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Original article

Metabolic syndrome criteria and its association with type 2 diabetes and cardiovascular diseases

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Abstract. Metabolic syndrome is a cluster of metabolic anomalies such as insulin resistance, obesity, abdominal fat deposition, hypertension and dyslipidemia, which put an individual at a higher risk of developing cardiovascular complications. Global variation in ethnicity, culinary habits, availability of nutritious elements, lifestyle, economic status and disease tolerance/susceptibility of the workforce is reflected in the definition of the syndrome given by various public health entities. The present review summarizes the recent advances in the understanding of metabolic syndrome which has been discussed at length by different organizations. A greater insight into diagnostic criteria of metabolic syndrome will improve our understanding and more importantly enable the prevention and management of this complex condition.

Key words: Metabolic syndrome, type 2 diabetes, NCEP-ATPIII criteria, IDF, WHO, Risk factors

Introduction

Metabolic syndrome refers to a cluster of physiological and biochemical factors that contribute to the development of atherosclerotic cardiovascular diseases. Knowledge of metabolic syndrome is primal; however, its definition was obscure. A Swedish physician, Kylin in 1920 attempted to underline the condition as an assemblage of metabolic fracas which involves the risk factors of atherosclerotic cardiovascular disease, cardiovascular disease (CVD), and hyperglycemia, hypertension and gout (1). In 1988, Reaven hypothesized that quite a few risk factors such as hyperglycemia, dyslipidemia, and hypertension generally huddled together and form the basis of multiple factors of risk pertaining to CVD. He christened this condition as "syndrome X"(2), though various over names such as the dysmetabolic syndrome, deadly quartet, metabolic cardiovascular risk syndrome are also prevalent now. Heterogeneity in the perception and definition of metabolic syndrome exist as international authorities, debate over its underlying causes.

However, the syndrome is nonetheless recognized as a potential risk factor for diabetes mellitus, CVD (3-5) and cardiovascular mortality (6). Other discrepancies in health conditions such as abnormalities in urine albumin ratio, fibrinolysis, endothelial dysfunction, non-alcoholic fatty liver and elevated markers of unremitting inflammation are linked with metabolic syndrome (7-11).

Type 2 diabetes mellitus is a multifaceted disorder, with disturbances in glucose metabolism, lipid levels, blood pressure, and coagulation factors (12). While the CVD risk with the prevalence of these factors is just 25%, still CVD is the major cause of mortality in diabetics (13, 14). Developing nations are now the fulcrum of industrialization, economic growth and modernization. People have become busier, less diet conscious, least physically agile and have adapted a sedentary lifestyle. These insidious factors amply pave the

ground for the onset of metabolic syndrome especially in genetically susceptible folks. Since the economic prosperity at individual level is uneven in developing nations, it may result in an ill assorted populace. Demographic factors may, consequently, impinge on the progression of the metabolic syndrome. Studies delineating the demographic and medical aspects of metabolic syndrome are imperative to reveal the solutions to regulate the risk factors so as to avert or decrease the fatal consequences. Besides, comprehension of the causative factors and the cascade of disease development provides ample opportunities for early intervention and possibly prevention of disease. Disease risk is directly affected by genetics and also by life style factors such as diet and exercise patterns. Thus, the prevalence varies at variance with race/ethnicity and other predictor variables (15) and hence from one country or area to another. In this review, attempt to conscientiously compile the different metabolic syndrome definition or criterion prepared by various organization and to find out the risk population that have higher risk of causing CVD and type 2 diabetes in future.

Clinical diagnosis of the metabolic syndrome

In the past decade, six organizations have recommended different overlapping clinical criteria for the diagnosis of metabolic syndrome: The World Health Organization (16); National Cholesterol Education Program Adult Treatment Panel III (17), International Diabetes Federation (18) European Group for the study of Insulin Resistance (EGIR) (19) and American Association of clinical Endocrinologists/ American College of Endocrinology(20) and Joint Statement, Harmonizing the Metabolic Syndrome, 2009 (21). The criteria of former three organizations are more popular in diagnosis of metabolic syndrome worldwide. The momentum for creating criteria for detecting MS is essential to classify potential patients at an increased risk of contracting cardiovascular complicacies and/or type 2 diabetes mellitus. In general, it seems that the disparity in the definitions proposed by discrete organizations can be attributed to the miscellaneous epidemiological and risk factors that pose as the harbinger of the disease. The explicit clinical criteria for definition of metabolic syndrome have been summarized in Table 1.

