The paradox of diabetes, obesity and cardiovascular risk

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Abstract

Weight loss to reduce cardiovascular risk is encouraged in both healthy overweight individuals and those at high cardiovascular risk, including patients with diabetes. However, a large body of studies suggest that, in comparison to overweight and even obese subjects, cardiovascular events may be more common among patients who lose weight or who fall into lower body mass index categories. In contrast, other studies confirm the traditional concept that weight loss and maintenance of a healthy body weight is not only associated with improvement in cardiovascular risk factors, such as blood pressure, lipid profile and blood glucose control, but also with a reduction in cardiovascular morbidity and mortality. Possible reasons for the difference in outcomes between these two groups of studies include differences in study design, bias and statistics, the health status of the study participants and differential treatment afforded to different patient groups. This article reviews studies supporting both points of view and describes potential explanations for the observed differences in outcomes according to body weight.

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Introduction

Obesity is a well-known independent risk factor for cardiovascular disease (CVD) and is strongly associated with the development of other CVD risk factors, including hypertension, dyslipidaemia, glucose intolerance and overt diabetes.[1] As such, weight loss is encouraged to reduce cardiovascular risk in both healthy overweight individuals and those at high cardiovascular risk, including patients with diabetes.[2-5] Therefore, it is surprising that, although the association between obesity and the initial incidence of a cardiovascular (CV) event is well established, numerous studies have found that overweight patients who survive a first CV event are less likely to experience a second event.[6-16] Similarly among diabetic subjects, some studies have suggested that obesity may be protective for, or at least non-contributory to an adverse CVD outcome; whereas leaner, normal weight patients apparently have an elevated risk for CVD death.[17-24] This 'obesity paradox' seems not only contrary to what common sense might suggest, but causes confusion when considering how to advise patients about weight management, especially when treatment itself (or non-treatment) may be associated with changes in weight.

The obesity paradox in patients with established cardiovascular disease

Obesity in childhood and in adulthood is associated with an increased risk of coronary heart disease in later life.[25] For example, in a long-term population-based study of men for whom body mass index (BMI) data were available at age 18 years or shortly thereafter, nearly half of those who were obese (≥ 30 kg/m^2) were subsequently diagnosed with type 2 diabetes, hypertension, myocardial infarction, stroke or venous thromboembolism, or died before reaching age 55 years.[26] In comparison to those with normal BMI (18.5 to < 25 kg/m^2), the incidence of diabetes among obese subjects was increased eightfold; venous thromboembolism fourfold; and event rate for hypertension, myocardial infarction and premature death was doubled.

Overweight and obesity are associated with early development and clustering of cardiovascular risk factors, including those characteristic of the metabolic syndrome (insulin resistance, high blood pressure, dyslipidaemia). However, the risk of myocardial infarction (MI) and ischaemic heart disease (IHD) is increased in obese people even in the absence of these comorbidities (Table 1).[27]

Table I: Risk of myocardial infarction according to combinations of body mass index category and the presence or absence of metabolic syndrome[27]

Body mass index	Metabolic syndrome	Hazard ratio (95% confidence interval)		
		Overall	Men	Women
Normal weight	No	1	1	1
Overweight	No	1.26 (1-1.61)	1.09 (0.81-1.48)	1.62 (1.09-2.40)
Obese	No	1.88 (1.34-2.63)	1.83 (1.19-2.82)	1.91 (1.12-3.27)
Normal weight	Yes	1.39 (0.96-2.02)	1.14 (0.67-1.92)	1.80 (1.06-3.06)
Overweight	Yes	1.70 (1.35-2.15)	1.45 (1.09-1.93)	2.26 (1.52-3.35)
Obese	Yes	2.33 (1.81-3)	2.03 (1.48-2.78)	2.79 (1.83-4.25)

Body mass index category: Normal 18.5-24.9 kg/m^2, overweight 25-29.9 kg/m^2 and obese ≥ 30 kg/m^2

