Defending the Con Side: Obesity Paradox Does Not Exist

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The elegant review of Hainer and Aldhoon-Hainerová, "Obesity Paradox Does Exist" (1), rightly points out that the so-called reverse epidemiology of a better outcome associated with obesity occurs only in patients with established cardiovascular (CV) disease (CVD) including heart failure (refs. 1–35 in the review by Hainer and Aldhoon-Hainerová (1). At the primary prevention level, however, studying large cohorts, e.g., the population of 359,387 participants recruited in the European Prospective Investigation into Cancer and Nutrition (EPIC) Study with a follow-up of 9.7 years (2), increased waist circumference as a surrogate of obesity clearly was a strong predictor of increased mortality, and there are numerous similar studies confirming the primary importance of obesity in the context of a higher total mortality or CV morbidity and mortality, as discussed further in this article. This notion has not been challenged in the article of Hainer and Aldhoon-Hainerová (1).

Furthermore, it has to be kept in mind that epidemiology never proves causality, even it is reverse and contrary to the expectation. Indeed, there may be many reasons why this reverse epidemiology may be seen in patients with CVD, including selection bias, treatment bias, distinct phenotypes of CVD patients including weight differences and differences in prognosis, a multitude of comorbidities and confounders, and last but not least, anabolic deficiency or the malnutrition-inflammation syndrome. This article attempts to address all of these important issues and, in the last part, also evaluates the beneficial effects of weight loss in prospective long-term studies on overall mortality, CV morbidity and mortality, and type 2 diabetes. Randomized controlled trials (RCTs) are thought to provide the top class of scientific evidence as well as the strongest recommendations for therapy. Most RCTs on weight loss and CV benefit, however, are still ongoing, and only a few have reported outcomes to date.

Observations at the primary epidemiology level

Also over the last decade, large-scale long-term observations of representative cohorts at the primary level have consistently and convincingly shown that overweight (BMI >25 and <30 kg/m^2) and obesity (>30 kg/m^2) or increasing obesity and surrogates of increased body fat accumulation, especially of visceral fat, are highly predictive for increased CV morbidity and mortality as well as total mortality (2–12). The number of subjects enrolled in these studies ranges from $>10,000$ to several 100,000 to up to 2 million and includes various ethnicities. The outcomes specifically studied comprise death from coronary heart disease (CHD), hospitalization for CHD, myocardial infarction (MI), heart failure, incident microalbuminurea, new manifestation of atrial fibrillation, stroke, and all-cause mortality. Most studies report on primary population cohorts; others on patients with impaired glucose tolerance, like Nateglinide And Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) Study Group (10); and others on patients with type 2 diabetes (7). The association of excessive weight with excessive CV morbidity and mortality seems to indicate a continuous relationship. When BMI categories are considered, the increased CV risk is usually already seen in the range of overweight (BMI >25 and <30 kg/m^2) but more pronounced with obesity (BMI >30 kg/m^2) and is further increased in the BMI range >35 kg/m^2. The disability-adjusted life years lost attributable to excessive body weight are considerable and contribute ~5% of the burden due to all noncommunicable diseases (5,13). According to the Report of the World Health Organization, 2.8 million people die each year as a result of being overweight or obese. In addition, overweight and obesity are also closely related to the development of hypertension, dyslipidemia, type 2 diabetes, and insulin resistance, which are risk factors or risk predictors of CHD and stroke in their own right (5).

This clear message of the impact of overweight and obesity has not been challenged by the review of Hainer and Aldhoon-Hainerová (1), notwithstanding the undisputed fact that a significant proportion of obese, and even morbidly obese, people do not show metabolic abnormalities, at least cross-sectionally or short term (14,15) and, therefore, seem to be at little risk for CV complications over the next decade. What has been shown, rather, is the so-called reverse epidemiology of overweight and obesity during follow-up in patients with established CVD, i.e., in patients after a first MI or stroke or with heart failure, etc. This notion, namely, that the obesity paradox requires a chronic disease in the first place, such as chronic kidney disease, chronic obstructive pulmonary disease, coronary artery disease, and other conditions with critical illnesses, is also nicely reviewed in a recent editorial (16) in the context of findings in patients with acute coronary syndromes in the Swedish

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Coronary Angiography and Angioplasty Registry (17). Compared with patients with normal weight, patients with overweight and even moderate obesity (up to a BMI range <35 kg/m^2) seem to have a better future prognosis (see also refs. 1–35 in 1). There may be many good reasons for this paradox, however, as discussed also in Hainer and Aldhoon-Hainerová's review (1) and further highlighted below. In addition, it should be reemphasized that the obesity paradox seems to be relevant for a BMI range between 25 and 35 kg/m^2 but not beyond that.

