Metabolic syndrome

Does its presence really matter?

ELIZABETH BLANCHARD BMedSci
KATHERINE SAMARAS PhD, FRACP

Does a diagnosis of the metabolic syndrome have a greater predictive power to detect or predict disease than individual risk factors?

Key points

- **Metabolic syndrome is a useful research construct that recognises the links between central obesity, diabetes and accelerated cardiovascular disease.**
- **In clinical practice, it is more important to detect and treat the individual components of the metabolic syndrome, where there is strong evidence of health benefit.**
- **There may be missed opportunities for early intervention for diabetes and heart disease prevention in patients with some but not all of the metabolic syndrome components who receive lesser clinical attention.**

ENDOCRINOLOGY TODAY 2014; 3(2): 21-25

Ms Blanchard is a Research Assistant in the Diabetes and Obesity Program at the Garvan Institute of Medical Research, Sydney.
Professor Samaras is Head of the Adipose Biology in Diabetes and Obesity Group at the Garvan Institute of Medical Research, Sydney; and Senior Staff Specialist in the Department of Endocrinology, St Vincent's Hospital, Sydney, NSW.

Metabolic syndrome originally entered medical parlance to describe the clustering of clinical and biochemical phenotypes associated with the development of type 2 diabetes and cardiovascular disease. The fundamental aetiopathology was, and still is, insulin resistance and/or visceral obesity, although additional novel players have entered the metabolic arena (see Figure 1).[1] The classic phenotypes of the metabolic syndrome are often closely associated and include hypertension, hyperglycaemia and dyslipidaemia. Over the past three decades, the application of the metabolic syndrome has expanded from the research setting where compelling disease associations demand further interrogation to a 'diagnosis' in medical practice, perhaps entering this domain prematurely. In doing so, it has received targeted attention from the pharmaceutical, supplement and complementary industries and attracted the angst of the worried well.

But does the metabolic syndrome really warrant the label of a 'disease' in itself and does its clinical presence or identification really matter?

The presence of the metabolic syndrome raises potential health concerns, particularly as we search for early disease markers with the aim of prevention and/or early intervention. A plethora of definitions has arisen, each seeking to identify with greater sensitivity and specificity those at risk of disease. Two widely accepted definitions are shown in Tables 1 and 2.[2,3] Table 1 represents the consensus view from major international bodies, but may still be in evolution.[2] For a clinician at the coalface, it would seem an appropriate judgement that the goal posts are moving.

Based on the International Diabetes Federation definition (Table 1), research conducted in Australia shows that an estimated 19 to 29% of adults aged over 25 years meet criteria for the metabolic syndrome;[4] data from around the world suggest similar or worse statistics. For example, depending on the definition used, 10% to almost 50% of the world's adult population could be identified as having the metabolic syndrome.[5]

The high rates of metabolic syndrome appear to be explained mostly by a parallel increase in rates of obesity and its metabolic sequelae. The multiple adverse consequences of excessive energy intake and sedentariness severely challenge public health services worldwide, as well as

