

Commentary

Metabolic syndrome as a marker of risk in type 2 diabetes

That atherosclerosis is a metabolic disorder has been known for centuries. The “gruel” or “athere” from which the name of an “atheroma” is derived was demonstrated to be a mixture of cholesterol and many other fats including triglycerides¹. John Hunter in his seminal observations on angina pectoris a century later reported that persons with disposition to stress, high arterial pressure and smoking were more prone to have angina and sudden cardiac death². Conglomeration of hypertension, hyperglycaemia and hyperuricaemia [an association with raised triglycerides and low high density lipoprotein (HDL) cholesterol has been clearly demonstrated] is known to be associated with increased risk for cardiovascular events for almost a century³. Lately, large prospective epidemiological studies from various countries have reported that many risk factors are important in pathogenesis of atherosclerotic diseases⁴. The INTERHEART study demonstrated that nine common risk factors (high apolipoprotein B:A₁ ratio, smoking, diabetes, hypertension, truncal obesity, psychosocial stress, physical inactivity, low fruit and vegetables intake and low alcohol intake) explain more than 90 per cent of incident myocardial infarctions⁵. All this implies that vascular atherosclerosis is a result of multiple metabolic abnormalities. Corollary to this observation, multiple risk scores have been developed to predict cardiovascular diseases, especially coronary heart disease, in asymptomatic individuals⁶. These range from newly developed Framingham Risk Score in asymptomatic individuals in primary care⁷ to other well established risk scores such as classical Framingham risk score, German PROCAM score, European SCORE project, British QRISK and QRISK-2 and others developed in Southern Europe, Eastern Europe, China, and Australia-New Zealand and World Health Organization⁸.

The US National Cholesterol Education Program (NCEP) in its 3rd Adult Treatment Panel report (ATP

III) coined the term of metabolic syndrome⁹ and suggested its use for identification of cardiovascular risk in subjects with normal or borderline elevated low density lipoprotein (LDL) cholesterol levels. This was not meant to be a risk prediction score but a loosely defined clinical condition with permutations of multiple metabolic abnormalities such as atherogenic dyslipidaemia (low HDL cholesterol, raised triglycerides), raised blood pressure, impaired glucose tolerance and truncal obesity.

Does metabolic syndrome predict future cardiovascular events?: Positive predictive ability of the metabolic syndrome for cardiovascular disease incidence was not addressed in the initial document⁹. Later prospective studies and post-hoc analyses of others reported that this constellation of metabolic abnormalities was predictive of diabetes as well as coronary heart disease¹⁰. A meta-analysis of 37 studies that included 43 cohorts and 172573 individuals reported a relative risk of cardiovascular events and death of 1.78 (95% confidence intervals 1.58-2.00)¹¹. The association was stronger in women, in studies enrolling low risk individuals, and in studies using factor analysis or World Health Organization (WHO) criteria for diagnosis as compared to the NCEP guidelines. On the other hand, a recent analysis of two large studies among elderly failed to show any predictive value for coronary heart disease¹². Sattar and colleagues¹² reported on incident cardiovascular disease and diabetes in 4812 non diabetic individuals in the prospective study of pravastatin in the elderly at risk (PROSPER) and 2737 non diabetic men in the British Regional Heart Study (BRHS) and compared hazard ratios of the cardiovascular disease in those with the metabolic syndrome or its individual components at 3.2 yr follow up (Table). It was observed that positive predictive capability of the metabolic syndrome for

Table. Metabolic syndrome and future cardiovascular events in Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) and British Regional Heart Study (BRHS)

Risk factors	Age-adjusted hazard ratios and 95% confidence intervals for cardiovascular events in non diabetic subjects	
	PROSPER (n=4812)	BRHS (n=2737)
Incident cardiovascular events	434	440
Metabolic syndrome	1.07 (0.86-1.32)	1.27 (1.04-1.56)
BMI >30 kg/m ²	0.99 (0.78-1.25)	1.08 (0.88-1.33)
Triglycerides >1.69 mmol/l	1.10 (0.90-1.35)	1.17 (0.97-1/40)
HDL cholesterol <1.04 mmol/l (men), <1.29 mmol/l (women)	1.15 (0.95-1.39)	1.46 (1.17-1.81)
Fasting glucose >6.1 mmol/l	0.94 (0.63-1.39)	1.05 (0.82-1.35)
BP >130/85 mm Hg or treatment	1.23 (0.79-1.92)	1.68 (1.26-2.24)

Source: Ref. 13

cardiovascular events in both the studies was similar to its individual components. The predictive ability of metabolic syndrome for coronary heart disease and stroke has been reported to be inferior to the Framingham Risk Score in the BRHS and some other studies¹³.