On the other hand, a growing number of studies indicate that, in patients who have experienced an initial CV event, recurrent events and mortality are more common among those with lower body weight. The International Verapamil SR/Trandolapril (INVEST) study was a prospective, randomised international study of 22 576 patients with hypertension and coronary artery disease (CAD), with a mean follow-up of 2.7 years. In comparison to patients with normal weight (BMI 20 to < 25 kg/m^2), overweight patients (BMI 25-30 kg/m^2) and obese patients (BMI ≥ 30 kg/m^2), including those with class II or III obesity (BMI ≥ 35 kg/m^2), had a 20-30% lower risk of death, nonfatal myocardial infarction or non-fatal stroke.[14] Kennedy and colleagues reviewed data from 3 large studies of patients with prior acute myocardial infarction (AMI) or stable CAD, namely Optimal Trial in Myocardial Infarction with the Angiotensin II Antagonist Losartan (OPTIMAAL), Cooperative New Scandinavian Enalapril Survival Study (CONSENSUS II) and 4S, which included over 12 000 patients. Weight loss, but not weight gain was independently associated with increased risk of mortality.[15] In another study, among a cohort of 4 880 consecutive patients undergoing percutaneous coronary intervention for CAD, compared to normal weight individuals, five-year survival was significantly better among those with BMI ≥ 27.5 and < 30 kg/m^2.[28] A review of 40 cohort studies including a total of 250 152 patients with CAD and at least 6 months follow-up showed a U-shaped risk profile for body weight and cardiovascular mortality. Overweight patients (BMI 25-29.9 kg/m^2) had the lowest risk for both total mortality and cardiovascular mortality, which was 12% lower than in those with a normal BMI.[16]

Similar results have recently been demonstrated after acute stroke or transient ischaemic attack (TIA). Obese patients had a lower risk of mortality or stroke recurrence than those with normal weight, whereas underweight patients (BMI < 18.5 kg/m^2) had the highest risk for all endpoints.[10-12]

The obesity paradox in patients with diabetes

The obesity paradox has been observed in diabetic patients with and without cardiovascular comorbidity. In the World Health Organization's Multinational Study of Vascular Disease in Diabetes, diabetic patients were followed up over a 13-year period between 1975 and 1988. Among patients with noninsulin-dependent diabetes (NIDDM), body weight was positively associated with blood pressure, age and cholesterol and negatively associated with duration of diabetes, retinopathy and use of insulin.[17] Among patients with insulin-dependent diabetes (IDDM), body weight was positively associated with blood pressure and, in men, with cholesterol, whereas fasting blood glucose was higher in the most obese groups in women only.[18] Although in NIDDM there was no strong relationship between BMI and mortality (after adjusting for other risk factors), weight loss in subjects with BMI ≤ 29 kg/m^2 was associated with a 2-3-fold increase in mortality risk compared to those who maintained a steady weight. Only in the most obese subjects at baseline (BMI > 29 kg/m^2), was weight gain associated with an increase in mortality risk. In patients with IDDM, there was an inverse "J" relationship between body weight and mortality, with the highest mortality rates among the leanest individuals. After adjustment for confounders, including duration of diabetes, smoking, proteinuria, blood pressure and cholesterol, the mortality rates among patients assigned to four BMI categories ranging from 20 to > 26 kg/m^2 were similar.

In the second Diabetes Insulin-Glucose in Acute Myocardial Infarction (DIGAMI 2) study, initiation or maintenance of insulin therapy after myocardial infarction in patients with diabetes was associated with a significant increase in weight and incidence of reinfarction within 12 months. However, the increase in weight did not explain the increased rate of reinfarction. The patients with the least increase in body weight experienced the highest CV mortality, and each kilogram increase in weight reduced the risk of CV death by approximately 6%.[19] Adjustment for baseline

BMI, hyperlipidaemia, mean arterial pressure, smoking, diabetes duration and gender did not significantly alter the results.

In the Proactive Prospective Pioglitazone Clinical Trial In Macrovascular Events (PROactive trial) population of 5202 patients with type 2 diabetes and pre-existing cardiovascular comorbidity, over a mean follow-up duration of 35 months, the lowest mortality occurred in subjects with BMI 30-35 kg/m^2. The rate of both mortality and hospitalisations were higher among patients with BMI 22 to < 25 kg/m^2. Weight loss, but not weight gain, was associated with increased mortality, and weight gain was associated with a significantly lower risk of cardiovascular death.

In a pooled analysis of 5 longitudinal cohort studies, (including 27 125 person years follow up), normal weight (18.5-< 25 kg/m^2) at time of diabetes diagnosis was associated with a twofold risk of total mortality and 50% increase in the risk of cardiovascular mortality compared with subjects who were overweight or obese at diagnosis.[29]

Various additional large observational studies suggest that diabetes in leaner patients, and those with a lower BMI may be associated with a higher incidence of CV death than in overweight or obese individuals.[20-23] In the UK Prospective Diabetes Study (UKPDS), despite a significant increase in weight compared to conventional therapy, intensive glucose control with insulin was associated with fewer microvascular complications without an increase in cardiovascular mortality.[30]

However, there are observational studies that suggest that lower BMI and weight loss may be associated with more favourable cardiovascular outcomes.

