METABOLIC SYNDROME: A GROWING THREAT

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INTRODUCTION

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.(Gan, n.d.)("Estimates for the year 2000 and projections for 2030," 2004)("WHO_TRS_844.pdf," n.d.)

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 64years 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 CVD which is responsible for up to 80 per cent of these deaths.(Gan, n.d.)(Turner et al., 1998)

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'. This 'clustering' of metabolic abnormalities that occur in the same individual appear to confer a substantial additional cardiovascular risk over and above the sum of the risk associated with each abnormality.(Sattar et al., 2003)

The 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.("WHO_TRS_844.pdf," n.d.)

DEFINITION

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. (Issues, 2007) 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.("Cardiovascular Morbidity and Mortality," 2001) In addition, people with metabolic syndrome have a fivefold greater risk of developing type 2 diabetes.(Model, 2004)

Part 1: Worldwide definition for use in clinical practice

Table 1: The new International Diabetes Federation (IDF) definition

According to the new IDF definition, for a person to be defined as having the metabolic syndrome they must have:

Central obesity (defined as waist circumference* with ethnicity specific values)

plus any two of the following four factors:

Raised triglycerides	≥ 150 mg/dL (1.7 mmol/L) **or specific treatment for this lipid abnormality**
Reduced HDL cholesterol	< 40 mg/dL (1.03 mmol/L) in males < 50 mg/dL (1.29 mmol/L) in females **or specific treatment for this lipid abnormality**
Raised blood pressure	systolic BP ≥ 130 or diastolic BP ≥ 85 mm Hg **or treatment of previously diagnosed hypertension**
Raised fasting plasma glucose	(FPG) ≥ 100 mg/dL (5.6 mmol/L), **or previously diagnosed type 2 diabetes** If above 5.6 mmol/L or 100 mg/dL, OGTT is strongly recommended but is not necessary to define presence of the syndrome.

** If BMI is >30kg/m², central obesity can be assumed and waist circumference does not need to be measured.*

*** These values have been updated from those originally presented to ensure consistency with ATP III cutpoints**

ETIOLOGY:

The underlying cause of the metabolic syndrome continues to challenge the experts but both insulin resistance and central obesity are considered significant factors.(Hu et al., 2004)(Carr et al., n.d.)

Genetics, physical inactivity, ageing, a proinfl ammatory state and hormonal changes may also have a causal effect, but the role of these may vary depending on ethnic group.("diagnosis n complications of DM.pdf," n.d.) (Detection, Evaluation, & Adults, 2001)

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 beta cells in 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 weakens and may eventually wear out the beta cells. 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),(Steinmetz, Fenselau, & Schrezenmeir, 2001) 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(SJ, Collins, JT, & al, 2001) and in the Lipid Research Clinics Prevalence Study(JACOBS et al., 1990) 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.(Aas, 2003)

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.(Brunzell & Ayyobi, 2014) (Stamler, Vaccaro, Neaton, & Wentworth, 1993)

Central obesity

Obesity 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.(Zimmet, 2002)The risk of serious health consequences in the form of type 2 diabetes, coronary heart disease (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),(Lee, JE, CH, RS, & Jr, 1993) but it is an excess of body fat in the abdomen, measured simply by waist circumference(Table No. 2), that is more indicative of the metabolic syndrome profile than BMI.2(Pouliot et al., 1994)(Rexrode et al., 1998)

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 antidiabetic, anti-atherosclerotic and anti-inflammatory functions.

Adiponectin is an anti-inflammatory cytokine that is produced by adipocytes. Adiponectin not only enhances insulin sensitivity, but also inhibits several steps in the inflammatory process. It also inhibits hepatic gluconeogenic enzymes and the rate of endogenous glucose production in the liver. It increases glucose transport in muscle and enhances fatty acid oxidation.(Eckel, Grundy, & Zimmet, 2005)

Adiponectin has been strongly correlated with cardiovascular health and decreased concentrations are associated with manifestations of the Metabolic Syndrome, including C reactive protein, fibrinogen, hypertension and endothelial function. Decreased levels of adiponectin are associated with higher BMI, insulin resistance, unfavorable plasma lipid profiles and the development of cardiovascular disease(Hutley & Prins, 2005)

Leptin is secreted by adipocytes and secretion is regulated by the size of fat stores. Leptin receptors are located mostly in the hypothalamus and the brain stem and signals through these receptors controls satiety, energy expenditure and neuroendocrine function. Most overweight and obese individuals have elevated levels of leptin that do not suppress appetite, or in other words, leptin resistance. Leptin resistance is thought to be a fundamental pathology in obesity(Hutley & Prins, 2005).

