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Metabolic syndrome—driving the CVD epidemic

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 or fifth leading cause of death in the developed world. If unchecked, by 2025 it is expected that diabetes will reach epidemic proportions, affecting 333 million people (a rise in prevalence to 6.3 per cent) globally. While much of this increase is expected to occur in developing countries, the reasons behind the increase are not country-specific but the consequence of population ageing, increasing urbanisation, unhealthy diets, obesity and sedentary lifestyles.[1–3]

Diabetes and the metabolic syndrome—driving the CVD epidemic

Each year, 3.2 million people around the world die from complications associated with diabetes. In countries with a high diabetes incidence, such as those in the Pacific and the Middle East, as many as one in four deaths in adults aged between 35 and 64 years is due to the 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 cardiovascular disease (CVD) which is responsible for up to 80 per cent of these deaths.[2,4]

These cardiovascular 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.[2,3] 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, hyperglycaemia 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.[2]

The metabolic syndrome is a cluster of the most dangerous heart attack risk factors: diabetes and prediabetes, abdominal obesity, high cholesterol and high blood pressure. It is estimated that around a quarter of the world's adult population have metabolic syndrome[5] 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.[6] In addition, people with metabolic syndrome have a fivefold greater risk of developing type 2 diabetes.[7] 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 comorbid disease on this scale, the burden on national healthcare systems and budgets is almost incalculable. It was estimated that in 2003 for the 25 European Union countries the total direct healthcare costs of all diabetes in 20 to 79 year olds was approximately 64.9 billion international dollars (ID), equivalent to 7.2 per cent of the total health expenditure for these countries.[2,8] 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.[2]

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',[9] the 'Deadly Quartet'[10] and more recently, the 'Insulin Resistance Syndrome'.[11,12] This '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,[6,13,14] 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.[15,16] 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.[7]

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.[17]

The underlying cause of the metabolic syndrome continues to challenge the experts but both insulin resistance and central obesity are considered significant factors.[18,19] Genetics, physical inactivity, ageing, a proinflammatory state and hormonal changes may also have a causal effect, but the role of these may vary depending on ethnic group.[20,21]

- **Insulin resistance**

Insulin resistance occurs when cells in the body (liver, skeletal muscle and adipose/fat 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 (hyperinsulinaemia) to be produced in an attempt to process the glucose. The production of ever-increasing amounts of insulin strains and may eventually wear out the beta cells in the pancreas, responsible for insulin production. Once the pancreas is no longer able to produce enough insulin then a person becomes hyperglycaemic (too much glucose in the blood) 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 both glucose and lipid metabolism, insulin resistance is an 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 dyslipidaemia** 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),[22] 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[23] and in the Lipid Research Clinics Prevalence Study[24] 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.[25]

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.[22,26–29]

- **Central obesity**

Obesity, now thought to affect 50 to 60 per cent of a nation's population,[2] is associated with insulin resistance and the metabolic syndrome. Obesity contributes to hypertension, high serum cholesterol, low HDL-c and hyperglycaemia, and is independently associated with higher CVD risk.[19,30,31] 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),[32] 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.[33–35] 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.[36]

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.[37]

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 which facilitates glucose absorption by the cells. Physical inactivity lowers levels of GLUT-4 making it less effective. Lack of exercise may also increase levels of FFA in the blood thus stepping up the storage of visceral fat, both of which are implicated in the aetiology of insulin resistance.

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