Zoppini examined a cohort of 3398 patients with type 2 diabetes and found that while moderate excess weight predicted better survival in patients older than 65 years, in younger patients it was associated with higher all-cause mortality.[20] Two large observational studies including in excess of 24 000 patients with no previous CVD found that both overweight and obesity at or after the diagnosis of diabetes independently increase the risk of cardiovascular disease and mortality in type 2 diabetes.[31,32] Bodegard recently reported that, in a cohort of 8486 newly diagnosed patients with type 2 diabetes followed for up to 9 years, compared to unchanged BMI, BMI increase within the first 18 months of diagnosis was associated with 83% increased risk of CV mortality and 48% increase in all-cause mortality. However, BMI decrease during this time was not associated with reduced risk of these outcomes.[33] In contrast, in a 12-year, prospective observational study including 4970 overweight individuals with type 2 diabetes aged 40-64 years of age, intentional weight loss was associated with a 25% reduction in total mortality and a 28% reduction in cardiovascular and diabetes-related mortality.[34]

Interestingly, in another prospective observational study including 1401 type 2 diabetics over the age of 35 years, compared to patients who did not try to lose weight, the mere intention to lose weight was associated with reductions in mortality regardless of whether weight loss actually occurred. Individuals who reported trying to lose weight had a 23% lower mortality than those who did not and this was the same regardless of whether attempts at weight loss were successful.[35] These results suggest that lifestyle changes and behaviours associated with weight loss attempts may improve longevity irrespective of the degree of weight loss, or they may reflect that achieved weight loss is difficult to maintain, but nevertheless may be associated with improved long-term health.

The Look AHEAD Study

The Action for Health in Diabetes (Look AHEAD) study is the first large randomised, controlled clinical trial to investigate the benefits of intensive lifestyle intervention in patients with type 2 diabetes.[36] It included 5145 patients between the ages of 45 and 75 years of age (mean age 59 years), with a median duration of diabetes at baseline of five years. Fourteen per cent of patients had a previous history of CVD. The patients were randomised to two groups; intensive lifestyle intervention with the aim of achieving and maintaining weight loss of at least 7% through restriction of caloric intake and increased physical activity, or diabetes support and education. The primary outcome was a composite of death from cardiovascular causes, non-fatal myocardial infarction, non-atal stroke, or hospitalisation during a maximum follow-up of 13.5 years.

The study was stopped early after a median of 9.6 years when interim analyses demonstrated no difference in CV outcomes between groups and suggested that longer follow-up was not likely to change that observation.

Despite the absence of an apparent benefit with regard to CV mortality, in both the Look AHEAD study and in Bodegard's study, intentional weight loss was associated with early improvements in glycaemia, blood pressure, triglycerides, high density lipoprotein cholesterol (HDL-C) and other markers of cardiovascular risk, such as C-reactive protein (CRP).[33,36-38] In Look AHEAD, although the differences were modest, intensive lifestyle intervention was associated with a significantly greater likelihood of complete or partial remission of type 2 diabetes during the first four years of

intervention.[39] This effect was most marked in patients with substantial weight loss or fitness change, shorter duration of diabetes or lower HbA1c at baseline, and those not using insulin.

Is there an explanation for the obesity paradox?

A number of theories have been proposed to explain the obesity paradox and differing results of clinical studies.

Low body weight and weight loss may be indicative of poor health

In patients with diabetes, poor glucose control may be associated with both weight loss and an increased risk of diabetic-related complications.[33] Therefore, in studies where BMI was measured after the diagnosis of diabetes, the initiation of diabetes treatment or progression of the underlying illness may account for poorer prognosis associated with lower BMI.[32]

Low BMI, independent of diabetes, may increase the risk of adverse outcomes. Low body weight may increase mortality from other comorbid disease (e.g. heart failure, hypertension, chronic obstructive airways disease), cancer, or increase risks arising as a complication from osteopenia-related fractures.[29,40]

Conversely, it is possible that in some disease states, rather than being harmful, overweight and even obesity may be protective against adverse outcomes. If chronic illness is a metabolically demanding state, survival may be better in overweight subjects who have greater metabolic reserves.[41] This might help, at least partially, to explain apparent decline in overweight-related risk that is apparent with increasing age.[20] Similarly, patients recovering from a cardiovascular event may benefit from greater body mass, where a post event catabolic state, with fever, sympathetic activation, endothelial and insulin sensitivity dysfunction leads to muscle wasting and overall weight loss.[42]