World Health Organization (WHO)

The first organization to formalize diagnostic criteria for metabolic syndrome was WHO in 1999 (16). Compared to the other prevalent definitions, the WHO priorities insulin resistance a striking portent of metabolic syndrome. Evidence of insulin resistance is required and it is identified by the presence of type 2 diabetes mellitus, impaired fasting glucose (IFG), or impaired glucose tolerance (IGT). According to the definition apart from the insulin resistance mandate the other potent precursors are: 1) An increased Body Mass Index indicating obesity 2) Dyslipidemia 3) Hypertension; and 4) Microalbuminuria (Table 1).

National cholesterol education program adult treatment III (NCEP)

The NCEP Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults is entrusted with demarcating the borderlines for the clinical testing of serum cholesterol and aiding in managing its levels. The Adult Treatment Panel I (ATP I) has laid more stress on LDL as the principal target for recommendation of therapies to lower the lipid levels (NCEP1988). In 1993, ATP II emphasized on coronary heart disease (CHD) risk status as a guide to the intensity of cholesterol lowering therapy. To make things clinically more transparent the NCEP-ATP III (17) proposed that the presence of any three of the prevalent five factors (elevated waist circumference, high triglyceride, low high density lipoprotein, increased blood pressure and high fasting plasma glucose; Table 1) are enough to earmark the risk in an individual. The NCEP-ATP III portrayed metabolic syndrome as a cluster of interrelated metabolic disorders that eventually raise CVD risks", and the underlying causes were overweight/obesity, physical inactivity and genetic factors. Although the ATP-III has not single out any pertinent risk factor as a precondition for the metabolic syndrome diagnosis, it has however, emphasized on abdominal obesity as the cardinal risk factor. The NCEP definition operates independent of

Table 1. Illustration of Metabolic Syndrome according to different clinical definitions

Metabolic syndrome criteria	WHO (1999)	NCEP-ATPIII (2001)	EGIR (2002)	AACE(2003)	IDF (2005)	Harmonized (2009)
	Glucose intolerance, IGT or diabetes and/ or insulin resistance together with two or more of the following.	Any three features	Insulin Resistance Defined as IGT or IFG hyperinsulinaemia top 25% of plus any of the following fasting insulin values among the non-diabetic population) Plus any two of the following	based on the clinical judgment	Central obesity plus any two of the following Four factors:	Any three features
Abdominal obesity Waist circumference BMI	> 30 kg/m^2	> 102 cm (> 40 in) M > 88 cm (> 35 in) F	≥ 94 cm (M), ≥ 80 cm (F)	≥ 25 Kg/m^2	Waist circumference with ethnicity-specific values	WC: ≥ 90 cm (men) & ≥ 80 cm (women)
Triglycerides	≥ 150 mg/dl	≥ 150 mg/dL	≥ 150 mg/dl	≥ 150 mg/dL	≥ 150 mg/dl	≥ 150 mg/dl
HDL -cholesterol	< 35 mg/dl M < 39 mg/dl F	< 40 mg/dL M < 50 mg/dl F	< 39 mg/dL in men or women	< 40 mg/dl < 50 mg/dl	< 40 mg/dl M < 50 mg/dl F	< 40 mg/dl M < 50 mg/dl F
Blood pressure	≥ 140/≥90 mmHg	≥ 130/≥85 mm Hg	≥ 140/≥ 90mm Hg	≥ 130/≥ 85 mm Hg	≥ 130/≥85 mmHg	≥ 130/≥ 85 mmHg
Fasting blood glucose 2 h plasma glucose	Glucose intolerance, IGT or diabetes	≥ 110 mg/dl	≥ 110 mg/dl ≥ 140 mg/dl (but not diabetes)	Between 110 and 126 mg/dl > 140 mg/dl (but not diabetes)	≥ 100 mg/dl	≥ 100 mg/dl
Microalbuminuria	Urinary albumin excretion_ rate ≥ 20 µg/min Urinary albumin: creatinine ratio ≥ 30 mg/g			Other features of insulin resistance such as Includes family history of type 2 diabetes mellitus, polycystic ovary syndrome, sedentary lifestyle, advancing age		