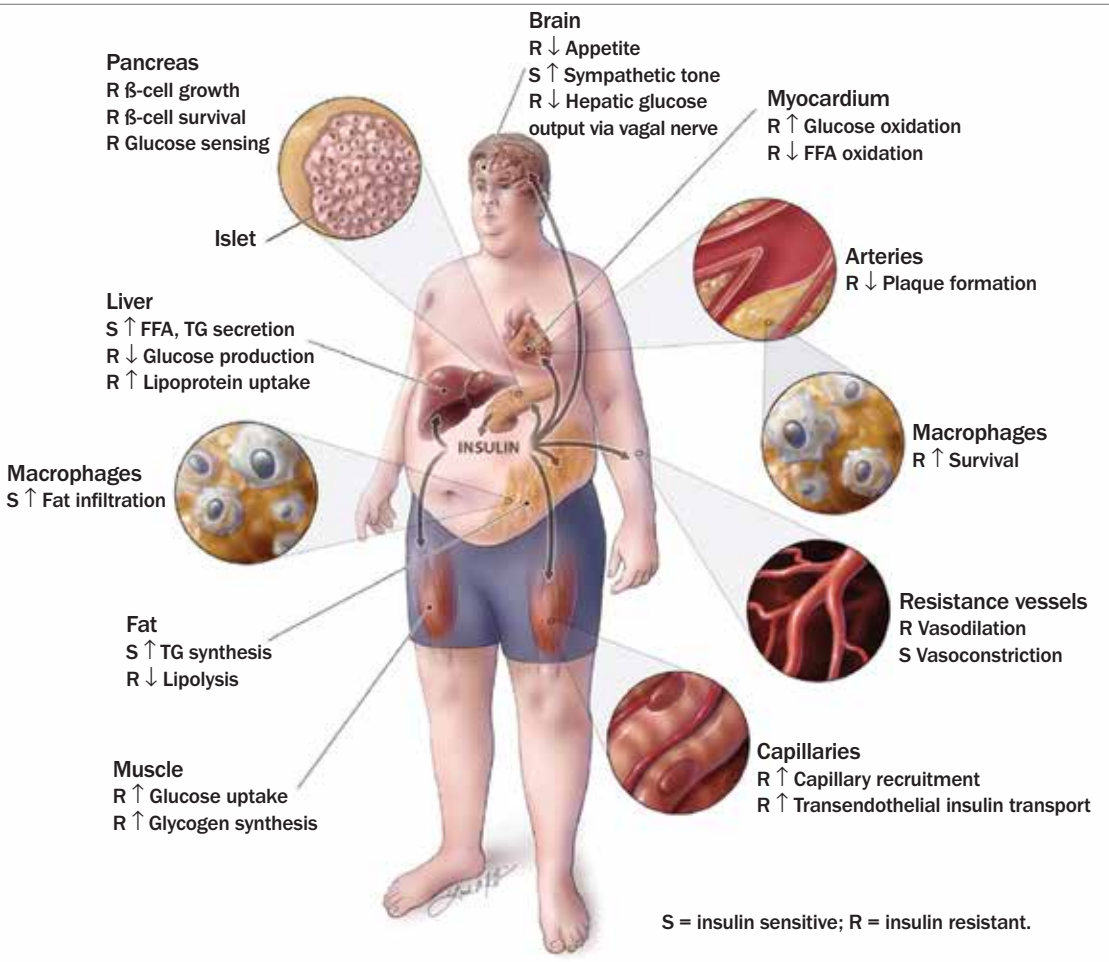


Figure 1. Physiology of insulin signalling in metabolic syndrome. R = insulin actions that are insulin resistant in metabolic syndrome; S = insulin actions that are insulin sensitive in metabolic syndrome. Abbreviations: FFA = free fatty acids; TG = triglycerides.

impacting on several biological systems from the obvious cardiometabolic diseases to a host of other chronic diseases, including liver disease, joint disease, infertility, cancer and inflammation. Metabolic complications include disorders of glucose metabolism (diabetes or the prediabetic conditions of impaired fasting glucose or impaired glucose tolerance), dyslipidaemia (low HDL cholesterol levels and hypertriglyceridaemia) and hypertension. Within all of these are individual genetic susceptibilities, which will determine that some individuals will develop metabolic complications with only modest central obesity. This susceptibility is clear in certain ethnic backgrounds, such as Indigenous Australians and people from the Pacific Islands, Southern and South-East Asia and the Middle East.

Diagnosis versus risk awareness

In clinical practice, the metabolic syndrome should promote early intervention to prevent chronic disease, rather than serve as a formal 'diagnosis'. In terms of public and health professional education, the concept is beneficial but some experts argue that the clinical practicality has been overinterpreted.[6]

An inherent danger in considering the metabolic syndrome as a 'diagnosis' is that treatable and important cardiometabolic risk factors might be ignored when all syndrome criteria are not met. For example, central obesity with one component alone (such as impaired fasting glucose) might not be as aggressively managed as when the full criteria are met and a label of the metabolic syndrome applied. This potential danger in ignoring treatable and important cardiometabolic risk factors is realised when single proven risk factors are ranked as less important in the absence of the whole syndrome.