Reasons for the reverse epidemiology paradox

The reasons for the reverse epidemiology paradox seem to be manifold and partially also closely interrelated among each other. The leading cause for the paradoxical weight phenomenon—less favorable outcome with lower body weight versus overweight and obesity seem to be protective against further CV complications—may vary at the individual level depending on the specific situation. They include the following.

Survival or selection bias. The West of Scotland Coronary Prevention Study (WOSCOPS) was perhaps the first to point out the possibility of a differential effect of risk factors on fatal and nonfatal CHD events in this longitudinal study (14.7 years of follow-up) in 6,082 men (mean age 55 years) with hypercholesterolemia but no history of diabetes or CVD (18). Whereas the risk of nonfatal CHD events was similar across all BMI categories, the risk of fatal CHD events was increased in men with BMI 30.0–39.9 vs. 25–27.4 kg/m^2 as the referent both in a minimally adjusted model (i.e., for age, sex, and statin treatment) (hazard ratio [HR] 1.75 [95% CI 1.12–2.74]) and a maximally adjusted model (including known CVD risk factors and social state or deprivation; HR 1.60 [1.02–2.53]). So, obviously more obese patients will die earlier from CHD and cannot be selected for further follow-up after a first event. Hence, a survival bias or selection of the fittest may be a likely explanation of the observed reversed epidemiology after a first CHD event.

It seems noteworthy that also in the meta-analysis of Pischon et al. (2), the Chicago Heart Association Detection Project in Industry (6,19), the Oksahi study (where subjects with a BMI <18.5 kg/m^2 were excluded) (4), or the study of Eeg-Olofsson et al. (7) in 13,087 overweight and obese patients with type 2 diabetes, all-cause or CV mortality was a key component of the composite outcomes driven by overweight and obesity, thus confirming the importance of a potential survival bias for the phenomenon of the obesity paradox.

Treatment bias. A huge gap between evidence-based medicine as reflected in treatment guidelines and the reality of therapy at the grass roots level has often been described (20,21). Sex issues and social class seem to play a key role (5). As shown in the World Health Organization report, the lowest social class is associated with the lowest degree of overweight and obesity. So, in the context of the obesity paradox, lower body weight may be a surrogate of underprivileged medical care in some areas of the world, heralding a poorer outcome after a first CV event. Conversely, marked overweight and obesity obviously draw the attention to potential health hazards and may persuade physicians to emphasize and reinforce a more stringent adherence to guideline-based multifactorial CV risk management. Certainly, difficult-to-control treatment bias is one of the potential factors to explain the obesity paradox.

Inhomogeneity of CV patients in terms of several distinct phenotypes. Over the last decades, a secular shift in the predominant phenotype of CV patients has occurred. In the 1960s and up to the 1980s, it was the excessively smoking, rather lean patient, perhaps in conjunction with some familial or genetic traits of hypercholesterolemia, who suffered from premature CHD and other CV complications. Now, it is the more and more overweight and obese patient with coexisting diabetes or prediabetes, dyslipidemia, and other features of the metabolic insulin resistance syndrome who prevails in the clinical picture of CV patients (20). Smoking has decreased considerably over time, and effective cholesterol- and blood pressure–lowering therapies have become available along with astoundingly successful measures of angioplasty and revascularization. Today, three-quarters of patients with MI or established CVD represent the dysmetabolic and obese phenotype (20). In patients with peripheral artery disease, it is well-known that the rather lean smoker has a significant higher risk for major amputations compared with the dysmetabolic nonsmoking diabetic patient (22), and it remains to be evaluated whether a similar primary difference in outcome between distinct phenotypes with CVD and other heart disease may be another factor in the context of the obesity paradox.

