obese, adopting sedentary life style, and have a degree of insulin resistance. Stress can also be a contributing factor. The most important factors are weight, genetics[11,12,13,14], endocrine disorders (such as polycystic ovary syndrome in women of reproductive age), aging, and sedentary lifestyle, (i.e., low physical activity and excess caloric intake)[15].There is debate regarding whether obesity or insulin resistance is the cause of the metabolic syndrome or if they are consequences of a more far-reaching metabolic derangement. A number of markers of systemic inflammation, including C-reactive protein, are often increased, as are fibrinogen, interleukin 6, tumor necrosis factor-alpha (TNFα), and others. Some have pointed to a variety of causes, including increased uric acid levels caused by dietary fructose[16,17,18]. A quarter of the world's adults have metabolic syndrome, People with metabolic syndrome are twice as likely to die from, and three times as likely to have a heart attack or stroke compared with people without the syndrome. People with metabolic syndrome have a five-fold greater risk of developing type-2diabetes. Up to 80% of the 200 million people with diabetes globally will die of cardiovascular disease, This puts metabolic syndrome and diabetes way ahead of HIV/AIDS in morbidity and mortality terms yet the problem is not as well recognized[19,20].

## METABOLIC SYNDROME AND RISK FOR ASCVD AND TYPE-2 DIABETES

Many recent reports document that the metabolic syndrome raises the risk for both ASCVD and type-2 diabetes[1]. Average relative risks are increased about two folds for ASCVD and five folds for type-2 diabetes compared with those for individuals without the metabolic syndrome. This higher relative risk translates into a high lifetime risk for both ASCVD and diabetes. Kahn et al. misunderstand the intention of introducing the metabolic syndrome [1]. It is not meant to be a risk assessment tool for short-term (10-year) risk to guide treatment of the major risk factors with drugs. The latter is best achieved by global risk algorithms such as that provided by the Framingham Heart Study. The metabolic syndrome is a simple clinical tool to identify people with a particular set of risk factors who are at higher long-term risk for both ASCVD and type-2 diabetes. Affected individuals deserve 1) lifestyle intervention (weight loss, increased physical activity, and a healthy diet) and 2) more detailed, short term risk assessment (e.g., Framingham scoring). On the basis of the latter, risk reducing drugs may be required for treatment of individual risk factors.

## METABOLIC SYNDROME AND MULKTIPLICATIVE RISK

Kahn et al specifically asked whether the risk accompanying metabolic syndrome is more than the sum of its parts. This question can be answered in at least four ways. First, risk factors are multiplicative, i.e. risk for ASCVD from risk factors rises geometrically, not linearly, as the number of risk factors increases[21]. Therefore, total risk is more than a summation of the individual risk factors. Second, several risk factors of the metabolic syndrome are hidden in routine clinical practice; examples include insulin resistance, pro thrombotic and pro inflammatory states, endothelial dysfunction, and



elevated apolipoprotein B. The risk conveyed by these factors therefore is not detected by the risk factors typically measured in the clinic. Third, some of the risks associated with the major risk factors of the syndrome, low HDL cholesterol and higher blood pressure, are confounded by these unmeasured risk factors. This is important because efforts to treat a low HDL cholesterol and blood pressure will not necessarily reduce the risk accompanying the hidden risk factors. And fourth, the metabolic syndrome is a progressive disorder that worsens over time. Thus, risk measured at any one time will underestimate the long-term risk resulting from the syndrome[21].

## RISK FACTORS

### Stress

Recent research indicates prolonged stress can be an underlying cause of metabolic syndrome by upsetting the hormonal balance of the hypothalamic-pituitary-adrenal axis (HPA-axis)[22]. A dysfunctional HPA-axis causes high Cortisol levels to circulate, which results in raising glucose and insulin levels, which in turn cause insulin-mediated effects on adipose tissue, ultimately promoting visceral adiposity, insulin resistance, dyslipedemia and hypertension, with direct effects on the bone, causing "low turnover" osteoporosis[23]. HPA-axis dysfunction may explain the reported risk indication of abdominal obesity to cardiovascular disease (CVD), type-2 diabetes and stroke[24]. Psychosocial stress is also linked to heart disease[25].