Tumor necrosis factor-alpha has also been implicated in the development of obesity and insulin resistance. Elevated levels of tumor necrosis factor-alpha are positively correlated with insulin resistance and chronic exposure of tumor necrosis factor-alpha induces insulin resistance.(Kershaw & Flier, 2004) Tumor necrosis factor-alpha may also impair insulin receptor tyrosine kinase activity and lead to impaired downstream insulin signaling (Abate, 2014) Tumor necrosis factor-alpha also impairs insulin signaling by increasing serum non-esterfied fatty acids, which can induce insulin resistance in many tissues (Kershaw & Flier, 2004)

Plasminogen activator inhibitor-1 is a regulator protein in the coagulation cascade and elevated levels in obese states are a known risk factor for thrombosis, as it decreases the generation of plasmin and thus decreases fibrinolysis. High levels of plasminogen activator inhibitor-1 along with obesity-induced increases in clotting factors and platelet activation create a hypercoagulable state, atherogenesis and increase cardiovascular risk. Plasminogen activator inhibitor-1 has also been implicated in the accumulation of visceral fat .(Hutley & Prins, 2005)

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.

Table 2: Ethnic specific values for waist circumference

Country/Ethnic group		Waist circumference
Europids* In the USA, the ATP III values (102 cm male; 88 cm female) are likely to continue to be used for clinical purposes	Male	≥ 94 cm
	Female	≥ 80 cm
South Asians Based on a Chinese, Malay and Asian-Indian population	Male	≥ 90 cm
	Female	≥ 80 cm
Chinese	Male	≥ 90 cm
	Female	≥ 80 cm
Japanese**	Male	≥ 90 cm
	Female	≥ 80 cm
Ethnic South and Central Americans	Use South Asian recommendations until more specific data are available	
Sub-Saharan Africans	Use European data until more specific data are available	
Eastern Mediterranean and Middle East (Arab) populations	Use European data until more specific data are available	

** In future epidemiological studies of populations of Europid origin, prevalence should be given using both European and North American cut-points to allow better comparisons.*
*** Originally different values were proposed for Japanese people but new data support the use of the values shown above.*

Although a higher cut-point is currently used for all ethnic groups in the USA for clinical diagnosis, it is strongly recommended that for epidemiological studies and, wherever possible, for case detection, ethnic group specific cut-points should be used for people of the same ethnic group wherever they are found. Thus the criteria recommended for Japan would

also be used in expatriate Japanese communities, as would those for South Asian males and females regardless of place and country of residence.11

