Body fat and cardiovascular risk: understanding the obesity paradox

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This editorial refers to ‘The influence of body mass index on mortality and bleeding among patients with or at high-risk of atherothrombotic disease’, by K.-H. Mak et al., on page 857

Large studies of initially healthy men and women consistently link adiposity with an increased risk of cardiovascular events.1,2 Compared with a reference body mass index (BMI) <25 kg/m², the relative risk of dying during the next decade ranges from 1.2 for overweight (25–29.9 kg/m²) to 3.8 for severely obese (≥40 kg/m²) subjects, after adjustment for age, smoking, alcohol, and physical activity.1 Abdominal fat, measured as the waist–hip ratio, more reliably predicts the risk of ischaemic heart disease and death than BMI, even within normal body weights and after additional adjustment for blood pressure and cholesterol.2,3

In striking contrast, among patients with known atherothrombotic diseases4,5 or multiple risk factors,6 just the opposite is seen (‘obesity paradox’): the leanest fare worse6 and the heavier fare better than the normal weight reference groups.4–6 Among stable hypertensive ischaemic heart disease patients, thin (<20 kg/m²) compared with normal weight patients had a 3-year hazard of death, non-fatal myocardial infarction, and non-fatal stroke of 1.5, similar to that conferred by a 10-year increment in age.4 At the other extreme, obese and very obese patients with non-ST-elevation acute coronary syndromes had a 3-year hazard of dying of 0.3 compared with normal BMI patients.5 In these studies, adjustment included age, risk factors, extent of coronary disease, left ventricular ejection fraction, prior stroke/transient ischaemia, heart failure, medications, and renal insufficiency.4,5

The study of Mak et al. offers further insight into the topic.7 It comes from the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) population with—or at risk of—coronary, cerebral, or peripheral atherothrombosis (~15,000 patients) randomized to receive aspirin + placebo or aspirin + clopidogrel for 28 months. After adjustment for age, sex, smoking, diabetes/diabetic nephropathy, hypertension, hypercholesterolaemia, and use of diuretics, the authors report an inverse relationship between BMI, on the one hand, and the risk of death (all-cause and cardiovascular), major cardiovascular events (death, including haemorrhagic; non-fatal myocardial infarction; non-fatal stroke), and severe bleeds, on the other hand, in both treatment arms and regardless of symptomatic status.7 The higher risk of leaner patients for both atherothrombotic and bleeding events is well emphasized, but while it is well recognized that lighter vs. heavier patients are more prone to serious bleeds,7–10 it is less clear how these same patients may be at increased risk of atherothrombotic events.8,7

First of all, does adiposity really increase cardiovascular risk? White fat, especially when infiltrated by macrophages, produces cytokines that affect metabolism, raise plasma insulin, glucose, and triglycerides, and reduce high-density lipoprotein (HDL) cholesterol.11,12 Tumour necrosis factor-α, in particular, uncouples the insulin/insulin receptor complex from its intracellular signalling, by blocking insulin receptor substrates 1 and 2, with consequent insulin resistance (Figure 1).11,12 Although it is debated to what extent diabetes, sedentary lifestyle, hypertension, and dyslipidaemia—often associated with adiposity and not always corrected for in data analyses—contribute to cardiovascular risk, fatness remains a strong harbinger of cardiovascular events among initially healthy subjects.1–3 especially when co-inflammation favours the ‘unhealthy fat’ phenotype (Figure 1).11

Why then should the lack of fatness identify patients with atherothrombotic diseases who are more likely to die sooner or to have recurrences than their heavier counterparts? The answer may simply be that when a disease develops in the absence of an ‘obvious cause’ (e.g. obesity or other risk factors), something else of significance must be harboured in its place. This ‘something else’, which may partly escape our current grasp, is what puts the slimmer patients in a high risk stratum. Notably, lighter compared with fatter patients are more likely to have suffered from stroke or transient ischaemia7 and to have peripheral vascular disease7 and impaired renal function.7 Moreover, they appear to be
undertreated in terms of β-receptor blockers, antithrombotic drugs, coronary interventions, and bypass grafting. Two examples may further elucidate the above concept. Patients with venous thromboembolism who lack a reversible precipitating factor, compared with those with an identifiable transient trigger, have a higher risk of recurrences, presumably ascribable to underlying thrombophilia;13 in this case, the absence of a reversible predisposing element indicates worse outcomes than its presence. Women with cardiovascular disease, despite their ‘protective’ gender, have a distinctly higher risk profile than men, mainly because they are 10 years older, on average, and have a heavier burden of co-morbidities;14 in this case, the protective female state must be ‘compensated for’ by age and co-morbidities to reach the threshold of disease.

At the same time, adipose tissue, while increasing the probability of developing atherothrombosis, may offer protection in the context of tissue damage, supporting the aphorism ‘survival of the fattest’. Possible defences conferred by adiposity include regenerative,7 metabolic,7 and haemodynamic8 compensation, and/or reversal to a ‘healthy fat’ phenotype (Figure 1). Thus, a condition signalling risk would confer protection in the midst of disease, just as pre-infarction unstable angina, while heralding thrombotic complications, protects myocardium against prolonged ischaemia.

In conclusion, it is time to appreciate more fully that leaner patients with, or at risk of, atherothrombotic disease are a high risk group. Lighter patients need concomitant (and possibly still unknown) cardiovascular risk factors in order to reach the ‘100% risk threshold’ of disease. Importantly, these patients also have increased bleeding rates,7–10 which adversely influence prognosis.15 Finally, suboptimal adjustment for other negative prognostic markers—such as co-morbidities,7 lack of compensatory processes, undertreatment,10 and lack of weight-adjusted drug dosing6—may amplify their poor outcomes compared with fatter counterparts.9 Lean and fat patients may thus conceal predisposing and protective elements for atherothrombotic diseases that we currently ignore.

Conflict of interest: none declared

References
A 45-year-old man was referred for urgent coronary angiography due to recent onset chest pain and ST-segment elevations. Cardiac enzyme levels were slightly elevated. Coronary angiography showed normal coronaries but revealed a thin, pointed radiopaque object in the projection of the right ventricle moving synchronously with cardiac contractions (Panels A and B).

The origin of the foreign body was initially unclear; the patient had no penetrating chest injuries and no scars were seen on the chest wall. Further review of history revealed that 5 years earlier the patient underwent wire fixation of his right acromioclavicular joint.

We removed the wire from median sternotomy. Opening the pericardium revealed the sharp tip of the wire outside the myocardium, pointing at the right margin of the right ventricle, reaching the diaphragm with every heartbeat (Panel C). Inspection after removal confirmed that the foreign body was in fact a 6 cm long part of a Kirschner wire (Panel D).

We have obtained all prior patient documentation to establish a timeline for the migration of the pin from the shoulder to the heart. Review of annual screening chest X-rays confirmed that one of the Kirschner wires was not removed as planned, 3 months after surgery. We believe that the wire entered the venous system and was carried with the blood flow into the right ventricle.

According to our knowledge, this is the first documented case when the embolization of a broken Kirschner wire to the heart mimicked acute coronary syndrome and was detected during coronary angiography.