Type 2 diabetes, mortality and the obesity paradox: the weight management dilemma

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Is there a survival advantage in obese patients with diabetes? The so-called ‘obesity paradox’, with reported lower risk of mortality mostly for body mass index (BMI) category of 25–30 kg/m², is neither entirely explained nor widely accepted. This apparent reverse epidemiology has also been reported in various retrospective longitudinal studies for other chronic disease such as heart failure, stroke and end-stage renal disease, as well as certain groups such as the very elderly. Table 1 gives a summary of important studies that describe the obesity paradox phenomenon in type 2 diabetes cohorts.

The latest publication in the New England Journal of Medicine may armour the opponents of this paradox theory, but is probably unlikely to result in silent retreat of its protagonists nor terminal end to the polarised views of the subject. Tobias et al. from Harvard analysed two large epidemiological cohorts – one that followed 24577 health professionals for 26 years and another of 8970 nurses for 36 years, both groups with incident diabetes and free of cardiovascular or cancer diagnoses at start. Using multivariate analysis they estimated the hazard ratios for mortality across BMI categories in over 3000 deaths, and including better control for smoking status influence. Despite variable linearity dependent on age categorisation below and above 65 years and smoking status, there was no evidence of reduced mortality for overweight or obese subjects compared to normal-weight subjects (weight used in the analysis was the one recorded at the time of diabetes diagnosis). On the contrary, there were more deaths in the overweight and obese subgroups, particularly below the age of 65. That is to say, there was no evidence of an obesity paradox in diabetes, and by extrapolation casting doubt on the ‘fat but fit’ and ‘healthy obesity’ notions.

Can we rationalise this obesity paradox?

We understand from epidemiological findings that association between variables does not necessarily imply causality. On occasions this ‘protective’ influence of mild obesity has been explained away through deeper analysis of potential residual confounding, unadjusted or unaccounted for, variables such as verifying smoking status, other significant or subclinical illness, the level of fitness, existence of depression, degree of alcohol consumption, or weight loss decades after diagnosis of diabetes. Additionally, the so-called collider stratification bias that results from conditioning on a variable (in this case BMI) affected by exposure (say, smoking) has been shown to distort associations and thus to produce spurious protective links. To minimise the confounding detrimental effect of chronic disease and smoking on weight (the reverse causality effect), some studies used BMI measurements at diagnosis of diabetes or within one year of it, rather than decades after diagnosis, and also through excluding deaths within two years of last BMI determination. Another explanation is that BMI represents a rough tool for assessing obesity or its consequences, as it does not discriminate between fat

<table>
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<th>Study</th>
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<tr>
<td>Carnethon MR, et al.¹</td>
<td>2625 participants. 449 deaths (178 from cardiovascular disease [CVD])</td>
<td>27 125 person-years of follow up</td>
<td>Mortality hazard ratios (HR) of normal-weight to overweight/obese participants: 2.08 (95% CI 1.52–2.85). Mostly non-CVD related</td>
<td>Pooled analysis of 5 longitudinal cohort studies, spanning 1979–2011 with variable periods. Excluded cases of &lt;2 years of diabetes duration. Smoking status considered</td>
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<td>McEwen LN, et al.⁸</td>
<td>8733 participants. 791 deaths (42% CVD)</td>
<td>Mean follow up: 3.7 years</td>
<td>BMI (kg/m²) &lt;26 vs BMI of 26–30. HR: 1.43 (95% CI 1.13–1.69).</td>
<td>Diagnosed with diabetes for at least 18 months at enrolment</td>
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<td>Doehner W, et al.⁹</td>
<td>5202 patients (with evidence of CVD at baseline)</td>
<td>34.5 months</td>
<td>BMI 30–35 at baseline vs BMI 22–25. HR: 1.88 (95% CI 1.11–3.21). Weight loss was associated with increased total mortality (HR per 1% body weight: 1.13 [95% CI 1.11–1.16]).</td>
<td>Intervventional with pioglitazone. The lowest mortality was seen in patients with BMI 30–35 at baseline</td>
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<td>Logue J, et al.¹⁰</td>
<td>106 640 patients. 9631 deaths</td>
<td>4.7 years</td>
<td>Mortality risk was higher in patients with BMI 20–24.9 vs BMI 25–30. HR: 1.22 (95% CI 1.13–1.32) in men; 1.32 (95% CI 1.22–1.44) in women</td>
<td>Excluded deaths within 2 years of BMI recording. BMI recorded within 1 year of diagnosis</td>
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Table 1. Studies which included type 2 diabetes populations that bolster the obesity paradox phenomenon. Retrospective observational analyses, with data collected prospectively.
and lean mass composition nor does BMI indicate the fat distribution – the metabolically active visceral fat and the relatively inert subcutaneous adiposity. Moreover, it has been suggested that normal-weight adults with type 2 diabetes could have a more severe type of diabetes representing metabolically obese but normal-weight phenotype (‘thin outside, fat inside’). A further explanation put forth is that of treatment bias with aggressive and intensive pharmacological therapy utilisation to modify cardiovascular risks in obese patients, more than one would necessarily use in slimmer individuals.

