No paradox: relationship between obesity and coronary atherosclerosis

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Online publish-ahead-of-print 9 June 2013

There is a global obesity epidemic, and most experts expect it will severely curb the reduction in cardiovascular mortality so far observed over the past three decades.1,2 Despite the clear associations of overweight and obesity with mortality,3 it is still debated if it constitutes an independent risk factor in its own right. Established causal risk factors may account for many of the deleterious effects observed in association with obesity, namely hypertension and diabetes, but also factors such as insulin resistance, physical inactivity, and low self-esteem. Epidemiological studies interrogating such relationships usually concentrate on elderly subjects, as only these populations are expected to yield a statistically adequate rate of hard clinical events. However, risk-factor associations with cardiovascular disease are attenuated with age, and accordingly, it becomes increasingly difficult to detect causal effects.

The classic Pathobiological Determinants of Atherosclerosis in Youth study suggests detrimental consequences of obesity are already observed early on in life at an age between 15 and 34 years.4 Using surrogate endpoints of vascular structure and function, clear abnormalities have been documented in obese children and adolescents compared with normal weight peers.5 The importance of childhood obesity per se remains disputed, but it is clear that in early adulthood and mid-life, obesity is associated with several years of life lost mainly due to cardiovascular diseases.6,7 On the other hand, elderly obese patients with cardiovascular disease appear to fare better than their lean counterparts; the so-called obesity paradox.8

The current report by Fujiyoshi et al.9 adds a significant piece of evidence to the complex puzzle of obesity and cardiovascular disease. In an international epidemiologic co-operation, ethnically different unselected male populations were examined: Koreans, Japanese, US Americans, and Japanese subjects living in America (Japanese Americans). Compared with other studies, the actual study participants were relatively young; their age was 40–49 years. Only individuals without overt cardiovascular disease or diabetes mellitus type I were included. A thorough analysis of cardiovascular risk was performed, including the established risk factors, alcohol and medication use, and body mass index (BMI). As outcome variable, coronary artery calcium (CAC) was measured using electron-beam computed tomography (EBCT). CAC is an integral part of coronary atherosclerotic plaque disease and is associated with the overall extent and severity of coronary atherosclerosis.10 Above-average CAC predicts an increased rate of hard cardiovascular events.11,12 Indeed, the predictive ability of CAC is superior to the established risk factors as well as C-reactive protein and carotid intima-media thickness.13–15 In the current report, the prevalence of CAC ranged between ~11% in Japanese and Korean males and 26% in US American whites and 32% in Japanese Americans. BMI as a measure of obesity was associated with CAC in all four populations. After adjustment for the major risk factors, age, and alcohol use, the association remained statistically significant in all populations except for Japanese Americans (where only a trend was apparent). Overall, the magnitude of the association of BMI with CAC appeared to be in the same order as for low-density lipoprotein cholesterol and age.

The findings are consistent with data from the Multi-Ethnic Study on Atherosclerosis (MESA).16 However, as opposed to Fujiyoshi et al., MESA did not report on ethnicity-specific associations between BMI and CAC. In this respect, a comparison with data from the CONFIRM-trial is interesting (CORony CT Angiography EvaluationN For Clinical Outcomes: An InternRtional Multicentre).17 In 13 874 persons from North America, Europe, and South Korea without previous myocardial infarction or coronary revascularization, BMI was strongly associated with the prevalence, extent, and severity of coronary atherosclerosis as determined by contrast-enhanced CT-angiography. There were no relevant regional differences or differences between ethnic groups.

Usually, age (and male sex) is the predominant influence on CAC. In the current report, BMI appeared to be of similar importance as age. When interpreting this, one needs to consider that the population was limited to 40- to 49-year-old males. Accordingly, the powerful influence of advancing age was not accounted for. Yet, the relatively young age of the participants may have allowed for better capturing the effects of obesity than would have been the case in older populations. As delineated above, obesity appears to affect cardiovascular risk in particular in young and middle-aged adults.

Although frequently used in epidemiological studies, BMI is only one of several possible measures of obesity. Indeed, body fat...
distribution appears to be more important than overall body weight used as part of the BMI.18 The metabolic abnormalities associated with an increase in cardiovascular risk are mainly associated with intra-abdominal, visceral adipose tissue. Further, regional fat distribution—admittedly difficult to assess—may play a role in coronary atherosclerosis. In a study using coronary contrast-enhanced computed tomography, Mahabadi et al.19 observed an association of pericoronary fat volume with an atherosclerotic plaque burden in the underlying coronary artery. Accordingly, although (abdominal) visceral adipose tissue appears to be the main correlate of most metabolic risk factors, pericardial fat may be of additional importance regarding CAC and incident coronary events.20,21

In summary, the current report provides significant insights regarding the relationship of obesity with cardiovascular risk. Because obesity is particularly important in early adulthood and mid-life, the relatively young age study of the study participants allowed for delineating an association between BMI and CAC which may escape investigators examining older subjects. The underlying patho-biological concepts include metabolic consequences of visceral adipose tissue as well as potential local toxic effects of pericoronary fat. Consistent observations in ethnically diverse populations add to the robustness of the data. In the end, there may be no paradox, i.e. protective effect of obesity. We only need to look at the right age-group and outcome variable. Certainly, for males aged 40–49 years, it is bad news to be overweight, it is bad news to have CAC detectable by EBCT, and it appears there is a connection between the two.

Conflict of interest: none declared.

References