### Overweight and Obesity

Central obesity is a key feature of the syndrome, reflecting the fact that the syndrome's prevalence is driven by the strong relationship between waist circumference and increasing adiposity. However, despite the importance of obesity, patients who are of normal weight may also be insulin-resistant and have the syndrome[26].

### Sedentary Lifestyle

Physical inactivity is a predictor of CVD events and related mortality. Many components of metabolic syndrome are associated with a sedentary lifestyle, including increased adipose tissue (predominantly central); reduced HDL cholesterol; and a trend toward increased triglycerides, glucose in the genetically susceptible. Compared with individuals who watched television or videos or used their computers for less than one hour daily, those who carried out these behaviors for greater than four hours daily have a twofold increased risk of metabolic syndrome[26].

### Aging

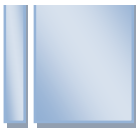
Metabolic syndrome affects 44% of the U.S. population older than age of 50 years. With respect to that demographic, the percentage of women having the syndrome is higher than that of men. The age dependency of the syndrome's prevalence is seen in most populations around the world[26].

### Diabetes Mellitus Type-2

An estimated 75% of British patients with type-2 diabetes or impaired glucose tolerance (IGT) have metabolic syndrome[27]. The presence of metabolic syndrome in these populations is associated with a higher prevalence of CVD than found in patients with type-2 diabetes or IGT without the syndrome[26]. Hypoadiponectinemia has been shown to increase insulin resistance[28], and is considered to be a risk factor for developing metabolic syndrome[29].

### Coronary heart disease

The approximate prevalence of the metabolic syndrome in patients with coronary heart disease (CHD) is 50%, with a prevalence of 37% in patients with premature coronary artery disease (age 45), particularly in women. With appropriate cardiac rehabilitation and changes in lifestyle (e.g., nutrition, physical activity, weight reduction, and, in some cases, drugs), the prevalence of the syndrome can be reduced[26].



**Lipodystrophy**

Lipodystrophic disorders in general are associated with metabolic syndrome. Both genetic (e.g., Berardinelli-Seip congenital Lipodystrophy, Dunnigan familial partial lipodystrophy) and acquired (e.g., HIV-related Lipodystrophy in patients treated with highly active antiretroviral therapy) forms of Lipodystrophy may give rise to severe insulin resistance and many of metabolic syndrome's components[26].

**Schizophrenia and other psychiatric illnesses**

Patients with schizophrenia, schizoaffective disorder or bipolar disorder may have a predisposition to metabolic syndrome that is exacerbated by sedentary lifestyle, poor dietary habits, possible limited access to care, and antipsychotic drug-induced adverse effects. It has been found that 32% and 51% of individuals with schizophrenia meet criteria for metabolic syndrome[30]; the prevalence is higher in women than in men[31].

**Rheumatic diseases**

There are new findings regarding the co-morbidity associated with rheumatic diseases. Both psoriasis and psoriatic arthritis have been found to be associated with metabolic syndrome[32]. Concerning the association of Metabolic Syndrome with history of Myocardial Infarction and Stroke, Applying National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) criteria, 10 357 NHANES III subjects were evaluated for the 5 component conditions of the metabolic syndrome: insulin resistance, abdominal obesity based on waist circumference, hypertriglyceridemia, low HDL cholesterol (HDL-C), and hypertension, as well as the full syndrome, defined as at least 3 of the 5 conditions. The syndrome was significantly associated with MI/stroke in both women and men. Among the component conditions, insulin resistance, hypertension, and hypertriglyceridemia were independently and significantly related to MI/stroke. These results indicate a strong, consistent relationship of the metabolic syndrome with prevalent MI and stroke[33].