Large observational studies have consistently and repeatedly shown that each of the metabolic syndrome components independently predicts adverse health outcomes and premature mortality. If we now create a 'diagnosis' of the metabolic syndrome, it creates a potential clinical practice loophole where individual patients who do not meet the criteria for the metabolic syndrome may miss opportunities for early diabetes and cardiovascular disease prevention.

Prognostic power of the metabolic syndrome

The critical question regarding the metabolic syndrome before it is absorbed into clinical practice is: does its presence have a greater power to detect or predict disease than its individual components? In other words, does the disease time bomb tick louder because of the presence of metabolic syndrome, or does it tick just as loudly for people having one, two, three or more individual risk factors? If the former is true then there is merit in identifying individuals with the metabolic syndrome. If on the other hand, individual risk factors are just as detrimental, then clinician efforts must continue to focus on targeting each traditional cardiometabolic risk factor.

On the surface, it appears that the metabolic syndrome is associated

with a higher risk: for example, a twofold higher rate of myocardial infarction or stroke and a fivefold higher rate of type 2 diabetes.[3] However, numerous studies have shown that the metabolic syndrome does not show better prediction of cardiovascular disease risk than its individual parts.[7-12] Data therefore suggest that the metabolic syndrome adds little or no additional information to predicting future cardiovascular disease or diabetes risk.

In some instances, research has shown that the syndrome is weaker in predicting disease than its components. For example, in the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) of 4812 participants without diabetes, the metabolic syndrome was associated with a 7% increased risk of incident cardiovascular disease, whereas low HDL cholesterol or high triglyceride levels each independently predicted a higher risk (15% and 10%, respectively).[11] In the British Regional Heart Study of 2737 participants without diabetes, the metabolic syndrome predicted a 27% increased risk of incident cardiovascular disease; in contrast, low HDL cholesterol levels independently predicted a 46% increased risk.[11] In both of these cohorts, the risk predicted by the metabolic syndrome was substantially less than the sum of its parts.

Table 1. The metabolic syndrome criteria of the International Diabetes Federation (IDF)[2]

Central obesity plus any two of the following characteristics need to be met for a diagnosis	
Characteristic	**Cut-off point**
Waist circumference	Population — Men — Women European/Caucasian — ≥94 cm — ≥80 cm South Asians — ≥90 cm — ≥80 cm Chinese — ≥90 cm — ≥80 cm Japanese — ≥90 cm — ≥80 cm Central/South American — Use south Asian data Middle Eastern — Use European data Sub-Saharan African — Use European data
Triglyceride levels	≥1.7 mmol/L or on medication for elevated triglycerides
HDL cholesterol levels	<1.03 mmol/L (men); <1.29 mmol/L (women) or on medication for reduced HDL cholesterol levels
Blood pressure	≥130 mmHg (systolic); ≥85 mmHg (diastolic) or on medication for hypertension
Fasting glucose level	>5.6 mmol/L or on medication for elevated blood glucose levels

Table 2. The metabolic syndrome criteria of the joint International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; and International Atherosclerosis Society[3]

Three out of five of the following characteristics need to be met for a diagnosis	
Characteristic	**Cut-off point**
Waist circumference	Population — Men — Women European/Caucasian — ≥102 cm — ≥88 cm Asian — ≥90 cm — ≥80 cm Central/South American — ≥90 cm — ≥80 cm Middle Eastern — ≥94 cm — ≥80 cm Sub-Saharan African — ≥94 cm — ≥80 cm
Triglyceride levels	≥1.7 mmol/L or on medication for elevated triglycerides
HDL cholesterol levels	<1.0 mmol/L (men); <1.3 mmol/L (women) or on medication for reduced HDL cholesterol levels
Blood pressure	≥130 mmHg (systolic); ≥85 mmHg (diastolic) or on medication for hypertension
Fasting glucose level	>5.5 mmol/L or on medication for elevated blood glucose levels

Further analyses of the British Regional Heart Study data examined how the metabolic syndrome rated against the Framingham risk score in predicting future heart disease over a period of 20 years. It found that the Framingham risk score was significantly superior.[13] Similar results were found in the San Antonio Heart Study and the Atherosclerosis Risk in Communities Study.[14,15]

In terms of future diabetes prediction, the metabolic syndrome strongly predicts incident diabetes. PROSPER found that the metabolic syndrome was associated with a fourfold increased risk of incident diabetes. However, isolated elevated fasting glucose predicted an 18-fold increase in incident diabetes in the same study.[11] In this study also, the metabolic syndrome appears to be substantially less than the sum of its parts.