BMI: body mass index; HDL-C: high density lipoprotein cholesterol; IFG: impaired fasting glucose; IGT: impaired glucose tolerance; WC: waist circumference

insulin resistance markers, rather it employs fasting plasma glucose level ≥110 mg/dl and diabetics as potential metabolic syndrome candidates (22). The fasting glucose level corresponds to the newer American Diabetes Association (ADA) definition of impaired fasting glucose (IFG) (23). The primary goals of NCEP in establishing the criteria for the diagnosis of metabolic syndrome were to identify individuals at increased CVD risk and to provide useful information for clinicians to encourage lifestyle changes for decreasing the risk.

Grundy, an author of the NCEP definition for metabolic syndrome (24-26) explained that the purpose of including metabolic syndrome in the 2001 NCEP ATPIII guidelines was to create awareness towards the escalating inclination of obese individuals to subsequently contracting type 2 diabetes mellitus and CVD. The NCEP definition is feasible as it can be computed from the Body Mass Index (BMI) if substituted for waist circumference (WC), if all the data are readily available, then no specific software is needed.

International diabetes federation (IDF)

In 2005, the IDF (18) published some new criteria for the diagnosis of metabolic syndrome even in diverse populations. The IDF definition however mandates abdominal obesity (waist circumference) with ethnicity based cutoffs. For this purpose the cutoffs for waist circumference of the Japanese were modified to match up with that of Asians. The presence of elevated waist circumference mandates any two of the four rampant criteria. Barring the ethnicity based WC cutoffs, (27) the IDF criteria are identical to those in the

NCEP definition (Table 1). The WHO however, necessitates insulin resistance, whereas IDF fundamental require ethnicity-adjusted measure of waist circumference.

American association of clinical endocrinologist criteria (AACE)

In 2003, the AACE modified the ATP-III criteria and highlighted insulin resistance as the key metabolic syndrome risk factor. The AACE uses the term insulin resistance syndrome. The criteria proposed by the AACE are a hybrid of the WHO and the ATP-III criteria (16). The categorization of an individual into MS patient largely depends on the discretion potential of the physician due to the lack of any defined and homogeneous risk factors. While IGT, hyperlipidemia, low HDL-cholesterol, high blood pressure, and obesity (Table 1), maintain the pivotal position still no explicit criterion has been defined for identification. As per AACE advice, the clinicians need to extract supplementary data regarding prior familial history of CVD or type 2 diabetes mellitus, polycystic ovarian syndrome (PCOS), and hyperuricemia. The AACE definition professes that when T2DM, has long established itself in an individual the nomenclature of insulin resistance holds no further justification. The WHO and AACE advise GTT (glucose tolerance test) if an abnormality is clinically suspected; in spite of normal fasting glucose.

European group for study of insulin resistance criteria (EGIR)

The EGIR in 1999 suggested certain amendments in the definition given by the WHO, however still the usage of insulin resistance syndrome rather than metabolic syndrome is rampant. The EGIR stressed on the prevalence of insulin resistance as a major causative behind metabolic syndrome and thus requires evidence for it in the diagnosis criteria. According to EGIR criteria, the level of serum insulin present in the higher quartile of the inhabitants defines insulin resistance. The EGIR lays more stress on higher waist circumference as the defining criteria much more than what the WHO does as it justifying that the incidence of insulin resistance results in the onset of type 2 diabetes.

Harmonizing the metabolic syndrome

The harmonizing definition of metabolic syndrome proposed a Joint interim statement of the following organizations: International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association**;** World Heart Federation International Atherosclerosis Society; and International Association for the Study of Obesity (21). This definition reflects the outcome of a meeting of different organizations to avail of a new unifying criterion. The meeting proposed that there should not be any obligatory component for defining metabolic syndrome. The meeting also underlined the different cutoff values of waist circumference according to ethnic variation. Table 1 summarizes the criteria of harmonizing definition.