## CLINICAL CRITERIA FOR DIAGNOSIS OF THE METABOLIC SYNDROME

Kahn et al. noted that the several proposed clinical "definitions" of metabolic syndrome create a state of confusion that interferes with using the syndrome in practice. The evolution of clinical criteria is reviewed[1]. The first tentative criteria for diagnosis were proposed only in 1998. These have now evolved and been largely harmonized in the recent update of the Adult Treatment Panel III criteria for the U.S.[1] and the International Diabetes Federation criteria[34]. The two are highly congruent (**Table 1**). Each contains five virtually identical components, three of which can confer a diagnosis.

They represent a simple way to identify individuals in clinical practice who are highly likely to have most or all features of metabolic syndrome. All people who meet either criterion deserve lifestyle intervention to reduce long-term risk for both ASCVD and diabetes and more detailed, short-term risk assessment for ASCVD to determine whether drugs are needed to treat risk factors. In diabetic subjects, oral glucose tolerance testing is an option to identify veiled diabetes or increased risk for diabetes[34].

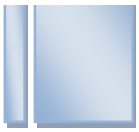
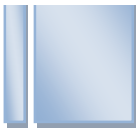


**Table 1 Comparison of diagnostic criteria for metabolic syndrome from the International Diabetes Federation (IDF) and American Heart Association (AHA)/National Heart, Lung, and Blood Institute (NHLBI)**

| IDF clinical criteria for metabolic syndrome | | AHA/NHLBI diagnostic criteria for metabolic syndrome | |
|---|---|---|---|
| Measure (central obesity plus any two of five other criteria constitute a diagnosis of metabolic syndrome) | Categorical cut points | Measure (any three of the five criteria below constitute a diagnosis of metabolic syndrome | Categorical cut points |
| Central obesity | Waist circumference ethnicity specific | Elevated waist circumference | General U.S. population: _102 cm (_40 in) in men, _88 cm (_35 in) in women; lower cut points for insulin-resistant individuals or ethnic groups (based on clinical judgment |
| Raised triglycerides | _150 mg/dl (1.7 m mol/l) or on specific treatment for this lipid disorder | Elevated triglycerides | _150 mg/dl (1.7 m mol/l) or on drug treatment for elevated triglycerides |
| Reduced HDL cholesterol | _40 mg/dl (1.03 m mol/l) in men, _50 mg/dl (1.29 m mol/l) in women or on specific treatment for this lipid abnormality | Reduced HDL cholesterol | _40 mg/dl (1.03 m mol/l) in men, _50 mg/dl (1.3 m mol/l) in women |
| Raised blood pressure | _130 mmHg systolic blood pressure or _85 mmHg diastolic blood pressure or on treatment for previously diagnosed hypertension | Elevated blood pressure | _130 mmHg systolic blood pressure or _85 mmHg diastolic blood pressure or on drug treatment for hypertension |
| Raised fasting glucose | Fasting plasma glucose _100 mg/dl (5.6 m mol/l) or previously diagnosed type-2 diabetes | Elevated fasting glucose | _100 mg/dl (5.6 mmol/l) or on drug treatment for elevated glucose |

## EXTENSION OF METABOLIC SYNDROME INTO TYPE-2 DIABETES

There has been a reluctance on the part of some diabetologists to allow a diagnosis of metabolic syndrome to carry into type-2 diabetes[2], although this proscription is by no means universally held[1,7]. Within the realm of diabetes, there appears to be ambivalence about the meaning of type-2 diabetes. Diabetes itself is defined as a fasting glucose _126 mg/dl or, alternatively, a 2-h postprandial glucose



