

Cardiac protection and the metabolic syndrome

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Introduction

The metabolic syndrome, formerly known as 'syndrome X', has moderately strict diagnostic criteria including intra-abdominal (visceral) adiposity, hyperglycaemia, impaired insulin resistance, dyslipidaemia and hypertension. The syndrome is considered by many to be the driving force behind the epidemic of obesity, diabetes and cardiovascular disease that has begun to emerge globally. A harbinger of serious morbidity and mortality, metabolic syndrome is poised to become the most important public health issue for the next few decades worldwide.

Metabolic syndrome is associated with hypertriglyceridaemia, low high density lipoprotein (HDL) cholesterol, high low density lipoprotein (LDL) cholesterol, other abnormal lipid parameters, elevated fasting blood glucose, hypertension, and impaired fibrinolysis and susceptibility to thrombotic events. Recent research also indicated elevated C-reactive protein, increasingly recognised as an independent predictor of cardiovascular risk. Increased visceral fat is now considered to be particularly dangerous because fat cells themselves promote the atherosclerotic process.

Previously thought to be benign cells, it is now widely accepted that the adipocyte is a very active endocrine cell

producing inflammatory cytokines including interleukin-6 and tumour necrosis factor-alpha and free fatty acid into the blood, all of which may promote the inflammatory atherosclerotic process. Increasing production of free fatty acids will also promote insulin resistance potentially leading to type 2 diabetes.

Future prevalence of obesity

Epidemiologically, the prevalence of metabolic syndrome is set to grow considerably in the coming decades. In the US, recent data from the Framingham Heart Study indicate that the burden of obesity-related conditions (including metabolic syndrome) is set to be far greater than previously thought, with estimates that 9 out of 10 young to middle-aged men and 7 out of 10 women are likely to be overweight by the year 2030.

The World Health Organisation (WHO) estimates that a similar prevalence of obesity will exist in Europe by the year 2050. At present, the WHO estimates that the metabolic syndrome affects approximately 26% of adult Americans and 20% of adult Europeans. The syndrome increases the risk of atherosclerotic cardiovascular disease 1.5-3 fold and raises the risk for type 2 diabetes 3-5 fold.

In recent months, however, there has been controversy surrounding the designation of syndrome to this constellation

Metabolic syndrome definitions

WHO

Required: Insulin in top 25%; glucose ≥ 110 mg/dl; two hour glucose ≥ 140 mg/dl

And ≥ 2 of:

HDL cholesterol	<35mg/dl (men) <40mg/dl (women)
Triglycerides	≥ 150 mg/dl
Obesity (Waist/hip ratio)	>0.9 (men) >0.85 (women)
BMI	≥ 30 kg/m ²
Hypertension	$\geq 140/90$ mmHg

NCEP

No specific required parameters

And ≥ 3 of:

Glucose	≥ 110 mg/dl
HDL cholesterol	<40mg/dl (men) <50mg/dl (women)
Triglycerides	≥ 150 mg/dl
Obesity (waist)	≥ 102 cm (men) ≥ 88 cm (women)
Hypertension	$\geq 130/85$ mmHg

Steps to recognising metabolic syndrome in clinical practice

- **Examine the patient's waistline:** is the patient overweight?
- **Measure waist circumference:** watch for >94cm (men) or >80cm (women) or waist:hip ratio.
- **If the waist circumference or waist:hip ratio are increased, assess the following:** triglycerides, HDL cholesterol, fasting blood glucose and elevated blood pressure.

of cardiovascular risk factors. In August 2005, the American Diabetes Association and the European Association for the Study of Diabetes issued a joint statement calling for a critical appraisal of the metabolic syndrome, its designation as a syndrome and its clinical utility.¹ The statement questions the rationale behind labelling subjects with a 'syndrome' and comments that "there is much fundamental, clinically important, and critically missing information about the metabolic syndrome to warrant a more serious examination of whether medical science is doing any good by drawing attention to and labelling millions of people with a presumed disease that does not stand on any firm ground".

They point out that anyone with a major cardiovascular risk factor should be evaluated for other risk factors and treated accordingly, regardless of whether these risk factors are signature metabolic syndrome characteristics.

Until further research provides solid evidence of a bona fide syndrome, they recommend that clinicians should avoid labelling patients as having metabolic syndrome and should not attempt to prescribe treatments for the syndrome as a whole.

Indeed, Dr Gerald Reaven of Stanford University School of Medicine, the clinician who first coined the term 'Syndrome X' and who is credited with elucidating the link between insulin resistance, hypertension, hyperlipidaemia and diabetes has agreed "almost entirely" with the joint statement. On the other hand, pharmaceutical companies may be unwilling to relinquish their hold on the term 'metabolic syndrome'.

Impressive results

There has been considerable interest in a selective CB1 endocannabinoid blocker, rimonabant, as a possible treatment for the metabolic syndrome and late breaking trials at recent cardiology meetings have generated interest in the apparent ability of rimonabant to improve multiple components of the metabolic syndrome. In the RIO-Europe trial, for example, investigators conducted analyses specifically in patients with metabolic syndrome and claimed an impressive 50% drop in the number of patients

with metabolic syndrome after two years on the drug.

Critics of the designation 'syndrome' point to the rising number of what they call manufactured diseases such as low bone density syndrome and female sexual dysfunction syndrome and claim that the term 'metabolic syndrome' may have originated in the need to encourage drug development rather than better living habits. Furthermore, critics also point to the ability of American physicians to claim reimbursement by Health Maintenance Organisations (HMOs) because the metabolic syndrome has, since 2001, its own ICD9 code, number 277.7.

Conclusion

It would appear that, while there is little doubt of associations between visceral obesity, insulin resistance, hypertension, hyperlipidaemia and evidence of an increased risk of both cardiovascular disease and type 2 diabetes with these risk factors, it may be that the designation of a discrete syndrome has taken on a life of its own. There are some inherent risks associated with this, not least being the risk that individual cardiovascular risk factors are inadequately treated.

There seems to be little doubt that in terms of preventing cardiovascular disease, we must consider risk factors both separately and in combination, given that these risk factors may interact multiplicatively (and more) with each other to greatly increase risk. There are advantages in designating the term 'syndrome' to the constellation of risk factors highlighted, particularly if this helps raise awareness of primary and secondary prevention of cardiovascular disease and diabetes. However, the inherent dangers of letting this take on a life of its own have been highlighted in a timely fashion by the joint societies' statement and it deserves close consideration.

Reference

1. Kahn R, Buse J, Ferrannini E, Stern M. The metabolic syndrome: time for a critical appraisal. Joint statement from the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetologia* 2005; DOI: 10.1007/s00125-005-1876-2. Available at: <http://www.springerlink.com>