

Metabolic Syndrome and Cardiometabolic Risk – Driving the CVD epidemic - Time to Act

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The constellation of dyslipidemia comprising of hypertriglyceridemia (with consequent increase in small density sLDL) and low levels of high-density lipoprotein cholesterol, elevated blood pressure, impaired glucose tolerance, and central obesity is identified now as metabolic syndrome, also called as syndrome X. Soon, metabolic syndrome will overtake cigarette smoking as the number one risk factor for heart disease among all the population on the globe. The National Cholesterol Education Program (NECP)- Adult Treatment Panel (ATP) III has clearly identified metabolic syndrome as indication for vigorous lifestyle intervention. Effective interventions are diet, exercise, and judicious use of pharmacologic agents to address specific risk factors. Weight loss significantly improves all aspects of metabolic syndrome. Increasing physical activity and decreasing caloric intake by reducing quantity of food consumed will improve metabolic syndrome abnormalities, even in the absence of weight loss. Specific dietary changes that are appropriate for addressing different aspects of the syndrome include reducing saturated fat intake to lower insulin resistance, reducing sodium intake to lower blood pressure, and reducing high-glycemic-index carbohydrate intake to lower triglyceride levels. A diet that includes more fruits, vegetables, whole grains, monounsaturated fats, and low-fat dairy products will benefit most patients with metabolic syndrome, in fact everyone. Family physicians have a strong role to play in helping patients to change their lifestyle behaviors by assessing each patient for the presence of specific risk factors, clearly communicating these risk factors in no uncertain terms to all patients and their spouses, prescribing appropriate interventions to address specific risks, and assisting patients in identifying barriers to behavior changes.

Diabetes: a growing threat

Diabetes is one of the most common chronic diseases worldwide affecting nearly 200 million people (approximately 5 per cent of the adult population), and is the fourth leading cause of

death in the whole world. If unchecked, by 2025 it is expected that diabetes will reach epidemic proportions, affecting 333 million people globally. While much of this increase is expected to occur mainly in developing countries, particularly Asian countries, the reasons behind the increase are the consequence of population ageing, increasing urbanization, unhealthy life styles and diets, fast foods, westernization without physical exercise, obesity and sedentary lifestyles.

Each year, 3.2 million people around the world die from complications associated with diabetes. In countries with a high diabetes incidence, such as the Asian Indians, as many as one in four deaths in adults aged between 35 and 64 years is due to this disease. Type 2 diabetes, which accounts for 90 per cent of all diabetes, has become one of the major causes of premature illness and death, mainly through the increased risk of cardio vascular disease (CVD) which is responsible for up to 80 per cent of these deaths. These cardio vascular complications of diabetes (which is also a leading cause of blindness, amputation and kidney failure) account for much of the social and financial burden of the disease. The prediction that diabetes incidence will double by 2025 heralds a parallel rise in cardiovascular-related illness and death, with an inevitable and profound impact on global healthcare systems. However, even before levels of blood glucose are high enough for a person to be diagnosed with diabetes, hyperglycemia and related changes in blood lipids (increase in triglycerides and decrease in the 'good' cholesterol HDL-c) increase a person's risk of cardiovascular disease. It is well established that the macrovascular complications of diabetes start right at the time of insulin resistance and pre-diabetes. The metabolic syndrome, now named as the *cardiovascular time bomb* is a cluster of the most dangerous heart attack risk factors: diabetes and pre diabetes, abdominal obesity, high cholesterol and high blood pressure. It is estimated that around a quarter of the world's adult population have metabolic syndrome and they 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. In

addition, people with metabolic syndrome have a fivefold greater risk of developing type 2 diabetes. The clustering of CVD risk factors that typifies the metabolic syndrome is now considered to be the driving force for a CVD epidemic.

Global burden

With a rise in co-morbid disease on this scale, the burden on national healthcare systems and budgets is almost incalculable. The annual direct healthcare cost of diabetes worldwide for this age group is calculated to be as much as 286 billion, or even more. If diabetes prevalence continues to rise as anticipated, it is possible that this figure will increase to 396 billion. This will mean a spend of between up to 13 per cent of the world's healthcare budget on diabetes care in 2025, with high prevalence countries spending up to 40 per cent of their budget. It is important to note that these estimates of burden on national healthcare systems are for type 2 diabetes only and do not, as yet, estimate the additional burden of the cardiovascular disease associated with metabolic syndrome where clinical diabetes is not yet present.

What causes the metabolic syndrome?

In most people with glucose intolerance or type 2 diabetes, there is a multiple set of risk factors that commonly appear together, forming what is now known as the 'Metabolic Syndrome', but which has previously been termed 'Syndrome X', the 'Deadly Quartet' and more recently, the 'Insulin Resistance Syndrome'. This important 'clustering' of metabolic abnormalities that occur in the same individual, and which appear to confer a substantial additional cardiovascular risk over and above the sum of the risk associated with each abnormality, has been the subject of intense debate with such groups as the WHO and the National Cholesterol Education Program – Third Adult Treatment Panel (NCEP ATP III) seeking to develop diagnosis and management guidelines around the combined presence of elevated blood sugar levels, an abnormal lipid profile, high blood pressure and abdominal obesity. If diabetes is not already present, the metabolic syndrome is a strong predictor for its development, the risk for type 2 diabetes being five times more likely in individuals with the syndrome. While each

individual component of the metabolic syndrome confers an increased risk of cardiovascular-related death, this risk is more pronounced when the metabolic syndrome itself is present. The more components of the metabolic syndrome that are evident, the higher is the cardiovascular mortality rate. The underlying cause of the metabolic syndrome continues to challenge the experts but both insulin resistance and central obesity are considered significant factors. Genetics, physical inactivity, ageing, a pro-inflammatory state and hormonal changes may also have a causal effect, but the role of these may vary depending on ethnic group.

