Can we reconcile 'the obesity paradox' with recent cardiovascular outcome trials in diabetes?

Alexandra Jamieson
UCL, Institute of Cardiovascular Science
London, UK

Nick Finer
UCL, Institute of Cardiovascular Science
London, UK

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CV outcome trials and the obesity paradox

Corresponding Author:
Nick Finer
National Centre for Cardiovascular Prevention and Outcomes, UCL Institute of Cardiovascular Science
Nomura House
1 St Martin's le Grand
London EC1A 4NP
E (Work):n.finer@ucl.ac.uk

Abstract

Several recent cardiovascular outcome trials (CVOT) in patients with type 2 diabetes have shown benefit in terms of both weight loss and cardiovascular benefit. At the same time a number of epidemiological studies have shown that a body mass index above 25 kg/m^2 may be beneficial - the so-called 'obesity paradox'. We discuss whether these CVOT support the potential benefits of intentional or therapeutic weight loss, but conclude that such conclusions would be simplistic and will require trials specifically designed for this purpose.

Abbreviations:

CVOT: Cardiovascular outcome trial

CV: Cardiovascular

T2DM: Type 2 diabetes mellitus

GLP-1: Glucagon like peptide -1

SGLT2: Sodium-glucose co-transporter 2

CAD: coronary artery disease

CHF: chronic heart failure

BMI: Body mass index

COPD: chronic obstructive pulmonary disease

SCOUT: Sibutramine Cardiovascular Outcomes

FDA: Food and Drugs Administration

LEADER: Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results

EMPA-REG: Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

SUSTAIN-6: Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes

MACE : major cardiovascular event

Introduction

Recent cardiovascular (CV) outcome trials of treatments for type 2 diabetes mellitus (T2DM) including Glucagon like peptide -1 (GLP-1) receptor agonists[1,2] and Sodium-glucose co-transporter-2 (SGLT2) inhibitor[3] have shown beneficial effects on both CV outcomes and body weight. The so-called 'obesity paradox' refers to the epidemiological inference that obesity, defined by a body mass index (BMI) >30 kg/m^2, when compared to normal weight (probably incorrectly defined as a BMI of 18.5-25 kg/m^2), is associated with 'counterintuitive improved health in a variety of disease conditions, including cardiovascular disease'? [4] Do the trial findings further undermine the belief in a paradox, and can they provide support for the benefits of intentional weight loss?

Obesity and cardiovascular disease

Obesity is a major modifiable cardiovascular risk factor for secondary prevention in coronary artery disease (CAD).[5] As a direct risk factor, obesity initiates several pathophysiological pathways such as 'reducing insulin sensitivity, enhancing free fatty acid turnover, increasing basal sympathetic tone, inducing a hypercoagulable state, and promoting systemic inflammation'[6] that contribute to the development and progression of CAD. Indirectly, obesity is a risk factor for the development of T2DM, dyslipidaemia, hypertension, and obstructive sleep apnoea,[7,8] all of which are 'cardiovascular risk factors in their own right'.[9] Obesity is associated with an increased mortality as a result of the maladaptive effects of the aforementioned risk factors.[10] The incidence and prevalence of both obesity and chronic heart failure (CHF) are rising, so that it is increasingly likely that the two conditions may co-exist in a patient,[11] 15–37% of CHF patients are obese.[12,13,14]

'***The obesity paradox'***

Reverse epidemiology infers that apparent risk factors such as obesity confer advantageous short and long-term prognosis.[4] An inverse relationship between obesity and cardiovascular mortality has been described in several studies with patients with coronary heart disease,[9,15,16] hypertension,[17] percutaneous revascularisation,[10] and coronary artery bypass grafting.[10] Furthermore, Angeras and colleagues reported a 'U-

shape relationship between mortality and body mass index (BMI) in patients with acute coronary syndromes',[4] consistent with the findings of Kapoor et al.[18] A meta-analysis of six studies (n=22,807) on the relationship between BMI and all-cause mortality, cardiovascular mortality and hospitalisation in patients with CHF found the risk for cardiovascular mortality and hospitalisation was highest in the underweight and lowest in the overweight.[19]

The source of the paradox has posed much debate in the literature. Some take the view that there is no paradox because the basis for defining an 'ideal', 'healthy' or 'normal' reference BMI of 18.5-25 kg/m^2 has no basis.[20,21] BMI also fails to account for variations in lifetime weight history,[22] body composition,[23] fat distribution[24,25] or physical or cardio-respiratory fitness.[26]

Two prominent schools of thought seek to explain the association. Firstly, it is proposed that there are properties and biological pathways within the obese phenotype that provide cardiovascular protection and increased prognostic value.[27] Secondly, causal inference from observational studies is statistically fraught, and that the association is coincidental due to study limitations and/or lack of adjustment for confounding factors in overweight and obese cohorts.