Differential treatment

Overweight patients may be managed differently to patients with a lower body weight. They may receive more frequent follow-up and more aggressive investigations and treatments. For example, it is conceivable that cardiovascular medications, including antihypertensive drugs, aspirin and statins, are more likely to be prescribed for overweight individuals and those with cardiovascular risk factors such as hypertension or hypercholesterolaemia.[29,33,41] In contrast, fewer cardioprotective measures may be used in patients who lose weight if that weight loss leads to improvement in modifiable CV risk factors.[43]

BMI is a simplistic measurement

BMI does not account for the proportion and distribution of muscle, bone and adipose tissue. For example, while lower BMI may indicate a fit individual following a healthy diet, it may also be associated with illness and undernutrition. Conversely, BMI well into the overweight range may occur in fit individuals, such as athletes or bodybuilders.

Insulin resistance may be an important pathogenic component underlying cardiovascular disease. Therefore, unmeasured lean mass, fat mass, fat distribution and insulin sensitivity may significantly confound the comparison of outcomes among individuals with a similar BMI.[29] In addition to fat mass, a higher proportion of lean muscle mass is also associated with a higher BMI. Muscle is more insulin sensitive than adipose tissue and therefore is more metabolically favourable.[29]

People with a BMI within the normal range (18.5-24.9 kg/m^2), but high body fat content (normal weight obesity) have higher prevalence of cardiometabolic dysregulation, metabolic syndrome and cardiovascular risk factors than those with less body fat. Among women, normal weight obesity (body fat >3 3.3% vs. < 28.9%) more than doubled the risk of cardiovascular mortality.[44]

Furthermore, different fat compartments may contribute differently to CV risk. Although subcutaneous (peripheral) fat is not metabolically neutral, intra-abdominal (visceral) fat correlates to a greater extent with metabolic abnormalities observed in overweight and obese subjects, is associated with more severe insulin resistance and may be more proatherogenic.[45,46] Indeed, cardiometabolic risk increases with increasing visceral adiposity and BMI, whereas increasing subcutaneous fat is not associated with uniform increases in metabolic CV risk factors. Furthermore, some studies have suggested that subcutaneous fat, at least in patients with a high amount of visceral fat tissue, may be metabolically beneficial, providing some protection against increased CV risk.[47]

The relative proportions of abdominal and subcutaneous fat may vary from person to person. Even among lean individuals, those with accumulation of intra-abdominal fat are more insulin resistant and at higher risk of developing the metabolic syndrome and cardiovascular risk factors than those with subcutaneous fat deposition.[48]

Body fat distribution may also differ among ethnic groups. For example, despite lower prevalence rates of generalised obesity, Asian Indians are a high risk group for type 2 diabetes, metabolic syndrome and coronary artery disease.[49] This has been partly explained by

a tendency towards an "Asian Indian phenotype", which describes central body obesity with primarily increased visceral fat, higher plasma insulin levels, insulin resistance and lower adiponectin levels.[49] This data from studies in Asian Indians suggests that body fat distribution, particularly visceral adiposity, is the principle anthropometric determinant of disease risk, rather than measures of whole body fat, i.e. BMI.

In patients with diabetes, weight accumulation related to intensive glucose control is not limited to the abdomen, but rather is generalised, being distributed between fat mass and lean mass. Furthermore, the increase in fat mass is predominantly peripheral rather than central, so it may not necessarily result in an overall increase in cardiovascular risk.[50,51]

Reverse causation bias, trial design and different definitions

Reverse causation usually refers to the situation in which, instead of the outcome resulting from the risk factor, the outcome precedes the risk factor. For example, does obesity cause insulin resistance, or does insulin resistance cause obesity? However, in terms of weight and mortality, the term is often used to imply that the illness (diabetes) affects both the risk factor (body weight) and the outcome (mortality).[40] In studies where BMI is measured and followed after the presence of diabetes, it may not be clear whether the weight is contributory to mortality, or coincidentally a symptom of the illness causing mortality. For the same reason, studies that measure BMI and follow patients from diagnosis are not comparable to studies that enrol patients with pre-existing diabetes and may produce different results.

Furthermore, it is important to distinguish between otherwise healthy patients with a naturally low BMI and patients with a low BMI consequent to weight loss (who may have been overweight for most of their life), including those with weight loss due to illness. In the same way, a higher BMI from natural weight gain may differ in outcomes from drug-related or disease-related weight gain, e.g. in heart failure, all of which may differ in outcome from long-standing obesity. Therefore, detailed information about life-long health status, CVD risk factors and prior weight changes at study baseline is required to fully adjust for such confounding factors.

