

Point/Counterpoint

The Metabolic Syndrome Is an Important Concept in Therapeutic Decision-Making

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Traditional risk factors can underestimate the true risk of developing atherosclerotic cardiovascular disease. Abdominal obesity is associated with a cluster of risk factors that include dyslipidemia, dysglycemia, and hypertension, termed metabolic syndrome (MS). The presence of MS increases cardiovascular risk 50%-100% beyond that defined according to traditional risk factors, and increases the risk of developing type 2 diabetes. Recognition of patients with MS is important to: (1) identify patients at increased risk beyond that conveyed by traditional risk factors; and (2) understand that the metabolic abnormalities associated with MS are largely reversed by measures that reduce abdominal obesity.

RÉSUMÉ

Les facteurs de risque traditionnels peuvent sous-estimer le risque réel de développement de maladies cardiovasculaires athérosclérotiques. L'obésité abdominale est associée à un ensemble de facteurs de risque comprenant la dyslipidémie, la dysglycémie et l'hypertension que l'on nomme le syndrome métabolique (SM). La présence du SM accroît le risque cardiovasculaire de 50 % à 100 % au-delà de celui qui est défini en fonction des facteurs de risque traditionnels, et accroît le risque de développement du diabète de type 2. La détection des patients souffrant du SM est importante pour : 1) déterminer les patients exposés à un risque élevé au-delà du risque transmis par les facteurs de risque traditionnels; 2) comprendre que les anomalies métaboliques associées au SM se résorbent en grande partie grâce aux mesures qui réduisent l'obésité abdominale.

The current worldwide obesity epidemic is linked to a substantial increase in the incidence of diabetes and cardiovascular disease. Central or visceral obesity is commonly associated with a cluster of risk factors (hypertension, dysglycemia, and dyslipidemia) that increase the risk of developing diabetes and cardiovascular disease. The term, metabolic syndrome (MS), is used to describe this cluster of risk factors. This discussion supports the view that MS is an important concept for the identification of patients at high risk of cardiovascular disease (CVD) that will lead to earlier initiation of appropriate preventative measures.

The following case illustrates the role of identification of MS in the recognition of increased CVD risk.

Case

A 55-year-old man had an acute anterior myocardial infarction. He had undergone a cardiac risk assessment

6 years earlier by his family physician with the following factors:

- Age 49
- Nonsmoker
- No diabetes
- Blood pressure (BP) 145/85
- No family history of premature CVD
- Total cholesterol 4.2 mmol/L
- High-density lipoprotein (HDL) cholesterol 0.8 mmol/L
- Triglycerides 2.6 mmol/L
- Low-density lipoprotein (LDL) cholesterol 2.9 mmol/L

His 10-year Framingham Risk Score (FRS) was 13.3%.

His CVD risk at this time was considered not adequately high to justify statin treatment. He was advised to lose weight and follow a more physically active lifestyle.

Additional information available 6 years previously included:

- European ethnicity
- Weight 87 kg
- Body mass index (BMI) 29.5
- Abdominal girth 104 cm
- Non-HDL cholesterol 3.4 mmol/L
- Fasting blood sugar 6.1 mmol/L
- Hemoglobin A1C 5.9%

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By not taking into account additional information that indicated features of the MS, use of the FRS resulted in underestimation of the CVD risk in this individual. This individual had 5 criteria for MS: increased abdominal girth, low HDL cholesterol, increased triglyceride levels, impaired fasting glucose level, and increased BP. Unless this information is considered and global cardiometabolic risk assessed, cardiovascular risk is significantly underestimated.

Assessment of Cardiovascular Risk

The Framingham study identified the major risk factors for cardiovascular disease that include age, smoking, hypertension, dyslipidemia, and diabetes.¹ Calculation of the FRS has become the most widely used method for the assessment of cardiovascular risk in North America. However, the FRS has important limitations, including a failure to include cardiometabolic risk as typified by dysglycemia and the MS.

FRS is commonly used to determine whether the proximate 10-year CVD risk is sufficiently high to warrant preventative measures, especially statin therapy. A study in 2003 showed that only 25% of younger patients (men younger than 55 years and women younger than 65 years) who had a myocardial infarction would have been eligible for statin therapy before the infarction based on Framingham criteria. It is notable that 45% of the patients had a BMI > 30 and 82% > 25.