_200 mg/dl after a 75-g glucose load or symptoms of diabetes plus casual plasma glucose concentration _200 mg/dl[35]. Furthermore, type-2 diabetes is defined as categorical hyperglycemia that is caused by a dual defect in glucose metabolism, namely insulin resistance and decreased insulin secretion. This definition of type-2 diabetes does not include the presence of other cardiovascular disease (CVD) risk factors, but it is commonly recognized that the majority of patients with type-2 diabetes carry multiple CVD risk factors[35]. A reasonable solution to this ambiguity is to maintain the accepted definition of type-2 diabetes, i.e., hyperglycemia secondary to a dual defect in glucose metabolism, and to allow metabolic syndrome to be independently identified in patients with diabetes [1,7]. The alternative, i.e., including multiple CVD risk factors in the definition of type-2 diabetes, seemingly has little support in the diabetes field. Despite this, many diabetologists seem to believe that a diagnosis of metabolic syndrome should not extend into the sphere of type-2 diabetes. The logic of this position is not clear. Even in individuals without type-2 diabetes, there is an overlap between metabolic syndrome and the condition called pre-diabetes. Again, the latter is defined by the American Diabetes Association strictly in terms of dysglycemic parameters. On the other hand, many people with categorical pre-diabetes carry multiple risk factors characteristic of the metabolic syndrome[36]. Kahn et al. reported that impaired fasting glucose, a form of pre diabetes, is present and associates with CVD and all cause mortality in a general population, at least as well as either the metabolic syndrome or any of its components(37). However, it is most unlikely that pre-diabetes is a cause of CVD to the same extent as metabolic syndrome. As a risk factor for CVD, pre-diabetes appears to be largely a marker for the atherogenic metabolic syndrome (36). By the same token, treatment of pre-diabetes with drugs to lower glucose, example metformin or thiazolidinediones, almost certainly will not reduce risk for CVD nearly as much as favorable modification of all of the metabolic risk factors. For these reasons, by the American Diabetes Association's definition, pre-diabetes is not a robust substitute for metabolic syndrome as a therapeutic target to prevent CVD.

## METABOLIC SYNDROME AND CLINICAL PRACTICE

Kahn et al. question whether the concept of metabolic syndrome has matured enough to be introduced into clinical practice. However, there are several reasons why physicians, other health professionals, and patients can benefit from using this concept in practice. First, and perhaps most importantly, recognizing the metabolic syndrome will help to focus attention on the need for lifestyle therapies to reduce all metabolic risk factors concurrently. Lifestyle therapies are a neglected part of present-day clinical management of risk. Second, the syndrome identifies patients who are at increased risk for both CVD and type-2 diabetes. This will reinforce the need for lifestyle modification to prevent both conditions.

Third, increased awareness of the possibility of metabolic syndrome changes medical perspective from a single–risk factor paradigm to one of multiple risk factors. In this regard, the presence of the syndrome calls for more refined risk assessment for both CVD and diabetes. For CVD risk, Framingham risk scoring is indicated; for diabetes risk, some authorities recommend glucose tolerance testing in those without diabetes[34]. Finally, patients with the syndrome deserve long term follow-up in clinical practice, including regular physician appointments and, ideally, medical nutrition therapy, behavior modification, and exercise training.

## THERAPEUTIC STRATEGY

One approach to treatment of the metabolic syndrome is to individually and separately treat the major risk factors (elevated LDL cholesterol, hypertension, and hyperglycemia) according to current guidelines, regardless of whether the syndrome is present[3]. This approach, even when necessary in higher-risk patients, tends to minimize the benefit of reducing all of the metabolic risk factors simultaneously through lifestyle intervention.

Furthermore, focusing only on the major risk factors neglects the benefit of treating other metabolic risk factors (low HDL cholesterol, elevated triglycerides, and the pro thrombotic state) with drugs already shown to reduce risk[1].

In 2001, ATP III recommended two major therapeutic goals in patients with metabolic syndrome. These goals were reinforced by a report from the American Heart Association and the National Institutes of Health (**Table 2**) and by clinical guidelines from The Endocrine Society[34]:

- Treat underlying causes (overweight/obesity and physical inactivity) by intensifying weight management and increasing physical activity.
- Treat cardiovascular risk factors if they persist despite lifestyle modification.

