

INTRODUCTION

In 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 was 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 hypertension¹⁻³. Although insulin resistance (i.e., resistance to insulin-stimulated glucose uptake) as a feature of type 2 diabetes was first described many years earlier⁴, hyperinsulinemia was also found to be a key feature of type 2 diabetes^{5,6}, as well as hyperlipidemia⁷⁻⁹, obesity¹⁰⁻¹³, and hypertension¹²⁻¹⁴. In addition, a cluster of heart disease risk factors seemed clearly related to type 2 diabetes¹⁵. This was put into a unifying term of metabolic syndrome¹⁶.

This concept of metabolic syndrome has evolved extensively in the past two decades. Several organizations have proposed the cluster of risk factors that metabolic syndrome encompasses into clinical practice. This constellation of risk factors provides an insight into the increasing incidence of diabetes type 2 and atherosclerotic cardiovascular disease¹⁷. The evaluation of this Syndrome was noted as early as 1936 by Dr. J.B. Morgagny and was further corroborated by Himsworth in 1936. Though Prof. Gerald Raevan¹⁶ introduced the concept of Insulin Resistance in his famous Banting Oration (1988), this syndrome has been christened as syndrome X, CHAOS, New World Syndrome and now

'Metabolic Syndrome'. Five Risk Factors of Metabolic Origin (obesity, dyslipidemia, dysglycemia, prothrombotic and pro-inflammatory states) commonly are seen together and have a metabolic basis. This constellation confers additional risk of developing diabetes type 2 and cardiovascular disease. The main point of contention has been the changing figures for obesity estimation based on ethnicity, the changing blood pressure levels and blood sugar levels as well as the lipid levels. Though this has been raised as a major issue, but if we look at various other syndromes, this phenomenon is not uncommon especially in relation to hypertension whereas the diagnosis of hypertension has seen a sea-change. The other associated features and abnormalities seen in these patients, which are gaining importance, are polycystic ovarian syndrome and acanthosis nigricans on nape of neck and non-alcoholic hepatic steatosis.

THE SYNDROME: THE CONTROVERSY

This syndrome has been well established in medical literature which led this syndrome being accorded a position of pride in the ICD Code. *The code No. being ICD-9 277.7*. In September 2005, the American Diabetes Association (ADA) raised a controversy in a statement issued jointly with the European Association for the Study of Diabetes that metabolic syndrome is an inadequately defined concept and that does not meet the medical definition of a syndrome and does not change how each individual aspect is medically managed¹⁸. The American Heart Association (AHA), along with the National Heart, Lung, and Blood Institute (NHLBI), on the other hand, published guidance on classifying, diagnosing, and medically managing an

individual with metabolic syndrome. They also called for more research in this area. The ADA explained that “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.” Their extensive review of published research led them to conclude that “too much critically important information is missing to warrant its designation as a ‘syndrome.’” Their recommendation: until much needed research is completed, clinicians should evaluate and treat all CVD risk factors separately, without regard to whether a patient meets the criteria for diagnosis of the metabolic syndrome or not¹⁸.

While the ADA was dismissing the concept as clinically useful, at least for now, the AHA, in collaboration with the NHLBI, has been trying to advance it. They admit that the conditions that make up metabolic syndrome have more than one cause, but are confident that these conditions in combination contribute to high risk of *type 2 diabetes* and atherosclerotic CVD. The AHA report’s authors noted differences between the diagnostic criteria given by various groups, but were not put off by them. In essence, the AHA and NHLBI say that an individual with certain abnormal measurements in just three of the following areas—abdominal obesity, lipids, blood pressure, and fasting plasma glucose—should be diagnosed and treated for metabolic syndrome. Markers of inflammation and the tendency to develop blood clots are also important to watch.

This difference in opinion among well-respected health organizations exemplifies the need for an evidence-based approach¹⁸. The IDF tried to create a unifying definition and ADA and AHA are working together for a consensus. The author has tried to answer in the subsequent paragraphs the validity and efficacy of this concept on basis of available evidence in the current literature.

As mentioned earlier, the various other names given to this constellation are syndrome X, insulin resistance syndrome, Pre diabetes, plurimetabolic syndrome. No single name has been universally accepted among these various names. Metabolic syndrome is widely used, easily understood and connotes the increased risk of diabetes and cardiovascular disease.