Should the presence or otherwise of the obesity paradox change weight management advice?

Intuitively and based on current evidence, the answer should be no change in advice when it comes to dealing with the higher degrees of obesity (BMI >30kg/m²). The obesity paradox does not consistently apply to such a group of patients and there is reassuring evidence at least for morbidity benefit from intentional weight loss, including for bariatric surgery in excess obesity cases. For example, in the Swedish Obese Subjects study, a 10-year follow up of individuals undergoing bariatric surgery, 36% of subjects with diabetes had resolution of diabetes compared with 13% of matched control subjects.

What about the mildly obese subjects? There is some evidence that intentionally losing weight is beneficial in type 2 diabetes, which is derived mainly from observational studies. An example of such studies is the Cancer Prevention study, a 12-year follow up of nearly 5000 patients with diabetes, that examined the effect of weight loss on mortality. Weight loss was associated with a 25% reduction in total mortality with intentional modest weight loss of 10–13kg being associated with the greatest reductions in mortality (33%), although profound weight loss in excess of 30kg was associated with small increases in mortality. In the National Health Interview Survey, 1400 overweight subjects with diabetes were sampled, and individuals who indicated that they were trying to lose weight had a 23% lower mortality rate than those who reported not trying to lose weight, regardless of any weight changes. This benefit was only seen in the 25–30kg/m² BMI range. Actual weight loss was associated with increased mortality only if the weight loss was unintentional – the latter being recognised to be often linked with poor health. So, even if weight loss is not achieved, eating less may have long-term beneficial effects, thus supporting lifestyle adaptations as being an important determinant of health status.

On the other hand, the impact of weight loss with diet and physical exercise in diabetic patients on mortality was questioned after the publication of the results of the Look AHEAD trial. This evaluated the effects of intensive lifestyle intervention and weight loss on cardiovascular (CV) morbidity and mortality in obese type 2 diabetic patients. The study was terminated early after a median 9.5-year follow up because the incidence of CV events was not different between the intervention and control groups. Nevertheless, despite the neutral effect on mortality, intensive treatment was associated with significantly positive changes in quality of life, glycaemic control and reduction in insulin use. This benefit of lifestyle changes in reducing features of the metabolic syndrome – inflammatory markers, lipids, prevalence of hypertension, and improved glucose tolerance – was also demonstrated in other studies.

Although treating obesity is associated with improvements in related comorbidities, the long-term success of obesity treatment is beset with challenges, with evidence pointing towards biological and behavioural adaptations following weight loss, such as energy expenditure reduction and increased drive to eat, that lead to weight regain. Some studies indicate that <10% of obese subjects are successful at maintaining weight loss for 5 years and this percentage could be even less for unreported studies. If weight loss advice is not the clear answer in overweight or mildly obese patients (BMI 25–30kg/m²), then an alternative approach which promotes weight stabilisation and preservation of muscle mass as a goal might be needed. A stable weight has been associated with reduced CV risk and less mortality in observational studies, compared to weight fluctuation in both weight increase and weight loss. Moreover, changes in dietary composition might be more important in addressing CV risk factors than weight loss per se. For example, altering the composition of diet (protein: carbohydrate:fat ratios) without altering the amount of food has been shown to positively influence glycaemic control in type 2 diabetes patients, even without weight loss.

Finally, it is crucial to reaffirm that obesity, not least in excess, remains detrimental to health and is not infrequently physically and psychosocially restrictive even if it does not lead to death. It seems obvious that prevention of obesity and weight gain makes more sense than trying to treat it. In reality and on an individual level it is a complex issue that cannot be over-simplified nor stratified into convenient statistical sets. Intuitively the maintenance of a healthy body weight as a cornerstone in diabetes management is desirable, although practically it is testing to attain longstanding weight reduction. An undisputed evidence for mortality risk minimisation as an endpoint from weight loss is presently not uniformly nor conclusively established.

The emerging pragmatic parallax means that, while striving for weight loss, we should not simply cast all individuals into a prevalent ‘ideal’ weight or ‘normal’ BMI range in isolation of other health parameters, lifestyle adaptations and without regard to initial BMI. This emanates from our realisation of the sparse tools we have to support a long-term weight loss strategy and the existence of uncomfortable, albeit diminishing residual, uncertainty of its terminal merits.

Nevertheless, when it comes to obesity, one could not be censured for discordance with Nietzsche and declaring that ‘What does not kill you does not make you stronger!’

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Declaration of interests
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References
References are available in Practical Diabetes online at www.practicaldiabetes.com.
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