Issues arising from the definition of the metabolic syndrome

A further controversy involves the numerous definitions of the metabolic syndrome in use internationally, including those from the International Diabetes Federation, World Health Organization and the National Cholesterol Education Program Adult Treatment Panel III (ATP III).[2,16,17]

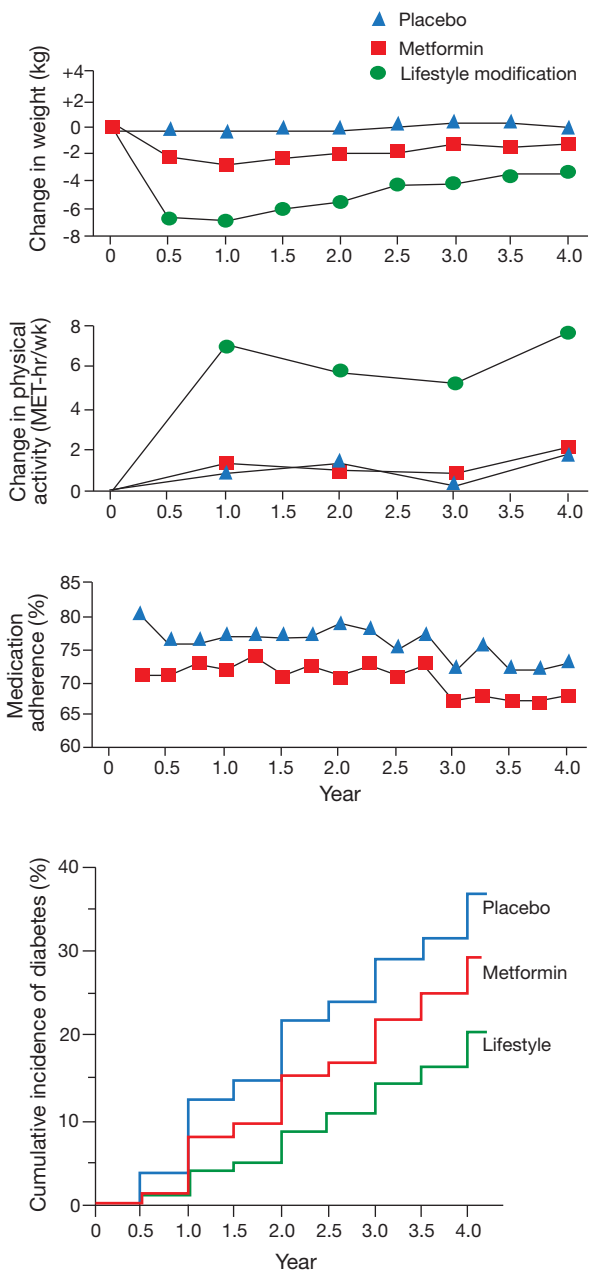


Figure 2. Metabolic benefits of weight loss: Diabetes Prevention Program. Changes in body weight (a, top), physical activity (b, middle) and medication adherence (c, bottom). Cumulative incidence of diabetes (d, bottom).

Abbreviation: MET-hr/wk = metabolic equivalent of task hours per week.
Reproduced with permission from: Knowler et al. N Engl J Med 2002; 346: 393-403.[19]

Some definitions of the metabolic syndrome have a requisite primary entry point of central obesity, with waist circumference cut-offs that are specific to sex and ethnicity; others do not. These definitions also rank risk factors differently, with different cut-off points. Additionally, despite an increase in research on the metabolic syndrome, there is yet to be agreement on a single pathophysiological mechanism nor general consensus on cut-off points for different risk factors.[18] However, attempts to harmonise the differences between metabolic syndrome definitions has led to some consensus.[3]

There are additional limitations of the metabolic syndrome that require mention. All metabolic syndrome definitions omit important and established risk factors, such as sex, age, family history, smoking, ethnicity and physical activity. In our individual assessment of patient risk, if we dichotomise to 'metabolic syndrome present: yes/no', important historical information is lost when building our risk assessment. Is this reasonable in today's setting of personalised medicine with individualised care plans?

