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EDITORIAL

METABOLIC SYNDROME : EARLY IDENTIFICATION PREVENTS TYPE II DIABETES AND CARDIOVASCULAR DISEASE

Praveen Sharma[1] and Sandhya Mishra[2]

Department of Biochemistry, SMS Medical College, Jaipur, India.

The global prevalence of type 2 diabetes is expected to double in the period 2000 to 2025 and may reach a level of almost 300 million people i.e. 5-7.6% of the total global population by the year 2025. Patients with type 2 diabetes are at increased risk of coronary heart disease and stroke, which are the most common causes of cardiovascular disease. Atherosclerotic cardiovascular disease is the principle cause of death, disability and excess health care cost in diabetes. The patients with diabetes are more likely to die from first event of cardiovascular disease than their non-diabetic counter parts. Thus the efforts for early diagnosis and prevention of type 2 diabetes may prevent its costlier complications i.e. cardiovascular and renal diseases. The association of type 2 diabetes and cardiovascular disease has led to the hypothesis that both arise from common antecedent or common factors like Insulin resistance, Obesity, Dyslipidemia, Hypertension etc. It is rare to see type 2 diabetes, dyslipidemia, obesity or hypertension in isolation. Initially Gerald Reaven in 1988 described this as Syndrome X, and proposed that resistance to insulin mediated glucose disposal and consequent hyperinsulinemia is the pathological interface of several complex metabolic alterations and diseases (1). This concept was later codified by World Health Organization (WHO) as Metabolic Syndrome. In 1998 WHO proposed a definition of metabolic syndrome which states that a person has metabolic syndrome if he or she has diabetes, impaired glucose tolerance, impaired fasting glucose or insulin resistance, plus 2 or more of the following abnormalities: Blood Pressure $\geq$ 160/90 mmHg, Triglycerides $\geq$ 150 mg/dl (1.695 mmol/L) & or HDL Cholesterol $\leq$ 35 mg/dl (0.9 mmol/L male) $\leq$ 39 mg/dl (1.0 mmol/L female), W:H Ratio $\geq$ 0.90 male, $\geq$ 0.85 female & or BMI $\geq$ 30 kg/m^2, Urinary albumin excretion rate $\geq$ 20 µg/min and or Albumin/Creatinine ratio $\geq$ 20.

Address for Correspondence :

Prof. Praveen Sharma, PhD (Med), FACBI
Department of Biochemistry,
S. M. S. Medical College & Hospital, Jaipur-302004, India
E-mail: drpsharma_in@hotmail.com or editor@ijcb.co.in

There is no simple, clinically applicable test for insulin resistance. Use of hyperinsulinemic clamp for quantifying insulin resistance is cumbersome and expensive. Measurement of insulin level is also not reliable because of poor specificity. Looking to this, the Third report of National Cholesterol Education Program expert panel on detection, evaluation and treatment of high blood cholesterol in adults (ATPIII) proposed a new working definition of metabolic syndrome in 2001 based upon anthropometric measurements, blood pressure and simple laboratory investigations like fasting blood glucose, triglycerides and HDL-cholesterol which could easily be estimated (3). A person has the syndrome if he / she has three or more than three of the following: Waist Circumference men > 102 cm (> 40 inches), women > 88 cm (>35 inches); Triglycerides $\geq$ 150 mg/dl; HDL cholesterol men < 40 mg/dl, women < 50 mg/dl; Blood Pressure $\geq$ 130 systolic & $\geq$ 85 mmHg diastolic and Fasting Glucose $\geq$ 110 mg/dl. The presence of any 3 constitutes the syndrome and is associated with 3 fold higher risk of heart attack and stroke almost as high as diabetes. Thus ATPIII has considered metabolic syndrome as coronary heart disease risk equivalent. This suggests that people with more than two risk factors have risk of myocardial infarction same as coronary heart disease i.e. 20% in 10 years.

According to the International Diabetic Federation (2005) for a person to be defined as having the metabolic syndrome he/she must have Central Obesity (defined as waist circumference $\geq$ 94 cm for Europid men and $\geq$ 80 cm for Europid women, with ethnicity specific values for other groups), plus any two of the following four factors: Triglyceride level: $\geq$ 150 mg/dl (1.7 mmol/L) or specific treatment for lipid abnormality; HDL cholesterol: < 40mg/dl (1.03 mmol/L) in males and < 50 mg/dL (1.29 mmol/L) in females, or specific treatment for lipid abnormality; Blood Pressure: Systolic BP $\geq$ 130 or diastolic BP $\geq$ 85 mm Hg, or treatment of previously diagnosed hypertension; Fasting plasma glucose (FPG) $\geq$ 100 mg/dl (5.6 mmol/L), or previously diagnosed type 2 diabetes. If FPG is above 5.6 mmol/L or 100 mg/dl, Oral Glucose Tolerance Test

is strongly recommended but is not necessary to define the presence of the syndrome (4).

