Metabolic syndrome

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Metabolic syndrome (MS) is a constellation of individual risk factors of cardiovascular disease. The World Health Organization (WHO) was the first to publish an internationally accepted definition for metabolic syndrome in 1998, but the criteria that have received the most widespread acceptance and use in the United States are those established as guidelines in the ATP III (the third report of the National Cholesterol Education Program expert panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults).

The scientific evidence related to definition was reviewed and considered from several perspectives: (1) major clinical outcomes (2) metabolic components (3) pathogenesis (4) clinical criteria for diagnosis (5) risk for clinical outcomes and (6) therapeutic interventions [1]. Hence, there are many definitions and many criteria for diagnosis of metabolic syndrome like ATP III adult panel, WHO guidelines, IDF and AACE. There is no universal agreement on criteria for the diagnosis.

ATP III identified 6 components of the metabolic syndrome [1] that relate to CVD:

- Abdominal obesity
- Atherogenic dyslipidemia
- Raised blood pressure
- Insulin resistance and/or glucose intolerance
- Proinflammatory state
- Prothrombotic state

For the purposes of ATP III, metabolic syndrome is present when ≥ 3 of the following criteria are present: waist circumference >102 or >88 cm in men and women respectively; triglycerides ≥ 150 mg/dl; HDL

cholesterol <40 or <50 mg/dl in men and women respectively; blood pressure $\geq 130/\geq 85$ mmHg; and fasting blood glucose ≥ 110 mg/dl.

The WHO guidelines also viewed CVD as the primary outcome of the metabolic syndrome. In WHO guidelines, unlike the ATP III criteria, stipulate that insulin resistance is required for the diagnosis along with two other risk factors out of the following: high blood pressure, raised triglycerides, low HDL and increased BMI (or increased waist: hip ratio) and microalbuminuria. In addition, a higher blood pressure was required for the ATP III criteria. Like the ATP III criteria, the presence of type 2 diabetes does not exclude a diagnosis of metabolic syndrome. A potential disadvantage of the WHO criteria is that special testing of glucose status beyond routine clinical assessment may be required.

The AACE has proposed a third set of criteria for the insulin resistance syndrome [2]. These criteria appear to be a mixture of the ATP III and WHO criteria except that no defined number of risk factors is specified and the diagnosis is left to clinical judgment. When a person develops diabetes, the term insulin resistance syndrome no longer applies. Finding abnormal 2-hour glucose will improve prediction of type 2 diabetes.

International Diabetes Federation defines metabolic syndrome to include central obesity with 2 of the following 4 factors: raised triglycerides, low HDL cholesterol, and raised blood pressure raised fasting plasma glucose.

Thus the definition, criteria, pathogenesis and therapeutic intervention in the metabolic syndrome is controversial. By definition, syndrome is a group of symptoms that collectively indicate or characterize a disease, psychological disorder, or other abnormal condition. To recognize a syndrome a group of symptoms alone is not sufficient. The syndrome should have a common etiopathogenesis and a common pathway which leads to the syndrome. Do we have such a

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unifying hypothesis in case of metabolic syndrome? To accept that metabolic syndrome is a risk for cardio vascular disease, the aggregate risk of metabolic syndrome should be more than the addition of individual risk factors. Each component of metabolic syndrome may have different cardiovascular risk, depending on the regional, ethnic, racial and geographical factors. In such a situation is it possible to have a universal definition and criteria for metabolic syndrome?

MS is a complex web of metabolic factors that are associated with a 2-fold risk of CVD and a 5-fold risk of diabetes. Individuals with MS have a 30%–40% probability of developing diabetes and/or CVD within 20 years, depending on the number of components present [2].

Metabolic syndrome is only a syndrome with multiple risk factors for future cardiovascular disease and diabetes mellitus and should not be misdiagnosed as a disease. How often do we dare to write in a case record of a person diagnosis of metabolic syndrome?

The association between MS and cancer mortality is yet to be proved. Research to focus on pre-cancer risk factors in metabolic syndrome is necessary. Studies have shown that MS is associated with an increased risk of all-cause cancer mortality in men. In a study by Jason R et al. [3] of 33,230 men aged 20–88 years, at baseline 28% of all the participants had MS. During an average of 14 years follow-up, there were a total of 685 deaths due to cancer. MS at baseline was associated with a 56% greater age-adjusted risk in cancer mortality. A relationship appears to exist between the number of MS components and the higher risk of all-cause cancer mortality and risk is escalated with the presence of three or more components. Thus MS and its implications extend beyond cardiovascular risk, like future risk of diabetes and may be cancer.