This explanation might also help to explain the different observations according to age where the obesity paradox appears to apply to older individuals, but is not apparent in younger populations.[20,32] Strandberg et al followed up a population of men into old age for whom BMI and CVD risk data were available from the age of 25 years.[52] They showed that, before midlife, mortality was higher among overweight compared to normal weight individuals. Thereafter, individuals who moved from overweight in midlife to normal weight had the highest CVD risk in midlife and the greatest total mortality, even after adjusting for diseases prevalent at midlife. In comparison, mortality risk in older age was no different among men with a constantly normal weight from midlife to old age, those who were constantly overweight and those who became overweight after midlife. They concluded that a population of people at old age, whether normal or overweight, is actually a mixture of individuals, each with a different weight and cardiovascular history: "Despite being a mortality risk factor in midlife, overweight or even obesity in late life may thus disguise itself as a protective factor in late life."

Statistics – index event bias

Obesity paradox studies, and especially those including patients who have already experienced an initial cardiovascular event, have a recurrence risk design. In other words they are selecting for a group of patients who have a very high risk of a repeat of the same or a similar outcome. Consequently, the influence of an individual risk factor is proportionately reduced, because the overall risk, i.e. the sum of the risk factors as a whole, plays a more dominant role. As a result, the association between an individual risk factor and recurrence of the event will be biased towards the null (no apparent effect) or even reversed (paradoxical protective effect).[32,42,53]

Therefore, statistically, it may appear that obesity is less important to cardiovascular outcomes, even though it remains in reality a significant modifiable risk factor. Smits et al recently published a simple numerical example of index event bias, which eloquently demonstrates its influence on the statistical outcome.[53]

Does the obesity paradox influence the approach to management of patients with diabetes?

Regardless of the obesity paradox, in addition to consideration of cardiovascular risk, there is considerable evidence that, in patients with diabetes, weight loss and maintenance of a healthy weight are associated with improvements in glycaemic control and quality of life. Excess adiposity and weight gain in type 2 diabetes are associated with a number of physical and psychological consequences that affect adherence, response to therapy and long-term glucose control. Increased fat mass is associated with insulin resistance, which exacerbates beta-cell dysfunction and increases requirement for insulin and further weight gain.[54] Higher BMI at initiation of treatment predicts a poorer response to insulin therapy.[55,56] This may severely compromise the long-term outcome, where sustained

improvements in glycaemia have been shown to significantly improve microvascular complications, and the long-term risk of cardiovascular events.[30,57,58]

Weight gain may compound feelings of depression and anxiety, which are already common in patients with diabetes and which are associated with poor adherence and self-care.[59] In the Diabetes Attitudes Wishes and Needs (DAWN) study, which surveyed the perceptions surrounding diabetes care and self-management among more than 5000 type 2 diabetics, 50% of patients expressed anxiety about their body weight, which contributed to a common poor sense of well-being.[60] The fear of weight gain discourages both initiation of and adherence to insulin therapy. Patients who are concerned about weight gain are more likely to omit insulin doses or adjust their insulin dose in order to aim for higher blood glucose targets and to avoid normoglycaemia in an attempt to manage their body weight. This behaviour is associated with a significant increase in risk of diabetes-related emergency room visits and hospitalisations, and higher rates of retinopathy and neuropathy.[61]

In contrast, weight loss increases the chance of remission of type 2 diabetes and reduces medication requirements. The fact that this is more likely to occur in newly diagnosed diabetics and those with better glycaemic control highlights the importance of early consideration of lifestyle interventions.[62] Reducing medications may reduce costs and drug-related adverse effects, including hypoglycaemia.[33,39,43]

In the Look AHEAD study, weight loss was safe and associated with a number of additional benefits, including reductions in sleep apnoea, urinary incontinence and depression, and improvements in physical functioning, mobility and quality of life.[36]

Conclusion

The obesity paradox is a controversial finding that has been observed, not only in patients with diabetes, but also associated with other chronic diseases. However, the mechanisms that might underlie the observation are not always clear and range from the pathology itself, to treatment modalities, study design and even statistical interpretation of the data.

In contrast, potential benefits of weight loss in overweight patients with established cardiovascular disease and/or diabetes clearly extend beyond estimation of cardiovascular risk, significantly influencing treatment choices and outcomes and the patient's quality of life. Therefore, lifestyle advice, including prudent dietary choices, exercise, weight loss and maintenance of a healthy body weight should remain the cornerstone of management for these patients.

References available on request