Heysmfield and colleagues suggest that adipose tissue may provide energy reserve during acute illnesses.[27] Direct cardioprotective effects such as a reduction in infarct size have been observed in individuals with excess adiposity during myocardial infarction.[27] It has been speculated that the 'anti-inflammatory, anti-apoptotic and anti-hypertrophic characteristics'[28] of hormones such as leptin and adiponectin released from adipose tissue are the cause of such effects.[29] Furthermore, cardioprotection in CHF has been supported by the work of Mehra and colleagues.[30]

Contrarily, it has been argued that these paradoxical findings may represent an epiphenomenon rather than a true causal relationship due to limitations of the studies in which they are presented. There is evidence of strong confounding by variables such as smoking and statistical adjustment for smoking is often insufficient.[31] Smokers tend to be leaner than non-smokers and the intensity of smoking is related to both BMI and

mortality.[31] Past and current smokers should be excluded from studies to ensure there are no confounding effects.[31]

Additionally, patients with obesity may be subject to aggressive secondary preventions such as treatment for T2DM, hypertension and cholesterol, all of which may manifest as cardioprotection.[32] Medical intervention and administration of medication earlier on in the stage of disease may be advantageous in obese patients and thus must be adjusted for.[33,34]

Reverse causation and the impact of disease on weight must also be addressed, as underlying disease states may result in unintentional weight loss and long-term sequalae of poor prognosis. Studies should exclude deaths from a set number of years after follow-up to reduce the effect of reverse causality, however, chronic conditions such as heart failure, chronic lung disease and depression may not have received clinical diagnosis and thus results must be critiqued with this in mind.[31]

Martin-Ponce and colleagues, speculate that their results, which favoured individuals whom were overweight and obese, were influenced by patient characteristics rather than 'specific beneficial effect of excess fat'[35] – i.e. selection or collider bias.[36,37] They observed that obese patients were 'younger, had better nutritional status and suffered less from sepsis, chronic obstructive pulmonary disease (COPD) and dementia'[34] (all of which have been classified as high mortality diseases). After conducting a multivariate analysis, they noted that obesity did not show an independent predictive value when assessed with short and long-term survival.

The effects of weight loss

Many observational studies and randomised trials show that weight loss markedly improves cardiovascular risk factors including blood pressure, lipids and glycaemia.[38] Furthermore, most evidence, but not all,[4,39] shows that moderate (intentional) weight loss, including those with T2DM, reduces mortality.[40,41,42] Even in the Sibutramine Cardiovascular Outcomes (SCOUT) trial, those who lost weight saw a 6.80% absolute risk reduction for primary outcome of cardiovascular events.[43] At the same time, weight gain has been linked to a worsening of such cardiovascular risk factors.[31]

It is evident that conflicting results surround epidemiological studies, and thus the significance of intentional versus unintentional weight loss cannot be underestimated. One can speculate that contradictory results are 'perhaps due to confounding of unintentional weight loss'[44], a notion supported by Sorenson and colleagues.[39]

Weight and Body Mass Index (BMI)

The limitations of BMI in discriminating between adipose tissue and lean mass are well documented.[9] Specifically, patients with cardiovascular disease with static or increased lean mass are associated with better cardiorespiratory fitness and thus better prognosis.[45] Individuals may be classified as 'metabolically healthy but obese phenotype'[46] and skew a favourable outcome.[9] Sarcopaenia and sarcopaenic obesity in contrast are associated with worse CV outcomes, so potentially biasing against a population with lower BMI.[47] Studies demonstrating the paradoxical association do not 'typically adjust BMI for other measures of adiposity' such as waist circumference, waist to hip ratio and body fat percentage.[11]

Diabetes Mellitus- Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat T2DM

As a complex metabolic disorder, T2DM is characterised by hyperglycaemia and 'associated with a high risk of cardiovascular, microvascular, and other complications.'[1] Obesity is a documented risk factor for T2DM,[48] however, T2DM can be induced in the absence of obesity in those with 'greater genetic susceptibility'.[49] In such cases, T2DM is more likely to develop 'at a lower BMI "stress"[50], with greater risk for comorbidities and poor prognosis.[48]

