

The metabolic syndrome

May be a guidepost or detour to preventing type 2 diabetes and cardiovascular disease

Type 2 diabetes mellitus is becoming extremely common; its prevalence worldwide is expected to reach 5-7.6% by 2025.¹ Atherosclerotic cardiovascular disease is the principal cause of death, disability, and excess healthcare costs in diabetes. Cardiovascular disease may already be present at the time when diabetes is diagnosed,^{w1} and patients with diabetes are more likely than their non-diabetic counterparts to die from a first event of cardiovascular disease.^{w2} These realities point to prevention of type 2 diabetes as the route to prevention of its costliest complications. The close association of type 2 diabetes with cardiovascular disease led to the hypothesis that the two arise from a common antecedent;^{w3} this concept has been codified by the World Health Organization and others as "the metabolic syndrome."^{w2}

The diagnosis of the metabolic syndrome in patients might hold promise for enhanced prevention of diabetes and cardiovascular disease. However, substantial uncertainties remain about the clinical definition of the syndrome and whether risk factor clusters collectively indicate a discrete, unifying disorder. Most importantly, it is unclear whether diagnosing the syndrome will confer benefit beyond risk assessments or treatment strategies associated with diagnosing and treating the syndrome's component traits. The current focus on the metabolic syndrome will possibly prove to be a distracting detour on the route to encouraging more widespread application of evidence based practices to prevent diabetes and cardiovascular disease.

The metabolic syndrome is characterised by the co-occurrence of obesity (especially central obesity), dyslipidaemia (especially high levels of triglycerides and low levels of high density lipoprotein cholesterol), hyperglycaemia, and hypertension. As yet no consensus exists for specific thresholds for establishing the diagnosis of each of these traits as components of the syndrome. Inclusion of insulin resistance or diabetes itself as diagnostic components is also controversial. The individual traits of the syndrome cluster together to a notably greater degree than expected by chance alone, a fact that lends substantial support to the existence of a discrete disorder.³

It has long been thought that insulin resistance (primarily in skeletal muscle and liver) may be the unifying pathophysiology underlying the syndrome.^{w4} However, although insulin resistance is a consistent early abnormality in the pathogenesis of type 2 diabetes, its association with cardiovascular disease is less certain.^{w5} Further, obesity is a major driving force

behind clustering of risk factor,³ yet not all obese subjects are insulin resistant.⁴ In addition factor analyses of traits of the metabolic syndrome consistently show that blood pressure elevation is not closely related to clustering of the other traits.⁵ The question then arises whether attempting to prevent diabetes and cardiovascular disease by treating the metabolic syndrome in itself will be as effective as prevention of obesity or interventions specific for the other constituent risk factors.

Evidence is accumulating that people with the metabolic syndrome are at increased risk of incident diabetes⁶ or cardiovascular disease relative to people without the syndrome.⁷ These findings do not come as a surprise, as the traits of the metabolic syndrome are each well established risk factors for diabetes and cardiovascular disease. The question is whether the metabolic syndrome increases risk for adverse outcomes to a greater degree than predicted by the presence of its individual components.

One recent analysis seems to indicate that syndrome traits interact to increase atherosclerosis of the carotid artery to a greater degree than expected solely by their additive effects.⁸ Another preliminary analysis of participants in the control arms of two large lipid lowering clinical trials shows that those with the metabolic syndrome and a Framingham risk score greater than 20% were at higher risk for cardiovascular disease events compared with participants with an elevated risk score but without the metabolic syndrome.⁹ Another recent analysis, however, did not find excess risk for cardiovascular disease associated with the syndrome after traditional risk factors for cardiovascular disease had been accounted for.¹⁰ Thus, although it is plausible to think that diagnosis of the metabolic syndrome will point us in the right direction for effective prevention of type 2 diabetes and cardiovascular disease, more definitive data on the outcomes and effects of interventions are required before we can confidently head along that route.

The goal of identifying metabolic risk factors is to prevent morbidity and mortality due to type 2 diabetes and cardiovascular disease. We already know that relatively modest lifestyle changes can substantially reduce risk for type 2 diabetes in mildly hyperglycaemic subjects.¹¹ We already know that control of raised blood pressure and blood lipids substantially reduces risk of cardiovascular disease events in patients with hypertension or hyperlipidaemia. Although insulin sensitisation in itself may be beneficial in preventing type 2



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diabetes,¹² we do not know if this strategy will ameliorate all the metabolic disturbances of the metabolic syndrome or prevent cardiovascular disease.

The worldwide epidemic of type 2 diabetes is fuelled in large part by a parallel epidemic of obesity and physical inactivity, clearly pointing to prevention of obesity as the most direct route to prevention of the metabolic syndrome and its sequelae. From this perspective, perhaps the best reason to consider a diagnosis of the metabolic syndrome is to identify obese people who are most likely to benefit from aggressive efforts to achieve a healthy weight, physical activity habits, and normal risk factor levels. In the end, even modest changes towards a healthy lifestyle may be the most direct route to treating the metabolic syndrome and preventing its type 2 diabetes and cardiovascular disease outcomes.