Insulin resistance

Insulin resistance occurs when cells in the body (liver, skeletal muscle and adipose tissue) become less sensitive and eventually resistant to insulin, the hormone which is produced by the pancreas to facilitate glucose absorption. Glucose can no longer be absorbed by the cells but remains in the blood, triggering the need for more and more insulin (hyper insulinaemia) to be produced in an attempt to process the glucose. The ever increasing stimulation of beta cells to release more amounts of insulin strains the pancreatic beta cells and eventually wears them out (beta cell apoptosis). Once the pancreas is no longer able to produce enough insulin then a person becomes hyper glycaemic and will be diagnosed with type 2 diabetes. Even before this happens, damage is occurring to the body, including a build-up of triglycerides which further impairs insulin sensitivity and damage to the body's microvascular system (leading to kidney, eye and nerve damage). Strongly associated with irregularities in glucose & lipid metabolism, insulin resistance is the important underlying feature of the metabolic syndrome and type 2 diabetes.

Free fatty acids

The mechanisms by which insulin resistance may exert an atherogenic effect include the build-up of triglycerides (TG) and free fatty acids (FFA). High concentrations of plasma FFA are common in type 2 diabetes, with early detection signifying a shift for the individual from impaired glucose tolerance (IGT) to type 2 diabetes. Insulin resistance in adipose tissue (fat

cells) results in a flux of FFA from the adipose tissue to the liver causing insulin resistance in the liver and in peripheral tissues. Fatty acids block glucose oxidation and glucose transport, but they also cause atherogenic dyslipidemia by inducing production in the liver of very low-density lipoprotein (LDL) particles that lead to the elevation of TG and apolipoprotein B (ApoB) and the lowering of high density lipoprotein cholesterol (HDL-c). An increase in TG, in addition to high LDL-c levels, significantly increases the risk for coronary heart disease (CHD), while low HDL-c is considered to be a particularly key risk factor for CVD in both non diabetic and diabetic individuals, as confirmed in epidemiological studies and in the Lipid Research Clinics Prevalence Study which found HDL-c to be an independent contributor to CVD in both men and women and a stronger risk factor for CVD in people with diabetes compared with non diabetic individuals. Significantly, low HDL-c and high TG are frequently found with insulin resistance, with or without type 2 diabetes. This complex lipid profile, observed with both type 2 diabetes and the metabolic syndrome, is considered an extremely high risk factor for CVD as all of the abnormalities have been implicated as being independently atherogenic.

Central obesity

Obesity, now thought to affect 50 to 60 per cent of a nation's adult population, is associated with insulin resistance and the metabolic syndrome. Obesity contributes to Insulin Resistance, hyperglycemia, hypertension, high serum cholesterol, low HDL-c and is independently associated with higher CVD risk. The risk of serious health consequences in the form of type 2 diabetes, CHD and a range of other conditions, including some forms of cancer, has been shown to rise with an increase in body mass index (BMI), but it is an excess of body fat in the abdomen, measured simply by waist circumference, that is more indicative of the metabolic syndrome profile than BMI. The International Obesity Task Force (IOTF) reports that 1.7 billion of the world's population is already at a heightened risk of weight-related, non-communicable diseases such as type 2 diabetes and metabolic

syndrome. The mechanism by which excessive body fat causes insulin resistance and impairs glucose metabolism is not clearly defined but fat stores particularly visceral adipose tissue are an important cause of increased FFA and TG in the skeletal muscle, which impairs insulin secretion, raising blood glucose levels and the likelihood of developing diabetes. Excess adipose tissue, particularly the visceral fat tissue in the abdomen, also releases *inflammatory cytokines* that increase insulin resistance in the body's skeletal muscles. Furthermore, central obesity is also associated with a decreased production of *adiponectin*, which is the adipose-specific, collagen-like molecule found to have anti-diabetic, anti-atherosclerotic and anti-inflammatory functions. Eighty-five per cent of obese individuals have some degree of insulin resistance which can be improved with weight loss. Inactivity also plays a role via the mechanism of GLUT-4, a chemical receptors on cell surface which facilitate glucose absorption by the cells. Physical inactivity lowers levels of GLUT-4 making it less effective. Lack of exercise will also increase levels of FFA in the blood thus stepping up the storage of visceral fat, both of which are implicated in the etiology of insulin resistance.

Worldwide IDF definition for clinical practice

As per the new International Diabetes Federation definition metabolic syndrome person must have

Central obesity (defined as waist circumference ≥ 90 cm for Indian men and ≥ 80 cm for Indian women, plus any two of the following four

1. **Raised TG level:** ≥ 150 mg% or history of treatment for triglyceridemia;
2. **Reduced HDL cholesterol:** < 40 mg% in men and < 50 mg% in women or history of treatment for low HDL;
3. **Raised blood pressure:** systolic BP ≥ 130 or diastolic BP ≥ 85 mm Hg or history of treatment for hypertension;
4. **Raised fasting plasma glucose** (FPG) ≥ 100 mg% or previously diagnosed type 2 diabetes or history of treatment for type 2 diabetes. If the PPG > 100 mg%, an oral glucose tolerance test (OGTT) is advised though this is not mandatory for the diagnosis of metabolic syndrome. This IDF definition is the consensus definition accepted by all groups.