

1. PATHOPHYSIOLOGY OF METABOLIC SYNDROME

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1 Introduction

The metabolic syndrome is a constellation of interrelated abnormalities (namely obesity, dyslipidaemia, hyperglycaemia, and hypertension) that increase the risk for cardiovascular disease and type 2 diabetes. This is a common metabolic disorder which increases in prevalence as the population becomes more obese. The disorder is defined in various ways. Diagnostic criteria for the metabolic syndrome have been established by the World Health Organisation (WHO) in 1998, by the National Cholesterol Education Program's Adult Treatment Panel III (NCEP: ATP III), in 2001, and more recently by the International Diabetes Federation (IDF), in 2005. The metabolic syndrome was introduced as a diagnostic category to identify the individuals that satisfy arbitrary chosen criteria to initiate lifestyle changes, and drug treatment when needed, with the goal of decreasing risk of cardiovascular disease and type 2 diabetes mellitus.

Table 1. Definitions of the metabolic syndrome. By: a) World Health Organisation, b) National Cholesterol Education Program's Adult Treatment Panel III, c) International Diabetes Federation (1, 2, 3)

a) World Health Organisation, 1998

Diabetes or impaired fasting glycaemia or impaired glucose tolerance or insulin resistance (hyperinsulinaemic, euglycaemic clamp-glucose uptake in lowest 25%)

Plus any two of the following:

Obesity: BMI > 30 or waist-to-hip ratio > 0.9 (male) or > 0.85 (female)

Dyslipidaemia: triglycerides \geq 1.7 mmol/L or HDL cholesterol < 0.9 (male) or < 1.0 (female) mmol/L

Hypertension: blood pressure > 140/90 mm Hg

Microalbuminuria: albumin excretion > 20 μ g/min

b) National Cholesterol Education Program's Adult Treatment Panel III (NCEP: ATP III), 2001

Any 3 of the following:

Central obesity: waist circumference > 102 cm (male), > 88 cm (female)

Hypertriglyceridaemia: triglycerides \geq 1.7 mmol/L

Low HDL cholesterol: < 1.0 mmol/L (male), < 1.3 mmol/L (female)

Hypertension: blood pressure \geq 135/85 mm Hg or medication

Fasting plasma glucose \geq 6.1 mmol/L

c) International Diabetes Federation, 2005

Central obesity (defined as waist circumference \geq 94 cm for Europoid men and \geq 80 cm for Europoid women)

Plus any two of the following:

Raised triglycerides > 1.7 mmol/L, or specific treatment for this lipid abnormality

Reduced HDL cholesterol: < 1.03 mmol/L in males, and 1.29 mmol/L in females, or specific treatment for this lipid abnormality

Raised blood pressure: systolic blood pressure \geq 130mmHg or diastolic blood pressure \geq 85 mmHg

Raised fasting plasma glucose ≥ 5.6 mmol/L, or previously diagnosed diabetes mellitus

2 Pathogenesis of metabolic syndrome

1 Insulin resistance

The most accepted hypothesis to describe the pathophysiology of the metabolic syndrome is insulin resistance. That is why the metabolic syndrome is also known as the insulin resistance syndrome. Insulin resistance has been defined as a defect in insulin action that results in hyperinsulinaemia, necessary to maintain euglycaemia. Concept of insulin resistance provides a conceptual framework with which to place a substantial number of apparently unrelated biological events into a pathophysiological construct.

A major contributor to the development of insulin resistance is an overabundance of circulating fatty acids, released from an expanded adipose tissue mass. FFA reduce insulin sensitivity in muscle by inhibiting insulin-mediated glucose uptake. Increased level of circulating glucose increases pancreatic insulin secretion resulting in hyperinsulinemia. In the liver, FFA increase the production of glucose, triglycerides and secretion of very low density lipoproteins (VLDL). The consequence is the reduction in glucose transformation to glycogen and increased lipid accumulation in triglyceride (TG). Insulin is an important antilipolytic hormone. In the case of insulin resistance, the increased amount of lipolysis of stored triacylglycerol molecules in adipose tissue produces more fatty acids, which could further inhibit the antilipolytic effect of insulin, creating additional lipolysis.

2 Obesity and increased waist circumference

The WHO and ATP III definitions of metabolic syndrome both include abdominal obesity, but it is a necessary requirement in the IDF definition (Table 1.). That reflects the IDF position - though the pathogenesis of the metabolic syndrome and its components is complex, abdominal obesity is a key causative factor. Despite the importance of obesity in the model, we should remember that patients of normal weight can also be insulin resistant. Those are called metabolically obese, normal-weight individuals, typically having increased amount of visceral adipose tissue. According to some theories, with increases in visceral adipose tissue, a higher rate of flux of adipose tissue-derived free fatty acids to the liver through the splanchnic circulation would be expected, while increases in abdominal subcutaneous fat could release lipolysis products into the systemic circulation and avoid more direct effects on hepatic metabolism.

3 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.

4 Glucose intolerance

The defects of insulin action in glucose metabolism include failure to suppress gluconeogenesis in the liver, and to mediate glucose uptake in insulin sensitive tissues (i.e. muscle and adipose tissue). To compensate for defects in insulin action, insulin secretion must be increased to sustain euglycaemia. If this compensation fails, defects in insulin secretion predominate and hyperglycaemia occurs.

Although free fatty acids can stimulate insulin secretion, prolonged exposure to excessive concentrations of FFA results in falls in insulin secretion. The mechanism for this alteration has been attributed to lipotoxicity.

5 Hypertension

The relation between insulin resistance and hypertension is well established. Several different mechanisms are proposed. First, insulin is a vasodilator when given intravenously to people of normal weight, with secondary effects on sodium reabsorption in the kidney. In the setting of insulin resistance, the vasodilatory effect of insulin can be lost, but the renal effect on sodium reabsorption preserved. Fatty acids themselves can mediate relative vasoconstriction. Hyperinsulinaemia may result in increased sympathetic nervous system (SNS) activity and contribute to the development of hypertension.

6 Other manifestations

Insulin resistance is accompanied by many other alterations that are not included in the diagnostic criteria for the metabolic syndrome. Increases in apo B and C-III, uric acid, prothrombotic factors (fibrinogen, plasminogen activator inhibitor 1), serum viscosity, asymmetric dimethylarginine, homocysteine, white blood cell count, pro-inflammatory cytokines, the presence of microalbuminuria, non-alcoholic fatty liver disease, obstructive sleep apnoea, and polycystic ovarian disease are all associated with insulin resistance.

Recommended literature:

1. KG Alberti and PZ Zimmet, Definition, diagnosis and classification of diabetes mellitus and its complications. Part1 diagnosis and classification of diabetes mellitus provisional report of a WHO consultation, *Diabet Med* 1998; 15:539–53.
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3. International Diabetes Federation. The IDF consensus worldwide definition of the metabolic syndrome, 2005. www.idf.org
4. RH Eckel, SM Grundy, PZ Zimmet. The metabolic syndrome. *Lancet* 2005; 365:1415-28.