Variations in the definitions of metabolic syndrome

The American Diabetes Association (ADA) in 1998, depicted the metabolic syndrome as an assemblage of interlinked clinical results of glucose intolerance, abdominal obesity, dyslipidemia and raised small dense low density lipoprotein cholesterol (LDL), increased blood pressure, augmented prothrombotic and antifibrinolytic factors, and a predisposition for atherosclerotic vascular disease (28). The six definitions of metabolic syndrome differ in their usefulness and their efficacy. All definitions include diabetic persons. For them, the description of metabolic syndrome has restricted expediency as they qualify for CVD risk and necessitates extensive (remedy) curing of all factors that pose potential risk elements. The definition IDF also needs the waist circumference size which is tricky to be obtained accurately in an office setting. Marker of abdominal obesity is not prerequisite in NCEP definition; however, WC is one of the criteria and individuals with 3 out of the 5 criteria are considered to suffer from metabolic syndrome by NCEP. The IDF definition differs from NCEP as the former stresses on the magnitude of abdominal corpulence through waist circumference computation in the analysis of metabolic syndrome second, the WC threshold was lowered in

IDF; third, ethnic-specific WC thresholds for diagnosis of central obesity were added.

There are some marked variation between the defining criteria of WHO and NCEP definitions: (1) Obesity is measured by body mass index (BMI) in WHO criteria whereas it is measured by waist circumference in NCEP-ATPIII (2) The WHO diagnostic criteria include urinary albumin excretion and albumin: creatinine ratio. (3) IGT is included in the WHO definition but not in the NCEP. (4) The diagnostic criterion of WHO includes higher blood pressure which is not mentioned in NCEP.

The fine line between the prevalent definitions lies in their organization. While the ATP-III does not discriminate conditionally among its constituents rather they profess that the blend of 3 out of 5 distinguishing criteria also pose the same type of adversity. This has been propped up by the American Heart Association (AHA). While the WHO mandates the proof of the incidence of insulin resistance, for the IDF the WC measure based on the patient ethnicity is de rigueur. Yet another subtle disparity in the definitions is regarding overindulging plumpness. Ethnicity-adjusted WC is the main compulsion of IDF while the ATP-III has accepted the fact that certain subjects are more liable to develop insulin resistance- prone individuals even at a bare minimum cutoff points.

Metabolic syndrome: development of cardiovascular diseases and type 2 diabetes

A conglomeration of metabolic disorders evident in lipid, fat and carbohydrate usage poses as risk factors for cardiovascular disease (2, 29). Over-secretion of insulin and peripheral resistance to its action is believed to be the insidious factor in the growth of the metabolic syndrome. The clustering of metabolic syndrome components results in a 5 and 2 fold increased risk for type 2 diabetes mellitus and CVD, respectively (17). It has been speculated that the extremely high prevalence of metabolic syndrome among diabetic patients may be due to the large number of patients who already have a history of CVD (30-32). Incidence of CVD among diabetic patients with metabolic syndrome was higher than those without metabolic syndrome (33). A recent review also proposed that metabolic syndrome could be a predictor for type 2 diabetes mellitus and CVD. Moreover the study have suggested metabolic syndrome is useful in clinical practice, especially for the prediction of diabetes (34).

Most prospective studies have shown that subjects with metabolic syndrome are at increased risk of CVD incidence (35, 36). Several researches have brought to limelight the disquieting rise in the pervasiveness of metabolic syndrome in children and teens (37). Children with metabolic syndrome have also been seen to harbor acute hyperinsulinemia, which hastily progresses intolerance of glucose and ultimately succumbs to diabetes (38, 39).