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1 King H, Aubert RE, Herman WH. Global burden of diabetes, 1995-2025: prevalence, numerical estimates, and projections. *Diabetes Care* 1998;21:1414-31.

2 Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diabet Med* 1998;15:539-53.

3 Wilson PWF, Kannel WB, Silbershatz H, D'Agostino RB. Clustering of metabolic factors and coronary heart disease. *Arch Intern Med* 1999;159:1104-9.

4 Ferrannini E, Natali A, Bell P, Cavallo-Perin P, Lalic N, Mingrone G. Insulin resistance and hypersecretion in obesity. European Group for the Study of Insulin Resistance (EGIR). *J Clin Invest* 1997;100:1166-73.

5 Meigs JB. Invited commentary: insulin resistance syndrome? Syndrome X? Multiple metabolic syndrome? A syndrome at all? Factor analysis reveals patterns in the fabric of correlated metabolic risk factors. *Am J Epidemiol* 2000;152:908-11.

6 Hanson RL, Imperatore G, Bennett PH, Knowler WC. Components of the "metabolic syndrome" and incidence of type 2 diabetes. *Diabetes* 2002;51:3120-7.

7 Lakka HM, Laaksonen DE, Lakka TA, Niskanen LK, Kumpusalo E, Tuomilehto J, et al. The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men. *JAMA* 2002;288:2709-16.

8 Golden SH, Folsom AR, Coresh J, Sharrett AR, Szklo M, Brancati F. Risk factor groupings related to insulin resistance and their synergistic effects on subclinical atherosclerosis: the atherosclerosis risk in communities study. *Diabetes* 2002;51:3069-76.

9 Girman CJ, Rhodes T, Clearfield M, Beere PA, Mercuri M. Metabolic syndrome and risk of cardiovascular outcomes in the placebo groups of two large clinical trials. <http://aha.agora.com/abstractviewer/results.asp>

10 Resnick HE, Jones K, Ruotolo G, Jain AK, Henderson J, Lu W, et al. Insulin resistance, the metabolic syndrome, and risk of incident cardiovascular disease in nondiabetic American Indians: the strong heart study. *Diabetes Care* 2003;26:861-7.

11 Tuomilehto J, Lindstrom J, Eriksson JG, Valle TT, Hamalainen H, Ilanne-Parikka P, et al. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N Engl J Med* 2001;344:1343-50.

12 Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 2002;346:393-403.

Sexual health

Report finds sexual health service to be a shambles

The House of Commons Health Select Committee has published its inquiry on sexual health and highlighted a major public health problem and increasing crises.¹ One hundred and sixty three written submissions were received, 67 witnesses gave evidence during the course of 10 sessions, and the committee visited north east England, south west England, Sweden, and Holland. The tone and recommendations of the report left no doubt about how concerned the members of parliament were by what they had heard and seen for themselves.

The report covered the trends and services for sexually transmitted infections, including HIV; contraception and unwanted pregnancy; sexual behaviour; and sex education. The picture is of a continuing decline in the nation's sexual health, with services unable to cope and an increasingly demoralised but willing workforce. The committee heard that all sexually transmitted infections had increased in England over the past six years, particularly new cases of gonorrhoea (86%), chlamydia (108%), and syphilis (500%). They also heard that two chlamydia pilot studies conducted in the Wirral and Portsmouth showed a prevalence of approximately 10% in women under the age of 25. Not surprisingly, the increases in infections have resulted in a doubling in attendances at departments of genitourinary medicine within England in the past 10 years, which have reached 1.1 million cases a year.

The annual total of new HIV diagnoses increases each year, and in conjunction with the success of anti-

retroviral therapy the pool of infected people is increasing, with implications for treatment costs and dangers of transmission. Apart from infection, teenage pregnancy rates are declining slowly and steadily, the committee heard, and 79% of women having abortions are beyond their teenage years. Add to this the nation's changing sexual behaviour over the past 10 years—decline in the age of first intercourse, increase in total number of lifetime partners and concurrent relationships, a decline in safe sex practice, particularly among homosexual men—and finally, the evidence from young people to the committee that sex and relationship education is patchy, too little, too late, and too biological. All of this gives us a pressure cooker situation.

Evidence given on the committee's visits to services confirmed and underlined that the heavy burden of infections, unwanted pregnancies, and high risk sexual behaviour was putting increasing pressures on existing services—for example, departments of genitourinary medicine have found it hard to deliver immediate, high quality, open access and self referral services. The length of waiting time has increased within the United Kingdom from five days for men and six days for women in 2001 to 12 and 14 days respectively in 2002. In a third of clinics patients had to wait longer than four weeks for an appointment. One clinic indicated that each week more than 400 patients attempting to make appointments by telephone were refused. The Department of Health's Monk Report of 1988 set a