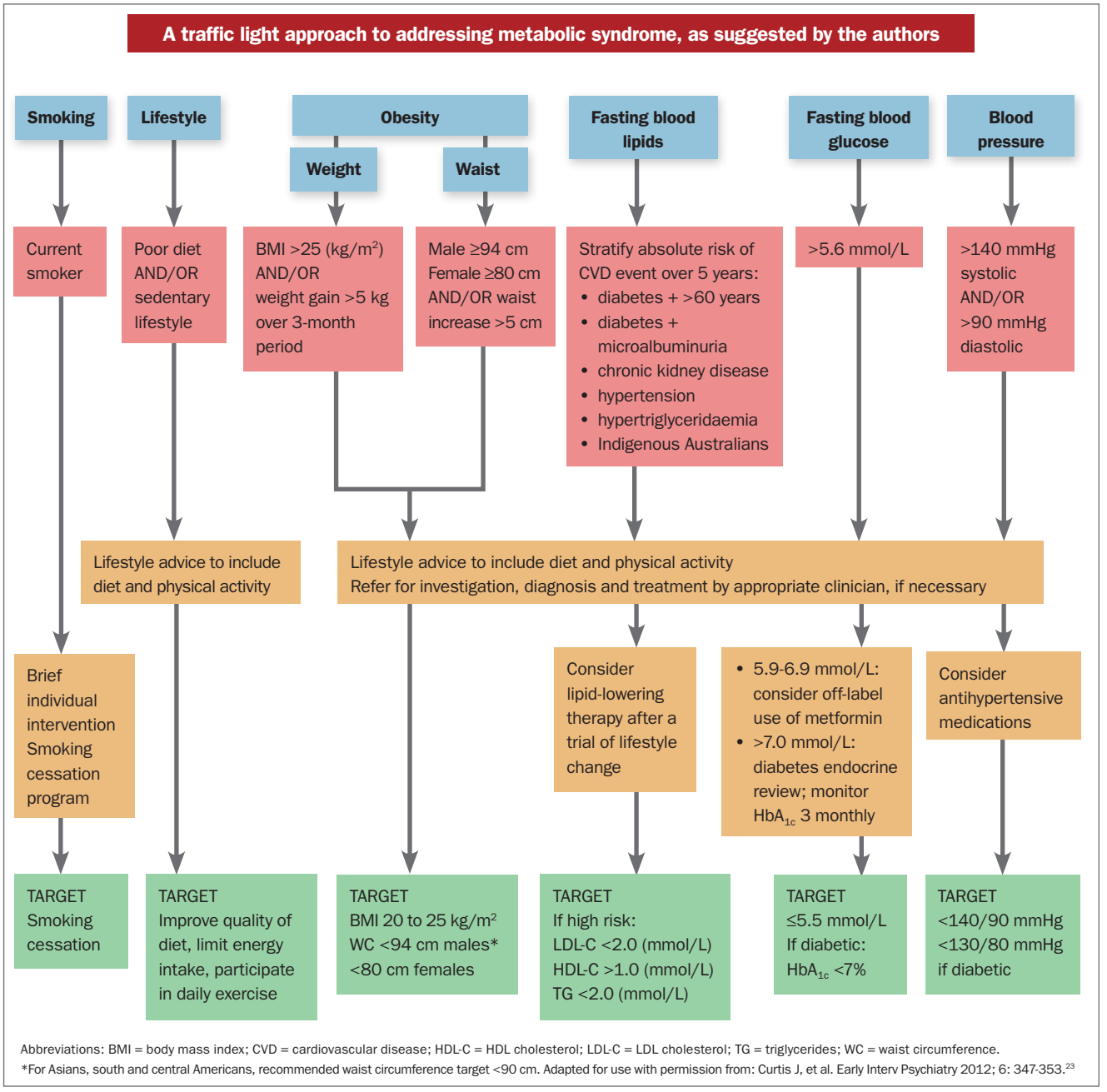
Although there is no question that further clinical and epidemiological research on the health consequences of the metabolic syndrome is essential, transferring the metabolic syndrome to clinical practice as a 'diagnosis', where it may sit side by side with diabetes and other diseases, is not yet justified. The clinical mandate remains to treat all cardiometabolic risk factors, given the evidence that treating these risk factors alters health and mortality outcomes.