Metabolic syndrome and cardiovascular risk in South Asians is also heightened by their higher body fat, truncal subcutaneous fat, intra-abdominal fat, and ectopic fat deposition (e.g. liver fat). Further, cardiovascular risk cluster manifests at a lower level of adiposity and abdominal obesity. The cutoffs of body mass index and waist circumference for defining obesity and abdominal obesity, respectively, have been lowered and the definition of the metabolic syndrome has been revised for the Asian Indians in a recent consensus statement, so that physicians could intervene early with lifestyle management [4].

In recently held National Obesity and Metabolic Syndrome Summit in New Delhi, India, a consensus on diagnostic cutoffs of obesity (BMI, waist circumference) and optimal definition of the metabolic syndrome for Asian Indians was reached. Recommendations were as follows: BMI (kg/m²) cutoffs, normal, 18–22., overweight, 23–24., and obesity, ≥ 25 ; waist circumference cutoffs, ≥ 90 cm (male) and ≥ 80 cm (females) [5].

Epidemiologists in India and international agencies such as the World Health Organization (WHO) have been sounding an alarm on the rapidly rising burden of CVD for the past decade. The prevalence of MS among South Asians is higher than in other Asians and Europeans [6]. In India, CVD is projected to be the largest cause of death and disability by 2020, with 2.6 million Indians predicted to die due to coronary heart disease, which constitutes 54.1% of all CVD deaths [7].

There is high prevalence of metabolic syndrome in the urban Indian population. In a study involving 19 973 subjects across India, prevalence of CVD risk factors among individuals aged 20–69 years, the overall prevalence of most risk factors was high, with 50.9% of men and 51.9% of women being overweight, central obesity was observed among 30.9% of men and 32.8% of women, and 40.2% of men and 14.9% of women reported current tobacco use. The study demonstrated very high levels of CVD risk factors among a relatively young population from 10 industrial settings across India [7].

There are many studies from Asia in general and India in particular. There are many studies on the urban prevalence of metabolic syndrome [8] and a few on the rural prevalence. Some studies [9, 10] compared Indian rural population with urban for prevalence of metabolic syndrome. Most of these studies have used one criteria for diagnosis (NCEP, ATP III, IDF, AACE or WHO criteria).

The study by Puneet Gowda et al. [11] is unique in that the same rural population of south India in Karnataka was studied both by modified National Cholesterol Education Programme-Adult Treatment Panel III definition and International Diabetes Federation criteria for the diagnosis of Metabolic Syndrome to evaluate the concordance or discordance of the diagnosis. There was significant discordance in the prevalence of metabolic syndrome using two criteria. The authors are of the opinion that the discrepancy could be the higher WC cut-off in the modified NCEP ATP III criteria, which excludes subjects considered obese as per IDF criteria. The differences in combinations of the individual parameters in the two criteria could also contribute to the discrepancy.

Nearly 70% of Indian population lives in the rural areas. The difference in health care, life style and economics are very wide between rural and urban India. The lower prevalence of obesity, hypertension, dysglycemia and dyslipidemia in rural areas is obviously due to dietary and lifestyle differences between rural and urban India. The psychological stress which is common in urban living cannot be quantified easily, though it is well accepted as one of the risk factors for cardiovascular disease. It is surprising that smoking which is a significant risk factor is not included in the metabolic syndrome. Increasing urbanization and internal migration of people from rural to urban areas contribute

to increasing prevalence of metabolic syndrome which is a pre-diabetic and cardiac risk factor.

Is the combined cardiovascular risk of each component of metabolic syndrome greater than the CV risk of metabolic syndrome? In fact, the individual components of the MS have been recognized and treated effectively by physicians for many decades. Life style modifications and pharmacotherapy wherever indicated will reduce the burden of metabolic syndrome.

Cardio-metabolic risk is high in South Asians, starting at an early age. Increasing awareness of the cluster of risk factors and how to prevent them should be emphasized in population-based prevention strategies in South Asian countries, primarily focusing on children and adolescent.

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