Comorbidities and confounders. As discussed in the preceding paragraph, certain risk factors like smoking may influence both body weight and the further prognosis of patients with CVD. Coexisting chronic kidney disease, chronic obstructive pulmonary disease, liver dysfunction, and cancer or inflammation together with old age and frailty seem to be other important players in a potential linkage between lower body weight and a poorer prognosis (23). Therefore, lower body weight may be not necessarily the result of a healthy lifestyle but, rather, a surrogate of additional serious diseases. More overweight and obese patients are less likely to suffer from these often unaccounted comorbidities. It might be noteworthy that in the context of the obesity paradox, it is frequently all-cause mortality, not specific CV mortality, that is an important component in outcome differences.

Anabolic deficiency or the malnutrition-inflammation syndrome. Cardiac cachexia is a well-known phenomenon seen in the context of severe chronic heart disease and indicates a poor prognosis for the individual patient. Cardiac cachexia represents a state of anabolic deficiency with mitochondrial fragmentation of muscle tissue and reduced muscular strength (24). So, good physical fitness seems to be an important issue, and more obese subjects seem to benefit the most from physical fitness (12). Early signs of reduced muscular strength may already be present in a subgroup of patients with hypertension and signal a more disadvantageous outcome. Anabolic deficiency can be most marked in heart failure patients and is associated with decreased blood lymphocytes, serum total cholesterol, albumin, and prealbumin and increased signs of inflammation and reflects a rather poor prognosis. In fact, evidence has been accumulated that A-type and B-type natriuretic peptides, produced in the myocardial tissue in response to ventricular stretch and cardiac overload—increased levels being a hallmark and highly diagnostic of heart failure—promote lipolysis, enhance adiponectin production, and augment the malnutrition-inflammation syndrome (25). It has been a puzzling finding for some time that higher adiponectin levels, which are usually thought to be preventive against the occurrence

of CV complications and type 2 diabetes and seen as a sign of good health (26), appear to indicate a much more adverse outcome in conjunction with CHD and heart failure (27,28). In the context of a discussion of the so-called obesity paradox, an adiponectin paradox seems to be another facet of the complex.

So, in aggregate, slim may not always be healthy (the review of Hainer and Aldhoon-Hainerová expands on that issue even further), and a selection and treatment bias may contribute to a relatively more healthy but obese phenotype. These two main notions seem to largely explain the reverse epidemiology of a better outcome of patients with existing CV complications and a higher body weight (29). An unqualified general linkage, however, of obesity and a better lifetime prognosis, i.e., an obesity paradox in general, does not seem to exist.

Prospective evaluation of weight loss/weight changes

Recently, the Mayo Clinic reported on weight loss as a marker of a more favorable long-term CV outcome, regardless of the initial BMI, in a prospective series of patients enrolled in its cardiac rehabilitation program and followed for a mean of 6.4 years (30). The weight loss group lost on average 3.6 ± 4.1 kg, whereas the non–weight loss group gained 1.5 ± 1.4 kg. The rate of the composite outcome (total mortality and acute CV events) was 24% in those who did lose weight vs. 37% in those who did not lose weight ($P < 0.001$). The difference remained significant after adjustment including the obesity status, and weight groups with a baseline BMI >25 and <25 kg/m^2 benefited similarly.

The long-term LookAHEAD (Action for Health in Diabetes) Study (RCT of intensive lifestyle management vs. standard therapy) in 5,145 overweight or obese patients with diabetes (BMI inclusion criteria >25 kg/m^2 [>27 if on insulin]) showed an impressive continuous linear relationship between weight loss and improvement of CV risk, i.e., a reduction of systolic and diastolic blood pressure, HbA_{1c}, and triglycerides and an increase of HDL cholesterol (31) The effect was most marked at 1 year follow-up, with a body weight reduction of 8.6% in the intensive lifestyle group. At 4 years' follow-up, effects were principally maintained, albeit somewhat less pronounced in the context of some weight regain (31). The study was halted, however, in mid-October 2012 as a result of failure to reduce death or macrovascular events up to a follow-up of 11 years despite a persistent weight reduction of 5%. The problem seemed to be mainly due to a much lower than expected CV event rate (only one-third) and perhaps also due to a more intensive drug management for lipids, hypertension, and diabetes in the control group (bias in drug treatment). This study clearly exemplifies the complexity of interactive and confounding factors when looking into the CV outcome benefits of weight-reducing measures in RCTs.