Hence there are many definitions of metabolic syndrome and no standard definition is routinely used. The prevalence of metabolic syndrome can differ depending on definition used. Besides this various anthropometric factors could differ with different ethnic population. There are certain points, which need special mention. First - the cut off point for low HDL is <50 mg/dl in women and not less than 40 mg/dl as it is in man. In CADI study 70% of women had HDL cholesterol <50 mg/dl although only 13% had total cholesterol level >240 mg/dl (5) and second – waist circumference is about 10 cm or 4 inches lower among Asian Indians than Whites. The new International Diabetic Federation Definition proposed central obesity to be measured as waist circumference $\geq$ 90 cm for South Asian men and $\geq$ 80 cm for women (4). Several reports suggest that for any given BMI Indians tend to have increased waist circumference. Further Indians also have excess body fat, abdominal and truncal obesity (6-9). For any given waist circumference they have increased body fat accumulation and insulin resistance. These features have been referred to as Indian phenotype or paradox. In view of this WHO has revised the BMI cut off for Asian Indians to be 25 kg/m^2 for obese as against 30 kg/m^2 recommended for Europeans (10).

The diagnosis of metabolic syndrome in an individual might help in prevention of diabetes and cardiovascular disease. However, substantial uncertainties still remain about the clinical definition of metabolic syndrome and whether the clustering of risk factors collectively indicate a discrete unifying disorder. Moreover, it is not clear whether diagnosing the syndrome confers benefit beyond risk assessment or treatment strategies associated with diagnosis and treating different components of the syndrome. Although, metabolic syndrome is characterized by the co-occurrence of central obesity, dyslipidemia (especially elevated level of triglycerides and low levels of HDL), hyperglycemia and hypertension, still no consensus exist about specific threshold for establishing the diagnosis of each of the component of the syndrome. The inclusion of insulin resistance or diabetes in WHO criteria is also controversial. The individual components of the syndrome normally cluster together rather than, by chance alone, suggesting the existence of a discrete disorder (11). It is long been thought that insulin resistance, primarily in skeletal muscle and liver is important pathophysiological cause of the syndrome, although insulin resistance is a consistent early abnormality in pathogenesis of type 2 diabetes, its association with cardiovascular disease is less certain.

Although, obesity is considered as an important component in most of the definitions and major driving force behind clustering of risk factors, yet not all obese subjects are insulin resistant. Further the clustering of elevated blood pressure with other components is also not clear. Moreover, the prevention of diabetes and cardiovascular disease by identifying metabolic abnormalities, would be as effective as prevention of obesity or other components, is debatable. Evidences support that people with metabolic syndrome are at relatively greater risk of developing diabetes and cardiovascular disease because components of metabolic syndrome are established risk factors for diabetes and cardiovascular disease. Whether metabolic syndrome increases greater risk for adverse outcome than predicted by the presence of individual components is still not clear. Golden et al (12) indicated that syndrome traits increase atherosclerosis of carotid artery to a greater degree than expected solely by their additive effect. Similarly another study showed that participants with Framingham score greater than 20% had greater risk for cardiovascular disease events as compared to participants with elevated risk score without metabolic syndrome (13). Metabolic syndrome is constellation of risk factors, acting synergistically and one or all of which may share a common etiology. Moreover, the confluence of risk factors that comprise the syndrome have a synergistic negative impact on prognosis (14).

Thus it is reasonable to think that diagnosis of metabolic syndrome may point us to right direction for effective prevention of Type 2 diabetes and cardiovascular disease, still, more comprehensive and definitive data on the outcome and effect of intervention are required before practicing this concept. Another question is about the addition of various elements in the definition of metabolic syndrome, which are common factors that increase risk, or those with common etiology. The elements, which have common pathophysiological pathway in the development of components of metabolic syndrome like inflammatory markers and oxidative stress, definitely need to be included. Data suggest that inflammation and oxidative stress may be important underlying etiology of metabolic syndrome which are also reported to be associated with insulin resistance (15-16).

Therefore carefully defining the metabolic syndrome is important for more effective preventive and treatment strategies. The goal of identifying metabolic abnormalities is to prevent morbidity and mortality due to type 2 diabetes mellitus and cardiovascular disease. As we know that modest life style changes can substantially reduce the risk of diabetes in mildly hyperglycemic subjects or controlling blood pressure

and lipids may substantially reduce risk of cardiovascular events in hypertension or hyperlipidemia. Insulin sensitization may be beneficial in preventing type 2 diabetes but it is not clear whether insulin sensitization will correct all the metabolic disturbances of the metabolic syndrome or prevent cardiovascular disease.

Diabetes is becoming an epidemic world wide especially Asian and developing countries. In the developed nations further urbanization is likely to be limited. Only ageing and the increase in population size will produce a relatively small increase in the future prevalence of type 2 diabetes, predominantly among the elderly. However, in developing nations urbanization is occurring rapidly and is producing lifestyle changes that adversely affect metabolism and are thereby causing a large increase in the number of diabetic patients. In the developing countries diabetes occurs at a younger age than in developed countries. Long-term complications of diabetes will also occur in a large proportion of diabetic patients in the developing countries during the most productive years of their lives, causing sever economic and social burden. Therefore, developing countries such as India are expected to confront an enormous health care burden. The prevalence of diabetes in India has increased 10 fold in three decades and by the year 2025 Indians will contribute almost 20% of total world diabetic population paralleled with obesity and physical inactivity. Probably obesity is the link between metabolic syndrome and insulin resistance. The best reason to consider diagnosis of metabolic syndrome is to identify obese people who are most likely to be benefited from aggressive efforts. Hence there is urgent need of some concrete strategies for screening and identification of metabolic risk abnormalities at early stage in these populations to save the community from the burden of diabetes and its costlier complications.

Authors are [1]Editor in Chief and [2]Associate Editor of Indian Journal of Clinical Biochemistry

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