Metabolic Syndrome and Its Pathogenesis

The term ‘Syndrome’ derives from the Greek word and means literally “to run together” and this explanation fits into the definition of metabolic syndrome. The existence of metabolic syndrome is further confirmed by the simple observation that the risk factors do not

cluster by chance alone and as is obvious from the various components of metabolic syndrome which are metabolically related, thus signifying that syndrome definitely exists. About the need for a single causative factor for a pathological process to be referred as syndrome is not necessarily warranted. Many of the syndromes are multi-factorial in origin. The two important conditions which are usually associated with the development of metabolic syndrome are **central obesity** and **insulin resistance**. The inter-relationship between obesity and IRS is appreciated as excess amount of nonesterified fatty acids and adipokines are released into circulation. This results in atopic fat accumulation in the abdominal wall, liver and muscle which, in turn, contributes to Insulin Resistance, dyslipidemia, prothrombotic and pro-inflammatory state. Obesity with a genetic basis for insulin resistance, the metabolic syndrome manifests in its worst form. The genetic predisposition triggered by lifestyle factors like physical inactivity, increasing age, endocrine imbalance and the resulting metabolic abnormalities (Fig. 1). From this simple explanation it is obvious that the pathogenesis of metabolic syndrome is much better explained than many of the other recognized medical disorders/syndromes. **Therefore, it is not prudent that multi-factorial ideology will rule out the existence of metabolic syndrome.**

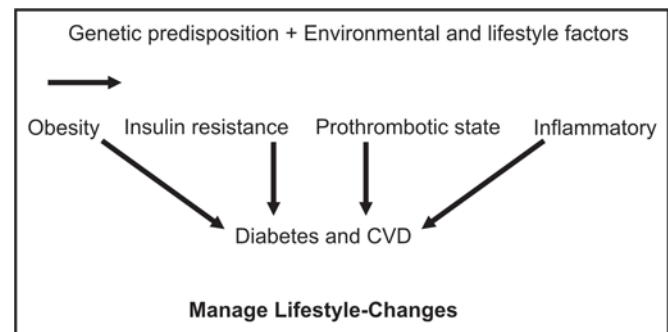


Fig. 1: Basics of metabolic syndrome

Diagnostic Parameters for Metabolic Syndrome

A series of definitions of metabolic syndrome have been propounded and this has created a state of confusion as this also interferes in the scientific data which emerges because the parameters used may vary from study to study. The first diagnostic criterion was proposed in 1998 and was evolved gradually in the ATP III of the US. The issue of measuring anthropometric measurements, the level of blood pressure, the blood sugar and measurements of various lipid fractions has now been finally resolved by a consensus definition of **IDF in the year 2006**. (Table 1)

Table 1: The 2006 International Diabetes Federation (IDF) definition of the metabolic syndrome

According to the new IDF definition, for a person to be defined as having the metabolic syndrome, they must have:

Central obesity (defined as waist circumference \geq 94 cm for European men and \geq 80 cm for European women, with ethnicity specific values for other groups)

plus any 2 of the following 4 factors:

- Raised TG level: \geq 150 mg/dL (1.7 mmol/L), or specific treatment for this lipid abnormality
- Reduced HDL-cholesterol: $<$ 40 mg/dL (1.03 mmol/L) in men and $<$ 50 mg/dL (1.29 mmol/L) in women, or specific treatment for these lipid abnormalities
- Raised BP: systolic BP \geq 130 or diastolic BP \geq 85 mm Hg, or treatment of previously diagnosed hypertension
- Raised fasting plasma glucose: FPG \geq 100 mg/dL (5.6 mmol/L), or previously diagnosed type 2 diabetes

If above 5.6 mmol/L or 100 mg/dL, an OGTT is strongly recommended, but is not necessary to define the presence of the syndrome.

TG = triglycerides; HDL = high-density lipoprotein; FPG = fasting plasma glucose; OGTT = oral glucose tolerance test

This represents a simple way to identify individuals in clinical practice who are suffering from metabolic syndrome and have various diagnostic parameters. All such people deserve lifestyle interventions to reduce the long term risk of diabetes and cardiovascular disease. In case the individual shows evidence of increased risk in short term evaluations by various risk engines like Framingham Score then it is important to start pharmacotherapy in addition to aggressive lifestyle management. Similarly, an OGTT may reveal the veiled diabetics and call for their management.