Finally, exclusive attention to the major risk factors fails to acknowledge that the field is rapidly evolving such that new drugs to simultaneously treat multiple risk factors likely will become available in the future.

Table 2. Definition of metabolic syndrome according to WHO, IDF, and NCEP ATP III.

| | WHO (main criterion + two factors)* | IDF (main criterion + three factors) | NCEP ATP (combination of three factors) |
|---|---|---|---|
| BMI (kg/m$^2$) | >30 | – | – |
| Abdominal obesity (men/women) | WHR <0.9/0.85 | **Waist ≥94/80** | Waist >102/88 |
| Triglycerides (mmol/l) | ≥1.7 | >1.7 | >1.7 |
| HDL cholesterol (mmol/l) (men/women) | <0.9/1.0 | <1.03/1.29 | <1.03/1.29 |
| Blood presure (mmHg) | ≥140/90 | >130/>85 or present | ≥130/≥85 |
| Type 2 diabetes** | Present | Present | – |
| Impaired tolerance test | **7.8–11.1** | – | – |
| Fasting glucose (mmol/l) | **≥6.1** | ≥5.6 | >5.6 |
| Urinary albumin excretion | ≥20 µg/min or ≥30 mg/g | – | – |

* According to the WHO, either BMI or abdominal obesity represents one criterion; ** according WHO, diabetes mellitus type 2, fasting glucose, impaired tolerance test are alternatives, fulfilling one criterion. WHO – World Health Organization; IDF – International Diabetes Federation; NCEP ATP III – National Cholesterol Education Program Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults.

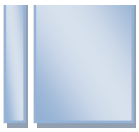
## PREVENTION

Various strategies have been proposed to prevent the development of metabolic syndrome. These include increased physical activity (such as walking 30 minutes every day)[39], and a healthy, low calorie diet[40]. Many studies support the value of a healthy lifestyle as above. However, one study stated these potentially beneficial measures are effective in only a minority of people, primarily due to lack of compliance with lifestyle and diet changes[15]. The International Obesity Taskforce states that interventions on a sociopolitical level are required to reduce development of metabolic syndrome in population[41].

A 2007 study of 2,375 male subjects over 20 years suggested the daily intake of a pint (~568 ml) of milk or equivalent dairy products more than halved the risk of metabolic syndrome[42]. Some subsequent studies support the authors' findings, while others dispute them[43].

## NEEDS FOR MORE RESEARCH

Researchers proposed that the field needs to wait for new research before introducing the metabolic



syndrome into clinical practice. Everyone favors acquisition of new knowledge. But what new knowledge must become available to trigger release of metabolic syndrome into clinical practice, Should it be a more detailed understanding of all of the pathogenic steps linking obesity and insulin resistance to metabolic syndrome? Should it be improved tools for risk assessment for determining long-term or short-term risk for ASCVD and type-2 diabetes? Should it be in the form of new drugs that simultaneously treat multiple risk factors? Or, should we wait for all national and international organizations in the cardiovascular and diabetes fields to get together and formulate more precise criteria for the diagnosis of the syndrome?

Many experts in both the CVD and diabetes fields hold the position that the questions posed by Kahn et al have been answered sufficiently for clinical management of metabolic syndrome to proceed[1,7]. New discoveries will be welcomed and can be incorporated into clinical practice.

## CONCLUSION

The fundamental questions raised were*: First,* whether the well established clustering of metabolic risk factors underlying both CVD and type-2 diabetes deserve to be called a "syndrome". Second, even if the metabolic syndrome can be accepted as a concept, does it mature enough to be introduced into clinical practice? New opinions are welcomed.

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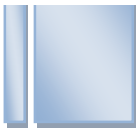


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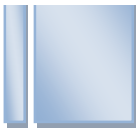

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