Managing cardiometabolic risk

Whether or not any individual patients meet all or some of the criteria for the metabolic syndrome, diligent clinical care is necessary to bring each risk factor to target to prevent future disease. The fundamental approach centres on lifestyle modification to address underlying chronic nutrient excess and its broad effects on lipid metabolism, blood pressure, glucose homeostasis, insulin resistance and adipose biology. The National Vascular Disease Prevention Alliance has an excellent online clinical tool that can be used to assess absolute cardiometabolic risk (available online at www.cvdcheck.org.au). In addition, clinical efforts must focus on reducing sedentariness and increasing physical activity. Central obesity must be specifically targeted within interventions addressing any of the cardiometabolic risk factors contained within the metabolic syndrome, to achieve modest weight reduction. For example, lifestyle modification in the Diabetes Prevention Program resulting in modest weight loss stopped the progression of prediabetes to diabetes in a large proportion of participants (Figure 2).[19] Some of our recent detailed clinical studies showed that even a modest weight loss of 5 to 6 kg rapidly improved type 2 diabetes and resolved impaired fasting glucose levels, inflammation and arterial stiffness.[20-22] Where lifestyle measures are insufficient to bring risk factors to target, medication prescription is appropriate, as per national guidelines for people with and without end-stage disease (coronary or vascular disease, renal disease and diabetes). The flowchart is suggested by the authors as a summary of cardiometabolic 'red lights' and 'green light' targets, for use in clinical care settings.[23]

Conclusion

The metabolic syndrome describes a group of cardiometabolic risk factors that each individually increase the risk of developing cardiovascular disease and diabetes. The current evidence



Abbreviations: BMI = body mass index; CVD = cardiovascular disease; HDL-C = HDL cholesterol; LDL-C = LDL cholesterol; TG = triglycerides; WC = waist circumference.
*For Asians, south and central Americans, recommended waist circumference target <90 cm. Adapted for use with permission from: Curtis J, et al. Early Interv Psychiatry 2012; 6: 347-353.[23]

indicates that the metabolic syndrome (as limited by its definitions) does not portend any greater risk of adverse health outcomes compared with individual risk factors. In this regard, clinicians should avoid the mistake of stratifying a patient's health risk as less when they have some, but not all, phenotypes of the metabolic syndrome.

Underlying the metabolic syndrome is the global disorder of sedentariness and excessive nutrient consumption and availability, particularly of energy-dense foods. Lifestyle protection or modification is key to preventing the development of metabolic complications when the body's biological systems attempt to deal with chronic energy excess. A clinician's role must extend not only to addressing disease when present, but to identifying early precedents through judicious risk factor assessment and to guiding our patients in their lifestyle choices from the cradle to the grave. Perhaps we can start by 'walking the talk'. **ET**

References

A list of references is included in the website version (www.medicinetoday.com.au) of this article.

COMPETING INTERESTS: None.

Metabolic syndrome: does its presence really matter?