Metabolic syndrome in type 2 diabetes: In many individuals who have a single cardiovascular risk factor such as smoking, hypertension, diabetes or dyslipidaemia or an overall low risk score, the risk for future cardiovascular events could be stratified according to the presence or absence of the metabolic syndrome into high or intermediate¹⁰. In line with this observation, the article by Dhanaraj *et al*¹⁴ in this issue is important. The authors have evaluated subjects with newly diagnosed type 2 diabetes and tried to identify those with high risk. Obviously, all these individuals had at least one major component of risk *i.e.*, diabetes. Presence of metabolic syndrome in this high risk group was 42-78 per cent depending upon the criteria used for diagnosis. This finding is similar to that among diabetic subjects reported in the United Kingdom Prospective Diabetes Study (UKPDS)¹⁵ and the San Antonio Heart Study¹⁶. In the UKPDS, the metabolic syndrome was reported in 61, 38 and 54 per cent among 4542 subjects using NCEP, WHO and International Diabetes Federation (IDF) criteria, respectively. Prevalence was similar in the San Antonio Heart Study. Alexander *et al*¹⁷ reported prevalence of the metabolic syndrome among the third

National Health Assessment and Nutrition Evaluation Survey (NHANES III) participants in the USA; 44 per cent of the US population above 50 yr met the NCEP criteria for the metabolic syndrome. Among the diabetic subjects, 86 per cent had features of metabolic syndrome while the prevalence among subjects with impaired fasting glucose, impaired glucose tolerance and normal fasting glucose was 71.3, 33.1 and 25.8 per cent respectively. Dhanaraj *et al*¹⁴ included only normal weight type 2 diabetics but reported a significantly greater occurrence of MS. This is a unique finding and shows that Indian type 2 diabetes subjects have greater cardiovascular risk as compared to the British and North American counterparts. In the San Antonio Heart Study, it was reported that hazard ratios for major cardiovascular events in male diabetics with metabolic syndrome were 3.09 (95% confidence intervals 1.49-6.43), diabetics without metabolic syndrome 2.34 (0.70-7.82), non diabetic metabolic syndrome 1.96 (0.99-3.88) as compared to subjects without metabolic syndrome. The hazard ratios were significantly greater in women with values of 8.19 (3.51-19.1), 3.53 (0.75-16.7) and 2.07 (0.72-6.00) respectively¹⁶. Larger prospective studies are needed to clarify the prognostic value of the metabolic syndrome in predicting cardiovascular diseases among high risk subgroups such as those with diabetes or dyslipidaemias or hypertension in India.

Another finding of importance reported by Dhanaraj *et al*¹⁴ relates to predictive ability of individual components of the metabolic syndrome to identify high risk subjects. High triglyceride levels had the highest predictive ability which is not surprising as all the subjects in the present study were newly diagnosed diabetics. Impaired fat metabolism is a very early finding in type 2 diabetes and is a marker of insulin resistance¹⁸. High waist circumference was also important and size of >90 cm in men and >88 cm in women were considered predictive. These observations are similar to a previous study from India¹⁹ and consistent with the revised IDF guidelines for diagnosis of the metabolic syndrome in South Asians²⁰. This study¹⁴ shows a weak association of low HDL cholesterol with metabolic syndrome which is unlike findings from previous international studies¹⁰. More studies are required to confirm this association.

Is the diagnosis of the metabolic syndrome relevant to practice?: And finally, the concept of the metabolic syndrome has been criticised by many authors^{21,22}. The syndrome does not fit with the classical definition "the

aggregate of symptoms and signs associated with any morbid process and constituting together the picture of the disease". For example, it is well known that each of the components of the metabolic syndrome is an independent and important cardiovascular risk factor, the risk can be quantified and can be reduced by appropriate intervention¹⁰. On the other hand, management of the metabolic syndrome involves management of the individual component and there is no evidence that reducing the overall components of the metabolic syndrome reduces risk more than the individual component²³. It has been argued that the metabolic syndrome is a creation of a few individuals to include as many "healthy" subjects into "ill" category and to enhance drug use among these subjects²². Conversely, some authors view this as a useful construct that identifies higher risk subjects within high-risk groups²⁴.

Most traditional cardiovascular risk factors such as smoking, blood pressure, LDL cholesterol, HDL cholesterol and blood glucose levels follow risk continuum with risk linearly related to increasing values²⁵. It is also known that majority of cardiovascular events occur in those with borderline levels of these risk factors and the traditional risk thresholds do not convey the whole risk²⁶. Multiple risk markers (genetic, inflammatory, biochemical, mechanical, radiological, etc.) are being identified to more accurately classify risks in such individuals²⁷. Presence of the metabolic syndrome in such individuals could identify higher risk subjects in those with otherwise low risk and in whom therapeutic implications are uncertain.

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