The INTERHEART study² showed that 9 modifiable risk factors could explain > 90% of the risk of myocardial infarction in a cohort from 52 countries. Although INTERHEART validated the Framingham Model risk factors, it identified additional factors including abdominal obesity. Abdominal obesity, assessed according to the waist to hip ratio, was an independent risk factor with relative and population-attributable risk similar to that of smoking. Furthermore, abdominal obesity was a more powerful risk factor than BMI, with increasing waist to hip ratio a risk factor at all levels of BMI. In the same study, the cluster of risk factors that define MS was a powerful predictor of myocardial infarction³ with odds ratios and population-attributable risks similar to those of diabetes and hypertension.

Metabolic Syndrome

The term MS refers to a cluster of diabetogenic, atherogenic, prothrombotic, and inflammatory metabolic abnormalities that impart an increase in risk for cardiovascular disease and type 2 diabetes. MS is not a disease, but a group of risk factors that include central obesity, dysglycemia (diabetes, impaired glucose tolerance, or impaired fasting glucose), hypertension, and dyslipidemia that are commonly found together in patients with, or at risk of developing CVD. More details about the arguments conveyed in the present document are to be found in the Canadian position paper developed by the Cardiometabolic Risk Working Group.⁴ The present discussion focuses on the clinical utility of MS in risk assessment and prevention.

The definitions of MS consistently include criteria for central obesity, dyslipidemia (elevated triglyceride levels and low HDL cholesterol), and increased BP (Table 1). Most patients with MS can be identified by the presence of abdominal obesity and elevated triglyceride levels. The

hyperglycemic waist,⁸ is a Canadian concept that readily identifies MS patients and has gained worldwide acceptance. All MS definitions identify patients with increased risk for CVD and diabetes. However, the absolute risk, the patient populations, and the prevalence of MS differ according to the definition used.

Is there a unifying pathophysiology?

MS is a condition associated with the maldistribution of benign fat from the arms, legs, and buttocks to metabolically active central fat that includes visceral adipose stores. The synthesis of tumour necrosis factor α by adipocytes in central fat promotes the production of inflammatory cytokines that might play a role in the development of insulin resistance. Insulin resistance in fat, liver, and skeletal muscle, and the effect of visceral adiposity on adipokine release, explain many of the factors associated with increased cardiometabolic risk.⁹ There is no simple test to measure insulin resistance, and MS as defined according either to the International Diabetes Federation or the American Heart Association criteria, and according to “hypertriglyceridemic waist” are surrogates to identify patients with insulin resistance.

The atherogenic dyslipidemia associated with MS is characterized by low HDL cholesterol, increased triglyceride, non-HDL cholesterol, and apolipoprotein B levels. These observations predict the presence of increased numbers of highly atherogenic small dense LDL cholesterol particles. In the Quebec Heart Study, middle-aged men with hyperinsulinemia, increased apolipoprotein B, and small LDL particles had an almost 6-fold increase in risk of coronary heart disease.¹⁰

Prevalence of MS

Globally it is estimated that up to 25% of the world's population have criteria for MS. In the United States, the third National Health and Nutrition Examination Survey (NHANES III) reported an overall age-adjusted prevalence of 23.7%¹¹ with greater prevalence in African-Americans and Mexican-Americans. Between 1999 and 2010 there appears to have been a small decline in the prevalence of MS despite an important increase in central obesity and dysglycemia.¹² Lower triglyceride levels attributed to increased use of lipid-lowering therapy, and lower BPs again likely from pharmacotherapy, were observed. Despite these favourable changes, 23% of the adult US population still has MS, 56% have abdominal obesity, and 20% impaired fasting glucose.

Cardiovascular risk with MS

A meta-analysis¹³ of 20 studies, showed that MS was associated with an increased relative risk (RR) of all-cause mortality (RR, 1.35; 95% confidence interval [CI], 1.17-1.56), cardiovascular mortality (RR, 1.74; 95% CI, 1.29-2.35), incidence of CVD (RR, 1.53; 95% CI, 1.26-1.87), coronary heart disease (RR, 1.52; 95% CI, 1.37-1.69), and stroke (RR, 1.76; 95% CI, 1.37-2.25). The risk of developing CVD was greater in women and when the World Health Organization rather than the Adult Treatment Panel III criteria was used to define MS. A systematic review and meta-analysis of longitudinal studies¹⁴ that included 43 cohorts and

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