Numerous investigations have revealed the nexus between metabolic syndrome, onset of diabetes and CVD. Disease incidence and death results may vary as per the benchmark employed for diagnostic criteria. In addition to this, the prevalence of the metabolic syndrome is ominously increasing among adolescent and young adults. Therefore, it is important to quantify the metabolic syndrome association with clinical coronary artery disease (CAD) in early life. A recent report summarizing its predictive value (40) concluded that the population-attributable risk (PAR) associated with the metabolic syndrome, based on the NCEP and WHO definitions, and it is approximately 6-7% for all-cause mortality and 12-17% for CVD. Similarly, a report from the Framingham Heart offspring (41) recently showed that the PAR for CVD and coronary heart disease (CHD) were respectively 34% and 29% in men and 16% and 8% in women. The metabolic syndrome components that contributed most to the CV outcomes were hypertension and low HDL-cholesterol with PAR estimates of 33% and 25% respectively. Predictive capacity of metabolic syndrome for CVD varies by ethnicity, gender and the presence or absence of hyperglycemia (42, 43). In the Botnia study participants with metabolic syndrome showed an elevated probability thrice that of normal occurrence for coronary heart disease and stroke, a 5-6 times more the risk mortality due to CVD and augmented risk of all-cause mortality was observed (4). The risk of death from all causes and CVD increased with growing numbers of abnormalities (6). Metabolic syndrome is quite synonymous with the occurrence and prevalence of type 2 diabetes (44, 45). The San Antonio

Heart Study researchers used three methods to foretell the outbreak of type 2 diabetes mellitus: 1) IGT detected by oral glucose tolerance test (OGTT), 2) the existence of the metabolic syndrome as per NCEP definition, and 3) the occurrence of the metabolic syndrome as per the amended WHO definition (barring OGTT). It was found that IGT is the most efficient prognosticator 43% predictive values while 31% predictive value in NCEP standards and 30% by the amended WHO definition (46). Using the NCEP and WHO definitions, Ford, (2005a) (47) found that the PAR for type 2 diabetes is approximately between 30-52%. The probability of the incidence of CHD or its lethal counterparts is two to four folds higher in individuals afflicted with diabetes as compared to non-diabetics. Metabolic syndrome individuals often posses insulin resistance ultimately leading to type 2 diabetes. Many who develop the metabolic syndrome first acquire abdominal obesity without any other risk aspects. Epidemiological analysis imply the prevalence of several risk factors exponentially shooting up the risk probability than the single risk factors (25). Physical inactivity and obesity in women autonomously enhances the progression of CHD (48).

In yet another San Antonio based investigation, the probability of contracting diabetes was seen to be as high as three folds in the metabolic syndrome patients, as per ATP III benchmark, the same was 3.3[2.27-4.40]. Metabolic syndrome is not a superior criteria than IGT in selection of probable diabetics, but when IGT is employed along with the NCEP risk factors, almost detect 70% of potential diabetics could be identified (46). Metabolic syndrome surveillance is also imperative as its prevalence indicate a three times possibility of the CHD based mortality (25). The comparative risk ratio of CVD was found to be between 2 and 5 in an European investigation (49) and the same was confirmed by yet another Verona Diabetes Complication research (50).

Metabolic syndrome is a (combination) confederate of stroke and myocardial infarction (MI) thus using it as diagnostic criteria for MI will have immense clinical implications (51). In an investigation conducted on European individuals by the DECODE metabolic syndrome was established as a primary marker of mortality for different reasons including CVD. About 15% of non-diabetic individuals had metabolic syndrome in Europe, within general vulnerability ratios death caused from CVD and all cause were 2.26 and 1.44 in males 2.78 and 1.38 in females. These ratios were documented after factor adjustment of age, serum TC and smoking activity (52). Ridker (23) also deduced (diagnosed that) metabolic syndrome subjects possess seven times probability of becoming diabetic and 70% to 200% elevated risk of getting CVD. The incidence of diabetes amplifies the probability of contracting CVD. Analysis of data from a NHANES-III population, has also confirmed that the occurrence of CHD is escalated with the presence of metabolic syndrome (30). An alarming 86% of over 50 years aged USA residents having type 2 diabetes mellitus also had metabolic syndrome, while those who did not have metabolic syndrome possessed (30) least CHD pervasiveness analogous to individuals with or without diabetes (8.7% and 7.5%, respectively). Campbell et al. (2016)(53) demonstrated the high prevalence of metabolic syndrome affects females, Hispanics and aged population in USA and thereby poses a huge burden of metabolic disorder on the health care system. Therefore, it is crucial to identifying high risk groups toward which to focus education and intervention to prevent the complication raised from metabolic syndrome.

