Obesity-Related Risk Factors of Cardiovascular Disease

Eiji Oda, MD

Metabolic syndrome (MetS) is a known risk factor of diabetes and cardiovascular disease (CVD). However, in 2005, the American Diabetes Association and the European Association for the Study of Diabetes jointly stated that no existing definition of MetS meets the criteria to classify it as a syndrome and there have been endless debates on the pros and cons of how to diagnose the syndrome. Dichotomous diagnosis may often cause misleading effects on CVD risk assessment for individuals. The criterion that regards obesity as an inevitable component of MetS has a serious pitfall because there are a substantial number of metabolically obese, normal-weight individuals and only approximately one-third of the most insulin-resistant individuals are actually obese. An essential drawback of the Japanese MetS (“visceral fat syndrome”) is that it regards subcutaneous adipose tissue (SAT) as a protective factor against the morbid effect of visceral adipose tissue (VAT) and ignores the important risk contribution of abdominal SAT. When correlations of VAT volume and SAT volume were compared with metabolic risk factors and markers of inflammation, oxidative stress and endothelial dysfunction in the Framingham Heart Study, it was clearly shown that the risk contribution of SAT cannot be ignored. As for the risk of coronary artery disease, the standardized odds ratios of VAT area, SAT area, body mass index (BMI) and waist circumference for coronary calcification detected by electron-beam computed tomography, which is considered as an early manifestation of coronary artery disease, were 1.9, 2.0, 2.2 and 1.9, respectively, in men and 1.8, 1.9, 1.9 and 2.0, respectively, in women. Thus, VAT area is not superior to SAT area, BMI, or waist circumference as a risk factor of coronary artery disease, although the superiority of VAT area to obesity indices is the original reason for proposing “visceral fat syndrome”. As for insulin resistance, Reaven reviewed the world literature comparing VAT area with SAT area and concluded that the correlations of VAT area and SAT area to insulin resistance are not statistically different. Koutsari and Jensen showed that free fatty acid (FFA) released by VAT contributes to only a small percentage of systemic FFA delivery and that upper-body SAT is the dominant contributor to circulating FFA, which is an important causal factor of peripheral insulin resistance. Japanese MetS and the MetS defined by the International Diabetes Federation (IDF) criteria, in which obesity is an inevitable component of MetS, were already shown to be inferior to the MetS defined by revised NCEP criteria in which obesity is not an inevitable component of MetS as a predictor of CVD in Japanese people.

In this issue of the Journal, Higashiyama et al report from the Suita Study that the multivariate-adjusted hazard ratio (95% confidence interval) for the incidence of CVD in a comparison of participants who did not smoke and were not with MetS defined by the revised NCEP criteria was 2.07 (1.26–3.40) in those who smoked, 2.09 (1.08–4.04) in those with MetS and 3.56 (1.89–6.72) in those who smoked and had MetS. The population-attributable fraction for the incidence of CVD in men was 21.8% because of smoking, 7.5% because of MetS and 11.9% because of both. This report clearly shows that the Japanese MetS and IDF MetS, as well as the revised NCEP MetS, are dangerous if we consider patients with MetS as the only high-risk population that should be targeted in preventive medicine. Cigarette smoking increases the white blood cell count (WBC) and triglycerides level, decreases high-density lipoprotein-cholesterol in relation to insulin resistance and has been established as a major risk factor of CVD. Inflammation is a fundamental underlying mechanism of both atherosclerosis and MetS. Among the markers of inflammation, oxidative stress and endothelial dysfunction, high-sensitivity C-reactive protein (hs-CRP) is the most strongly correlated with VAT volume, SAT volume, waist circumference and BMI. MetS may be the systemic manifestation of adipose tissue disease, which is induced by chronic energy overload, defined as an increased aggregation of activated macrophages from bone marrow into adipose tissue, and characterized by a crown-like structure. Some investigators, including me, think that inflammatory cells originating from bone marrow, rather than enlarged and dead adipocytes, are the leading players in MetS. Other predominant underlying mechanisms of MetS appear to be insulin resistance, leptin resistance, autonomic dysfunction and endothelial dysfunction. Other than hs-CRP, the following are reported as obesity-related risk factors of CVD: WBC, gamma glutamyltransferase (GGT), resting heart rate and chronic kidney disease. Low vital capacity and restrictive lung disease are reported as risk factors of diabetes and CVD. Low-density lipoprotein-cholesterol (LDL-C), which is a well-known risk factor of CVD, is not usually considered as a component of MetS. However, a cross-sectional study of the association between LDL-C and MetS in Japanese men and women...
found that LDL-C was significantly associated with MetS, especially in the women. Increased serum levels of hs-CRP, increased WBC, increased serum levels of GGT and/or alanine aminotransferase, increased urinary excretion of albumin, increased resting heart rate, and decreased vital capacity are also reported as associated components of MetS. Thus, I propose an extended concept of MetS developing through adipose tissue disease, as shown in Figure.

References