ELIZABETH BLANCHARD BMedSci; **KATHERINE SAMARAS** PhD, FRACP

References

1. Rask-Madsen C, Kahn CR. Tissue-specific insulin signaling, metabolic syndrome, and cardiovascular disease. Arterioscler Thromb Vasc Biol 2012; 32: 2052-2059.
2. Alberti KG, Zimmet P, Shaw J, IDF Epidemiology Task Force Consensus Group. The metabolic syndrome – a new worldwide definition. Lancet 2005; 366: 1059-1062.
3. Alberti KG, Eckel RH, Grundy SM, et al. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation 2009; 120: 1640-1645.
4. Zimmet PZ, Alberti KG, Shaw JE. Mainstreaming the metabolic syndrome: a definitive definition. Med J Aust 2005; 183: 175-176.
5. Eddy DM, Schlessinger L, Heikes K. The metabolic syndrome and cardiovascular risk: implications for clinical practice. Int J Obesity 2008; 32 Suppl 2: S5-10.
6. Simmons RK, Alberti KG, Gale EA, et al. The metabolic syndrome: useful concept or clinical tool? Report of a WHO Expert Consultation. Diabetologia 2010; 53: 600-605.
7. Chien KL, Hsu HC, Sung FC, Su TC, Chen MF, Lee YT. Metabolic syndrome as a risk factor for coronary heart disease and stroke: an 11-year prospective cohort in Taiwan community. Atherosclerosis 2007; 194: 214-221.
8. Deedwania P, Barter P, Carmena R, et al. Reduction of low-density lipoprotein cholesterol in patients with coronary heart disease and metabolic syndrome: analysis of the Treating to New Targets study. Lancet 2006; 368: 919-928.
9. Lawlor DA, Smith GD, Ebrahim S. Does the new International Diabetes Federation definition of the metabolic syndrome predict CHD any more strongly than older definitions? Findings from the British Women's Heart and Health Study. Diabetologia 2006; 49: 41-48.
10. Wang J, Ruotsalainen S, Moilanen L, Lepisto P, Laakso M, Kuusisto J. The metabolic syndrome predicts cardiovascular mortality: a 13-year follow-up study in elderly non-diabetic Finns. Eur Heart J 2007; 28: 857-864.
11. Sattar N, McConnachie A, Shaper AG, et al. Can metabolic syndrome usefully predict cardiovascular disease and diabetes? Outcome data from two prospective studies. Lancet 2008; 371: 1927-1935.
12. Kohli P, Greenland P. Role of the metabolic syndrome in risk assessment for coronary heart disease. JAMA 2006; 295: 819-821.
13. Wannamethee SG, Shaper AG, Lennon L, Morris RW. Metabolic syndrome vs Framingham Risk Score for prediction of coronary heart disease, stroke, and type 2 diabetes mellitus. Arch Int Med 2005; 165: 2644-2650.
14. Stern MP, Williams K, Gonzalez-Villalpando C, Hunt KJ, Haffner SM. Does the metabolic syndrome improve identification of individuals at risk of type 2 diabetes and/or cardiovascular disease? Diabetes Care 2004; 27: 2676-2681.
15. McNeill AM, Rosamond WD, Girman CJ, et al. The metabolic syndrome and 11-year risk of incident cardiovascular disease in the atherosclerosis risk in communities study. Diabetes Care 2005; 28: 385-390.
16. World Health Organization. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus. Geneva: WHO; 1999.
17. Grundy SM, Brewer HB Jr, Cleeman JI, et al. Definition of metabolic syndrome: report of the National Heart, Lung, and Blood Institute/American Heart Association conference on scientific issues related to definition. Circulation 2004; 109: 433-438.
18. 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; 48: 1684-1699.
19. Knowler WC, Barrett-Connor E, Fowler SE, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 2002; 346: 393-403.
20. Samaras K, Viardot A, Botelho NK, Jenkins A, Lord RV. Immune cell-mediated inflammation and the early improvements in glucose metabolism after gastric banding surgery. Diabetologia 2013; 56: 2564-2572.
21. Viardot A, Lord RV, Samaras K. The effects of weight loss and gastric banding on the innate and adaptive immune system in type 2 diabetes and prediabetes. J Clin Endocrinolo Metab 2010; 95: 2845-2850.
22. Samaras K, Viardot A, Lee PN, et al. Reduced arterial stiffness after weight loss in obese type 2 diabetes and impaired glucose tolerance: the role of immune cell activation and insulin resistance. Diab Vasc Dis Res 2013; 10: 40-48.
23. Curtis J, Newall HD, Samaras K. The heart of the matter: cardiometabolic care in youth with psychosis. Early Interv Psychiatry 2012; 6: 347-353.