There arises an obligation to design a multifaceted therapy which will address all aspects of CVD risk in metabolic syndrome individuals. Particular attention is required regarding hypertension and obesity, which are the most prevalent components of the metabolic syndrome in the population studies. These studies have firmly established that metabolic syndrome as an ally of diabetes, the presence of which in an individual aggravates the risk of diabetes and its fulminant complications. So as to reduce the probability of occurrence (tendency) of diabetes in the populace, it is suggested to monitor individuals with the diagnostic risk factors of metabolic syndrome. In diabetic subjects any components of the metabolic syndrome, a thorough clinical investigation should be made to detect the presence of CAD and all the associated conditions should be treated aggressively so that some of the insidious factors and life threatening consequences of the disease may be prevented or alleviated. It is therefore recommended that in the management of type 2 diabetes, risk factors of the metabolic syndrome should also be assessed from time to

time and appropriate treatment should be provided. This will help to reduce the CVD and cardiovascular mortality. Annually the patients should be assessed for their metabolic syndrome score so that early and effective intervention could be designed to extirpate the risk features and for its control.

The features of metabolic syndrome prolong in numerous diabetics even with aggressive therapy targeted at increased glucose concentration and CVD risks. Thus, therapy targeting multiple factors of CVD risk in type 2 diabetes patient is indispensable (54, 55).

Treatment approaches in metabolic syndrome

Treatment of metabolic syndrome required a multifaceted treatment which is needed for the therapy of individual risk factors such as dyslipidemia, hypertension, and obesity. It is advocated that for the management of abdominal obesity, a low-calorie diet with regular physical activity is necessary for reducing the comorbidities of obesity (56). For targeting blood glucose, a modification in diets such as high fiber (increased intake of fruits and vegetables) and low saturated fat needed in managing glucose levels (24). The modification in life habits is also playing a good role in preventing the individual components of metabolic syndrome. Curbing alcohol consumption, smoking cessation and engaging in regular work-out are concerns to be highlighted by the physician to every individual that has a risk of developing metabolic syndrome (57).

Pharmaceutical drugs such as metformin and thiazolidinedione are given to the patients of metabolic syndrome for managing the glucose level and insulin resistance. The treatment of hypertension in the metabolic syndrome get benefited from a therapeutic lifestyle change, and some drugs-related with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, are prescribed as these drugs have a well potential in preventing complications of diabetes and cardiovascular diseases (58).

The previous research has recommended that the first-line pharmacological therapy for the dyslipidemia are statins, moreover, it has been suggested that the combination therapy with fibrates or nicotinic plus a statin is the best approach for the treating of dyslipidemia in metabolic syndrome patients (58). However, there is no solely paramount therapy and the treatment may have to focus on the individual component and the complications present in metabolic syndrome patients.

Conclusion

Criteria–based definitions of metabolic syndrome remove all obscurities while also aid in precisely labeling the metabolic anomalies which lead to atherosclerosis, abdominal obesity and insulin resistance. The aim of reviewing metabolic syndrome is to draw attention towards its different components, its presumed threat and to identify metabolic syndrome in those without diabetes. These individuals have abnormal glucose metabolism (eg, IGT or IFG), therefore alterations in major lifestyle and diet modifications will substantially be of immense help in the prevention or regression of diabetes and vascular complications.

As the major factors contributing to the prognosis of metabolic syndrome encompass gestational complications, oxidative stress and of cytokines from surplus adipocytes. The disparity between the definitions should be erased for clinical ambience and for uniformly targeting the risk population from the well-defined and homogeneous factor of metabolic syndrome. Studies designed to explore the association of abdominal obesity with metabolic risk and CVD in other populations are needed if ethnicity based WC is a definition criteria to abide by. In our opinion the most applicable consensus definition is harmonizing definition of metabolic syndrome that was proposed and updated from International Diabetes Federation and the American Heart Association/National Heart, Lung, and Blood Institute. The metabolic syndrome scenario and its implications should be completely elucidated specially in children and teens. These will give valuable insights and pave the way for early intervention and possible prevention of the incidence of the disease.

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