Interesting 20-year follow-up data of the Whitehall II study on rising obesity curbing the decline in the incidence of MI were published earlier in 2012 (32). From 1985 to 2004, some 10,000 men and women in the Whitehall II cohort were followed for incident MI and risk factor trend. Over 20 years, the age- and sex-adjusted hazard of MI decreased by 74%. Main determinants of this reduction were declining non–HDL cholesterol levels, increased HDL cholesterol concentrations, reduced systolic blood pressure, and reduced cigarette smoking. Rising BMI, however, was found to be counterproductive, reducing the scale of the decline by 11% (5–23%) in isolation.

The DaQing study has released 20-year follow-up data on CV outcomes in response to its randomized controlled lifestyle intervention approach including weight-reducing diet over 6 years in Chinese subjects with impaired glucose tolerance (33). The DaQuing study was the landmark study to demonstrate the effectiveness of intensive lifestyle management to prevent the manifestation of type 2 diabetes. While the effectiveness of preventing type 2 diabetes tended to fade away during the second decade after intervention, a beneficial effect of reducing CV complications seemed to emerge gradually at the same time, though it was nonsignificant owing to small numbers.

The most compelling evidence for the effectiveness of weight loss to significantly decrease mortality and long-term CV events in severely obese patients comes from the controlled Swedish Obese Subjects cohort (34). Various techniques of bariatric surgery were applied to induce strong and long-lasting weight loss in some 2,000 middle-aged severely obese people (BMI >34 kg/m^2 in men and >38 kg/m^2 in women; mean BMI at baseline somewhat above 40 kg/m^2). People were followed for up to 20 years (mean follow-up 14.7 years), during which time the operated subjects kept off a significant weight reduction of 16–23% of their original body weight. Bariatric patients were compared with a similar group of obese matched control subjects. Bariatric surgery was associated with a reduced number of CV deaths (28 vs. 49 in control subjects; HR 0.47 [95% CI 0.29–0.76]; $P = 0.002$). The number of total first-time (fatal and nonfatal) CV events (MI or stroke) was lower in the surgery group (199 vs. 234; adjusted HR 0.67 [0.54–0.83]; $P < 0.001$). These results are considered as a proof of principle that marked and maintained weight reduction can successfully decrease CV deaths and major complications like MI and stroke. In earlier publications, the same group demonstrated beneficial effects of weight loss induced by bariatric surgery on total mortality and cancer incidence and, recently, also on the prevention of type 2 diabetes (35–37).

If these striking benefits of reducing body weight in obese subjects in terms of life expectancy and preventing CV complications can be extrapolated to other approaches to losing weight, they clearly point to a strong primary recommendation to reduce body weight in obese subjects. This notion is also underscored by the results of the Whitehall II cohort or the DaQing Study (32,33). In light of the discussion of the obesity paradox, the results of the Mayo Clinic Rehabilitation Program contribute important information in that appropriate weight management is also beneficial in patients with existing CVD irrespective of the baseline body weight (30). This view is also taken in the new guidelines of the European Society of Cardiology on Acute and Chronic Heart Failure 2012 (38).

Conclusions

The perspectives are clear. The discussions over the existence of the obesity paradox should not prevent doctors and patients from proper lifestyle management (including regular physical exercise not discussed in detail in this debate) in patients with established CVD Obesity is of primary importance for the development of CVD and patients with CVD may miss an important opportunity for successful future prevention of CV complications. The counterintuitive reverse epidemiology of body weight observed in some studies in patients with existing CVD does not necessarily mean that an obesity paradox exists. There seem to be a multitude of reasons why a lower or

normal body weight in those patients may be bad news rather than good news, signaling serious comorbidities, cardiac cachexia, and anabolic deficiency induced by heart disease or also underprivileged care. Selection or survival bias and treatment bias are other important factors to be recognized and underline the need for evidence-based and guideline-based medicine for all patients.

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