Metabolic Syndrome as a Risk Factor for Diabetes Type 2 and Cardiovascular Disease

A series of studies and reports are available which have shown that metabolic syndrome increases the risk for diabetes and cardiovascular disease. The risk for diabetes increases by about 5-folds while the cardiovascular risk increases by about 2-times. Since we are trying to assess the risk by the constellation of symptoms before overt disease manifests itself, therefore studies based on 10 years cannot answer this question categorically, and the objection of Kahn, et al¹⁸ that metabolic syndrome does not confer an increased risk over a 10 year period cannot be taken as valid. Let us understand this from the perspective of epidemiologists and people planning for public health. The projections are alarming and the epidemiologists and health care providers have to plan an effective strategy to combat this epidemic of lifestyle

diseases and the affected individuals at least deserve information about lifestyle interventions especially in relation to activity and healthy food while the other short-term risk assessment tools like Framingham Scoring call for an aggressive use of Pharmacotherapy to reduce the risk. A significant proportion of the studies by top cardiologists have emphasised the association between diabetes and CVD. Professor Lars Rydén²⁰, Karolinska Institute, Stockholm, Sweden; Dr. Salim Yusuf²¹, Population Health Research Institute, Hamilton, Ontario, Canada; and Dr. Richard W. Nesto²², Lahey Clinic Medical Center, Burlington, Vermont, reported that for every 1% rise in glycosylated hemoglobin (A1C) in people with diabetes, there is an 18% rise in the risk of cardiovascular events. Similarly, for every 1% rise in A1C, there is a 28% increase in peripheral arterial disease in people with diabetes. In addition, people who have had a cardiovascular event very often have diabetes or prediabetes. People with the metabolic syndrome have at least a 2-fold increase in the risk of CVD events, and a much poorer prognosis following the event. High levels of triglycerides and of small, dense low-density lipoprotein (LDL) particles and low levels of high-density lipoprotein cholesterol (HDL-C) are both components of the metabolic syndrome and risk factors for CVD. The metabolic syndrome more strongly predicts congestive heart failure and CVD mortality than its individual components.

Several studies have brought out the effects of intensive treatment of blood glucose abnormalities during and after the acute CVD event in patients with different stages of dysglycemia. Professor Klas Malberg²³ (Karolinska Institute) presenting the results of the Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction (DIGAMI) study showed a benefit of intensive glucose control on cardiovascular morbidity and mortality, while the DIGAMI 2 study did not confirm to these conclusion. The jury is still out on this important question. Professor Raymund Erbel²⁴, Essen, Germany, pointed out in his presentation that people with diabetes and prediabetes also fail to enjoy the full benefits available from modern cardiological and surgical procedures.

Metabolic Syndrome – A Risk Marker

The various factors that make up metabolic syndrome lead to the risk for cardiovascular disease and diabetes rise geometrically rather than in a linear fashion. Higher the number of factors, the greater is the risk. Some of the discrepancies which arise is the predictability of risk in patients of metabolic syndrome

due to the fact that some of the factors cannot be evaluated clinically e.g. Insulin Resistance prothrombotic and pro-inflammatory states, endothelial dysfunction and increase in the levels of ApoB. The risk due to these factors cannot be appreciated by the risk factors typically measured in day to day practice. The risk associated with the major risk factors like low HDL cholesterol, high blood pressure, dysglycemia, obesity are confounded by these unappreciated and measured factors. Another important aspect which is lost sight of is the fact that some of the parameters in metabolic syndrome are progressive in nature like dysglycemia, hypertension and lipid parameters which worsen over a period of time and thereby changing the risk profile of the individual. This makes it quite obvious that the risk measured will vary over a period of time. The importance of metabolic syndrome as a risk marker needs refinement and understanding rather than dumping it without giving it a fair chance and time to answer some of the unexplained issues.

The Importance of the Concept in Clinical Practice

Some of the common reasons why physicians, diabetologists and cardiologists want to introduce the term "Metabolic Syndrome" because of their conviction that their patients can benefit from using this concept in clinical practice. The reasons advocated:

- Recognition of metabolic syndrome helps the clinicians to focus his attention on the need for life style therapies to reduce all metabolic risk factors concurrently.
- The benefit of lifestyle therapeutics though neglected has been shown to be of immense help in trials like the MALMO Trial and DPP Trial.
- The Syndrome definitely helps to identify the patient at increased risk for diabetes and atherosclerotic CVD and thus re-emphasise the role of lifestyle measures.
- The growing awareness of metabolic syndrome changes the perspective from a single risk factor paradigm to multiple risk factors. This refines the evaluation of risk for both diabetes and cardiovascular disease.
- Finally these patients need to be observed for a long term in longitudinal manner so that the emphasis on nutrition, exercise and behavior can be re-enforced from time to time.

