In his Banting Award lecture for the American Diabetes Association in 1988, Professor Gerald M. Reaven discussed the clustering effect of the insulin resistance syndrome, or syndrome X, as an important risk factor for atherosclerosis. Although Professor Reaven was not the first to describe the insulin resistance syndrome, his research had expanded the concept of insulin resistance from its origins in the pathophysiology of type 2 diabetes mellitus to several chronic human diseases that relate to cardiovascular diseases. The intimate association of type 2 diabetes with cardiovascular disease led to the hypothesis that these two arise from a common antecedent and play a pivotal role in the subsequent development of cardiovascular diseases.

The importance of insulin resistance has been acknowledged since early 1990. In 1998, the World Health Organization (WHO) provided the first definition of the metabolic syndrome. In 2001, a clinically oriented definition of the metabolic syndrome was proposed by the adult treatment panel III of the National Cholesterol Education Program. A third criterion was proposed by the American Association of Clinical Endocrinologists (AACE) in 2003. The WHO and AACE definitions center mainly on insulin resistance and, thus, recommend an oral glucose tolerance test for patients without elevated fasting glucose. However, the definition from the ATP III of the NCEP stresses the equal importance of 5 components and that the presence of 3 of these factors is considered sufficient for diagnosis.

There is accumulating evidence that subjects with the metabolic syndrome are at increased risk of incident diabetes or cardiovascular diseases and total mortality relative to subjects without the syndrome. These findings are not particularly surprising since individual components of the metabolic syndrome contribute to diabetes and cardiovascular disease. The question is whether the clustering of these components, that is, the metabolic syndrome, implies a greater risk than that predicted by the presence of its individual components. Recent publications seem to indicate that this is the case. The study by Lakka et al. prospectively examined the relationships between the metabolic syndrome and cardiovascular disease and overall mortality rate in middle-aged men participating in the population-based Kuopio Ischemic Heart Disease Risk Factor Study, who were followed up for 11.4 years. They demonstrated that even in the absence of diabetes or prior cardiovascular disease, the presence of the metabolic syndrome was associated with significantly increased risk of cardiovascular disease and all-cause mortality. Golden et al. found that the metabolic syndrome interacted to increase carotid intimal-medial thickness to a greater degree than expected solely by its additive effects. On the other hand, Resnick et al. indicated that, although the metabolic syndrome and insulin resistance both predict diabetes, neither predicts cardiovascular disease independently of other established traditional risk factors. Therefore, further studies on the outcomes are needed to clarify whether the metabolic syndrome per se contributes to cardiovascular diseases. The recent development of the insulin sensitizer, thiazolidinedione, has shed some light on these issues and studies of the effects of intervention by thiazolidinedione on cardiovascular events are currently ongoing.

From the viewpoint of clinical practice, there are 2 reasons to recognize and diagnose metabolic syndrome. One reason is to always consider that individual components would likely cluster in the same subjects. The other reason is to identify subjects who are most likely to benefit from aggressive efforts to achieve optimum weight by increasing physical activity. We should remember that even modest weight loss and a moderate increase in exercise prove very useful in treating the metabolic syndrome. In fact, studies from the US and Finland have...
indicated that relatively modest lifestyle changes substantially reduce the risk for type 2 diabetes in subjects with impaired glucose tolerance. In addition, it is well documented that controlling blood pressure and blood lipids substantially reduces the risk of cardiovascular disease events in patients with hypertension or hyperlipidemia.

A pro-inflammatory state that may relate to excessive adipose tissue and insulin resistance has recently been well established. Recent observation from the Framingham Offspring Study indicated that both C-reactive protein (hs-CRP) and the metabolic syndrome were independent predictors of new cardiovascular events. Whether biomarkers of inflammation should be listed as one of the components of the metabolic syndrome is now the subject of intensive investigation.

The study by Chuang et al. in this issue of the Journal attempted to determine the prevalence of the metabolic syndrome in a large group of subjects (n = 24,329) obtained from a private physical check-up enterprise in Taiwan from 2000 to 2001. They found that prevalence of the metabolic syndrome is 12.9% (15.5% in men and 10.5% in women) based on the modified criteria of the ATP III of the NCEP (waist circumference 90 cm for men and 80 cm for women). These figures are lower than those reported from the study population of Kinmen, an island off the coast of southern China. Their findings are also lower than those reported from US study populations. In age-adjusted estimates from the National Health and Nutrition Examination Survey III (1988 to 1994), approximately 24% of adult Americans had ≥ 3 of the 5 metabolic syndrome criteria. Prevalence rates were highest in Hispanics and were successively lower in whites, African Americans and other racial groups. These large variations in the prevalence of the metabolic syndrome could be partly accounted for by differences in study populations, lifestyles, socio-economic status, etc. In addition, a significant association between the metabolic syndrome and a history of stroke and heart disease was also found in the authors’ reports. These observations are compatible with previous prospective studies in Caucasians. In a group of non-diabetic individuals, we recently found that the metabolic syndrome was more prevalent in subjects with angiographically documented CAD than in subjects without CAD (51.8% vs. 18.7%; p < 0.001). Multiple logistic regression analysis showed that hypertension was the strongest predictor of CAD, followed by higher fasting glucose and lowered HDL cholesterol. These 5 factors accounted for 41.3% of the total risk for CAD without diabetes. Certainly, prospective studies that aim to investigate the predictive power of metabolic syndrome in subsequent cardiovascular disease and mortality are needed in Asian populations.

Several unsolved issues related to the metabolic syndrome need to be explored in the future. Studies on whether improved strategies for successful weight reduction and maintenance and increased physical activity lower the risk of metabolic syndrome are needed. A better understanding of the genetic and metabolic contributions leading to the development of the syndrome is currently under study. However, the efficacy of treating insulin resistance and atherogenic dyslipidemia beyond LDL-lowering therapy needs to be investigated further. The relationship between a pro-inflammatory state and the metabolic syndrome and the efficacy of interventions on this state are still unclear at present. Therefore, establishment of the benefit and cost-effectiveness of a specific goal for drug therapies directed toward the metabolic syndrome as a whole or particular risk components is clearly needed.

REFERENCES