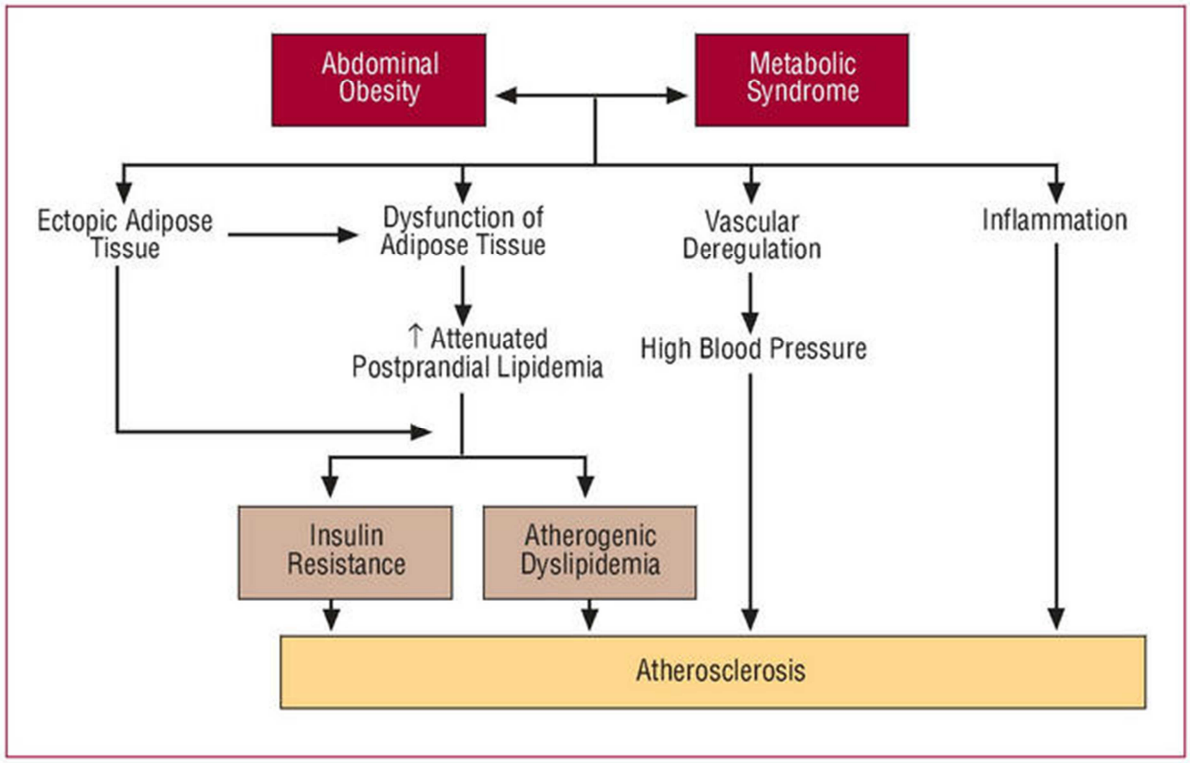

Fig. Pathogenesis of Metabolic syndrome due to abdominal obesity

Dyslipidaemia

In general, with increases in free fatty acid flux to the liver, increased production of very low-density lipoproteins (VLDL) occurs. Under physiological conditions, insulin inhibits the secretion of VLDL into the systemic circulation. In the setting of insulin resistance, increased flux of free fatty acids to the liver increases hepatic triglyceride

synthesis. Thus, hypertriglyceridaemia is an excellent reflection of the insulin resistant condition and is one of the important criteria for diagnosis of the metabolic syndrome.

The other major lipoprotein disturbance in the metabolic syndrome is a reduction in HDL cholesterol. This reduction is a consequence of changes in HDL composition and metabolism.

In the presence of hypertriglyceridaemia, a decrease in the cholesterol content of HDL results from decreases in the cholesteryl ester content of the lipoprotein core with variable increases in triglyceride. In addition to HDL, the composition of LDL is also modified in a similar way. In fact, with fasting serum triglycerides > 2.0 mmol/L, almost all patients have a predominance of small dense LDL. This change in LDL composition is attributable to relative depletion of unesterified and esterified cholesterol, and phospholipids, with either no change or an increase in LDL triglyceride. In some studies, this alteration in LDL composition is an independent risk factor for cardiovascular disease. However, more often this association is not independent, but related to the concomitant changes in other lipoproteins and other risk factors.

IDF consensus group has highlighted a number of other parameters that appear to be related to the metabolic syndrome (Table 3) which should be included in research studies to help determine the predictive power of these extra criteria for CVD and/or diabetes. The use of these additional factors in research will also allow further modification of the definition if necessary and the validation of the new clinical definition in different ethnic groups.

Table 3: Additional metabolic measurements for research

Abnormal body fat distribution	General body fat distribution (DEXA) Central fat distribution (CT/MRI) Adipose tissue biomarkers: leptin, adiponectin Liver fat content (MRS)
Atherogenic dyslipidaemia (beyond elevated triglyceride and low HDL)	ApoB (or non-HDL-c) Small LDL particles
Dysglycaemia	OGTT
Insulin resistance (other than elevated fasting glucose)	Fasting insulin/proinsulin levels HOMA-IR Insulin resistance by Bergman Minimal Model Elevated free fatty acids (fasting and during OGTT) M value from clamp
Vascular dysregulation (beyond elevated blood pressure)	Measurement of endothelial dysfunction Microalbuminuria
Proinflammatory state	Elevated high sensitivity C-reactive protein Elevated inflammatory cytokines (eg TNF-alpha, IL-6) Decrease in adiponectin plasma levels
Prothrombotic state	Fibrinolytic factors (PAI-1, etc) Clotting factors (fibrinogen, etc)
Hormonal factors	Pituitary-adrenal axis