The Growing Ambit of Metabolic Syndrome

Some diabetologists are reluctant to make a diagnosis of metabolic syndrome in patients of diabetes type 2 as

it is not universally accepted. However, we must understand that diabetes type 2 is a definitive and categorical point in the diagnosis of hyperglycemia and which clearly suggests the insulin resistance as well as reduction in insulin secretion. In a study by Steve Hefner¹³ it was clearly shown that the risk of cardiovascular disease was much higher in diabetic people.

Treatment of the Metabolic Syndrome

Lifestyle Modification

This is one of the most important aspect in managing metabolic syndrome and prevention of diabetes mellitus and ASCVD. Interventional studies from the United States, Finland, China, and India all showed the beneficial effects of lifestyle interventions. The MELMO trials which led the foundation following the lifestyle modification were confirmed by the DPP trial where there was nearly 58% reduction in the incidence of overt diabetes. The importance of reducing weight, increasing physical activity and eating healthy has shown a great potential and needs to be followed at the community level.

Since one of the important components of diabetes and CVD is insulin resistance, therefore medications which improve the insulin resistance have been shown to have a beneficial effect. Trials with metformin, acarbose and glitazones have shown promising results. New investigational pharmacologic agents, such as glucagon-like peptide (GLP)-1, dipeptidyl peptidase (DPP)-IV inhibitors, and the endocannabinoid receptor blocker rimonabant, have also demonstrated promising results (Table 2).

At present we do not have a single common mechanism for the Syndrome. There is no single effective treatment. Effective management of obesity, dyslipidemia, hypertension and dysglycemia has shown benefit. Similar observation has been reported from various studies. The table below shows the important features of management of Metabolic Syndrome.

CONCLUSION

In conclusion, there is a wealth of data in literature and is being discussed at various international meetings which clearly indicates that the risk factor clustering which we have come to know as the Metabolic Syndrome is a powerful concept. The presence of multiple risk factors predicts the onset of diabetes and CVD much better when multiple risk factors are present than a single factor alone. It is also a well observed

Table 2: Management of metabolic syndrome**Lifestyle Measures**

1. Reduce weight
2. Increase Physical Activity
3. Diet

Important Tenets of Treatment and Prevention

- DPP Study
- RIO Lipids

**Reduce Metabolic Syndrome and Diabetes**

But as yet, No evidence of Reduction of ASCVD Mortality

“Look ahead study May Answer”

phenomenon that the morbidity due to CVD is much worse in people with metabolic syndrome than otherwise.

The disagreement with this constellation of risk factors whether it is a Syndrome or not may persist for some time, but it is hard fact that this constellation is a predictor of diabetes and CVD over a long period of time. In their endeavor to close ranks the ADA, AHA and other organizations are trying to bridge the gap of a semantics and formulate a uniform concept of cardio metabolic risk.

As Scott Grundy, MD (a cardiologist), observed that the concept of calling this group of risk factors is Metabolic Syndrome (Syndrome X and/or Insulin Resistance Syndrome)¹⁹ came from the diabetologist. It is also ironic that although the association between metabolic syndrome and diabetes is accepted and contested in CVD¹⁹. Metabolic Syndrome is accepted by most cardiologist organizations but disputed by the diabetologist. Probably the future results will put metabolic syndrome on a much firmer pedestal. At present it may be construed that metabolic syndrome is a useful concept, it draws attention to the fact that clustering of risk factors in an individual predisposes him to an excess risk of diabetes and CVD. Even the ATP-III Guidelines explicitly state that identification of one of the risk variables in an individual should prompt the search for others. Just because this concept does not fulfill the literal definition, it should not be brushed aside and be seen in a broader perspective it describes and the conclusions below sum it up well:

- Pre-diabetes and the metabolic syndrome are extremely prevalent;
- People with pre-diabetes and the metabolic syndrome are at high risk for diabetes and CVD;
- Intensive lifestyle changes are effective and should be encouraged; and

- Effective pharmacologic therapies must also be identified.

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