In 2008, following concerns surrounding therapeutic induced adverse cardiovascular effects,[49] the Food and Drug Administration (FDA) released guidance for the pharmacological industry on the development of new anti-diabetic therapies,[51] driving large randomised cardiovascular outcome trials (CVOT) during drug development. Drugs from two classes of hypoglycaemic drugs, both of which are associated with reductions in body weight, have now reported favourable cardiovascular outcomes. Can such trials inform about the potential benefit or harm for weight loss in generally high-risk patients (with T2DM)?

Sodium-Glucose Co-transporter 2 Inhibitor (SGLT2i) (empagliflozin)

In the EMPA-REG OUTCOME study, empagliflozin, when added to standard care in patients at high CV risk significantly reduced the primary composite outcome (i.e. CV death, nonfatal myocardial infarction or stroke) and all-cause death as well as a 30-40% lower hospitalization for heart failure.[3] Mean BMI at baseline was >30 kg/m^2; benefit for the primary outcome and for cardiovascular death was confined to those with a BMI <30 kg/m^2. Alongside significant metabolic and blood pressure improvement, weight was reduced by about 2 kg.

Glucagon-like peptide-1 receptor agonists (GLP-1) (liraglutide and semaglutide)

Liraglutide is a once-daily human GLP-1 receptor analogue approved for the treatment of T2DM (at a dose of up to 1.8 mg/day) and chronic weight management (at 3.0 mg/day).[52,53,54,55] In the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) double blind trial of liraglutide, 1.8 mg subjects had a mean BMI of 32.5 kg/m^2.[1] Placebo-subtracted weight loss was 2.3 kg in the liraglutide group. In contrast to EMPA-REG, the benefit in composite primary outcome was confined to those with a BMI >30kg/m^2.[3]

Semaglutide, a GLP-1 analogue with an extended half-life of approximately 1 week allowing once-weekly subcutaneous administration, was also evaluated in a CVOT (SUSTAIN-6) in which the primary composite outcome was the first occurrence of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke.[2] At two years mean body weight in the semaglutide group, as compared with the placebo group, was 2.9 kg lower in the group receiving 0.5 mg and 4.3 kg lower in the group receiving 1.0 mg. CV benefit was significant in those with a BMI ≤ 30 kg/m^2.

Relevance to the 'obesity paradox' and potential benefits of weight loss

All three of these trials were designed to demonstrate the safety of the individual drugs in patients with T2DM. They were not weight-loss trials, and the populations studied heterogeneous in terms of age, weight, BMI as well as cardiovascular morbidity, co-medication. None of the trials included dietary or exercise advice for weight loss. Specific mechanisms by which the drugs induced weight loss likely differed: to

simplify, GLP-1 agonism has direct effects on suppressing hunger[56] while SGLT2i produce obligatory energy losses from increased urinary glucose excretion as well as a modest osmotic diuresis,[57] although these may be offset by metabolic adaptations.[58] Additionally, both drugs have the potential for cardioprotection over and above improved glycaemia.[59,60,61,62] Finally, the CV benefit differed between trials as to whether it was the obese or non-obese who derived significant benefit.

Conclusion

The LEADER, SUSTAIN-6 and EMPA-REG trials undoubtedly demonstrate that GLP-1 agonists and/or SGLT2i provide a therapeutic option for individuals at high risk of cardiovascular events with T2DM that enables robust control of glucose, weight reduction and major cardiovascular event (MACE) outcome risk reduction.[1,2,3] While post-hoc analyses of these trials might allow further hypotheses to be generated concerning the possible contribution of weight loss to the effects seen, specific cardiovascular outcome trials will be needed to further explore the relevance of weight loss. Such trials should better phenotype the trial population for their obesity, although quantitating fat (and ideally lean) mass and its distribution will be problematic for such large trials. 'The obesity paradox' is a complex phenomenon. The reconciliation of such paradoxical associations requires inherent statistical limitations of clinical studies to be addressed, consistent utilisation of more accurate measurements of adiposity, and better understanding of the underlying mechanisms of obesity, T2DM, incretin-related drugs and their complex interplay with cardiovascular disease.

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Conflicts of Interest Statement

Nick Finer is an employee of Novo Nordisk, but writes here from his academic postion.

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