Recommendations for treatment

Once a diagnosis of the metabolic syndrome is made, the future management of the condition should be aggressive and uncompromising in its aim to reduce the risk of CVD and type 2 diabetes. Patients should undergo a full cardiovascular risk assessment (including smoking status) in conjunction with the following:

• **Primary intervention**

IDF recommends that primary management for the metabolic syndrome is healthy lifestyle promotion. This includes:

- moderate calorie restriction (to achieve a 5–10 per cent loss of body weight in the first year)
- moderate increase in physical activity
- change in dietary composition

The results of Finnish and American prevention of diabetes studies have shown the marked clinical benefits associated with a small weight loss in terms of preventing (or at least delaying by several years) the conversion to type 2 diabetes among high-risk individuals with glucose intolerance who were, generally, obese.(Tuomilehto et al., 2001)

• Secondary intervention

In people for whom lifestyle change is not enough and who are considered to be at high risk for CVD, drug therapy may be required to treat the metabolic syndrome. While there is a definite need for a treatment that can modulate the underlying mechanisms of the metabolic syndrome as a whole and thereby reduce the impact of all the risk factors and the long term metabolic and cardiovascular consequences, these mechanisms are currently unknown and specific pharmacological agents are therefore not yet available.

As defined in Table 4, it is currently necessary instead to treat the individual components of the syndrome in order that a reduction in the individual risk associated with each one will reduce the overall impact on CVD and diabetes risk.

Table 4: IDF recommended treatment of the individual components of the metabolic syndrome

Atherogenic dyslipidaemia
Primary aims for therapy: • Lower TG (as well as lowering ApoB and non-HDL cholesterol) • Raise HDL-c levels • Reduce LDL-c levels (elevated levels represent a high risk in the metabolic syndrome) Options: • Fibrates (PPAR alpha agonists) improve all components of atherogenic dyslipidaemia and appear to reduce the risk for CVD in people with metabolic syndrome. The Veterans Affairs High-Density Lipoprotein Intervention Trial (VA-HIT) showed that raising HDL-c concentrations using a fibrate in patients with well-established CHD and both a low HDL-c and a low LDL-c level will significantly reduce the incidence of major coronary events.(Aas, 2003) • Statins to reduce all ApoB-containing lipoproteins and to achieve ATP III goals for LDL-c as well as for non-HDL-c (ATP III, 2001). Several clinical studies have confirmed the benefits of statin therapy.(SM, CM, TJ, & al, 1999)(Diabetic et al., 1998) • Fibrates in combination with statins but may be complicated by side effects

Elevated blood pressure
• Categorical hypertension (BP ≥ 140/≥ 90 mm Hg) should be treated according to the USA Seventh Report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure (JNC 7) recommendations.(Chobanian et al., 2003) • In patients with established diabetes, antihypertensive therapy should be introduced at BP ≥ 130/≥ 80 mm Hg. Options: • Angiotensin converting enzyme inhibitors and angiotensin receptor blockers are useful antihypertensive drugs, with some clinical trials (but not all) suggesting they carry advantages over other drugs in patients with diabetes. At this time, however, the majority of clinical trials suggest that the risk reduction associated with antihypertensive drugs is the result of blood pressure lowering per se and not due to a particular type of drug. • No particular agents have been identified as being preferable for hypertensive patients who also have the metabolic syndrome.

Insulin resistance and hyperglycaemia
There is growing interest in the possibility that drugs that reduce insulin resistance will delay the onset of type 2 diabetes and will reduce CVD risk when metabolic syndrome is present. The Diabetes Prevention Program (DPP) showed that metformin therapy in patients with prediabetes will prevent or delay the development of diabetes and recent thiazolidinedione studies have also demonstrated efficacy in delaying or preventing type 2 diabetes in patients with impaired glucose tolerance (IGT) and insulin resistance.(Group, 2002) (Buchanan et al., 2002) urbin, R. J. (2004)(Durbin, 2004) Similarly, other studies have shown that both acarbose and orlistat can be used to delay the development of type 2 diabetes in patients with IGT.(Chiasson, RG, Gomis, & al, 2003) (Torgerson, Hauptman, Boldrin, & Sjöström, 2004) Data do not yet exist to show whether any of the currently available thiazolidinediones reduce the risk of CVD in those with the metabolic syndrome, IGT or diabetes.

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