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The Obesity Paradox in Diabetes

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Abstract Overweight or obese adults have demonstrated a survival advantage compared with leaner adults in several population-based samples. This counterintuitive association has been termed the obesity paradox. Evidence for an obesity paradox among persons with diabetes has been less consistent. In the present review, we identified 18 longitudinal studies conducted in cohort studies, patient registries and clinical trial populations that tested the associations between obesity and survival in patients with diabetes. The majority of these studies reported that mortality was lowest in overweight and obese persons, and that leaner adults had the highest relative total and cardiovascular mortality. Some of these studies observed the patterns most strongly in older (age > 65 years) adults. To date, little research has been conducted to identify mechanisms that could explain elevated mortality in leaner adults with diabetes, or to identify strategies for diabetes management or mitigation of elevated mortality risk.

Keywords Obesity · Mortality · Survival · Obesity paradox · Diabetes

Introduction

The "obesity paradox" refers to the observation that leaner adults have higher mortality than overweight (BMI=25–29.9 kg/m^2) and moderately obese (BMI=30-34.9 kg/m^2) adults, despite the positive correlation between body mass index (BMI) and many chronic conditions. A recent systematic review and meta-analysis of 141 studies describes the consistency of the obesity paradox in relation to all-cause mortality across multiple population-based cohort studies [1••]. Participants in these studies represented a range of ages, both genders, and multiple race and ethnic groups. With few exceptions, the lowest mortality was observed in overweight (RR=0.94, 95 % CI: 0.91-0.96) and modestly obese (RR=0.95, 95 % CI: 0.88-1.01; participants as compared with normal weight adults (BMI <25 kg/m^2). While the studies included in the review were not restricted to healthy adults, separate estimates were not presented for adults with existing chronic diseases.

Prior research suggests that the obesity paradox is also present in the setting of cardiovascular diseases [2] including heart failure [3, 4] and chronic kidney disease [5]. Chronic kidney disease and heart failure, in particular, require intensive medical management and lifestyle changes. Weight loss is common as these diseases progress, providing a plausible mechanism for the observed obesity paradox. Other mechanisms have been proposed to explain a possible obesity paradox in other chronic cardiovascular diseases such as hypertension and diabetes. Insulin resistance and obesity are at the core of the metabolic syndrome and thus closely correlated with hypertension and diabetes [6]. One hypothesis is that hypertension occurring independent of obesity may represent a different and possibly more severe disease process that could predispose to mortality. By the same rationale, persons with type 2 diabetes, but who are not obese, may also experience elevated mortality. Relatively fewer studies have evaluated whether there is an obesity paradox specifically in the setting of type 2 diabetes.

Over 85 % of persons with type 2 diabetes are overweight or obese [7, 8], and obesity is closely tied to the etiology of

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type 2 diabetes. Consequently, the question of whether there is an obesity paradox in type 2 diabetes has historically been relevant only to a small (15 %) percentage of the population. There are some population groups that are more prone to normal weight diabetes, especially older adults and racial ethnic minorities. Shifting population demographics including the aging of the population and the diversification of the population by race and ethnicity make the obesity paradox in diabetes question relevant to a growing segment of society. Further, addressing the question provides insights into genetic, behavioral and phenotypic mechanisms that contribute to health outcomes independent of overall obesity and that could be used as targets for intervention. Given attention paid to the topic by a number of recent studies, the objective of the present review is to describe the current literature on the characteristics of persons with type 2 diabetes in the absence of overweight or obesity, report findings on the obesity paradox with mortality in type 2 diabetes, discuss the biological plausibility of those findings and highlight future directions for research including the management of this unique population subgroup.

Who Develops Diabetes in the Absence of Obesity?

In 1981 Ruderman [9] published the following observation: "Individuals exist who are not obese on the basis of height and weight but who, like people with overt obesity, are hyperinsulinemic, insulin resistant and predisposed to type 2 diabetes, hypertriglyceridemia, and premature coronary heart disease." He labeled these individuals as "metabolically obese normal weight" and created a scoring algorithm for defining the phenotype that included a combination of cardiometabolic disorders in the absence of obesity. Diabetes and insulin resistance carried the greatest weight in the scoring algorithm because insulin resistance was thought to be at the core of the phenotype and to predispose to the other cardiometabolic disorders. Subsequent papers have investigated correlates of the metabolically obese normal weight phenotype [10, 11], but few have focused specifically on normal weight diabetes because of the relatively small number of persons in any one study who experience this combination. Future studies should investigate correlates of normal weight diabetes because those characteristics may provide insights into mechanisms that could influence mortality in this subgroup.

Is there an Obesity Paradox in Relation to Mortality?

We identified 18 longitudinal studies published between 1991 and 2013 that tested the contribution of weight status on mortality in adults with diabetes (Table 1). Our criteria for selecting studies were as follows: 1) all participants had diabetes determined by self-report, measurement or clinical diagnosis; 2) anthropometric measures of BMI were available at baseline; and, 3) participants were followed longitudinally for mortality. Some studies measured diabetes and BMI by self-report whereas in others, measurements were collected using research or clinical protocols. In most studies the relationship of weight status with mortality was assumed to be non-linear and so weight status was categorized. Many, but not all, studies chose categories corresponding with the recommended WHO categories of underweight (BMI<18.5), normal weight (BMI 25–29.9), class 1 (BMI 30–34.9) and class 2 obesity (BMI >35). At least two studies (Tseng et al. [12••] and Yano et al. [13]) were conducted exclusively in Asian adults where the recommended BMI cutpoint for overweight is>23 kg/m^2 [14]. We chose to discuss findings based on the most comprehensively adjusted multivariable models.

Inverse Association of Weight Status with Mortality

In one of the largest studies to date, Tseng and colleagues [12••] reported higher mortality from all causes, cancer and diabetes complications in Taiwanese diabetes patients whose BMI was <18.5 as compared with those whose BMI was 18.5-22.9. McEwen et al. [15] reported elevated total and cardiovascular mortality in normal weight vs. overweight diabetes patients selected from a network of managed care organizations in the US as part of the TRIAD study. In a post hoc analysis of patients in the placebo arm of the PROActive clinical trial of diabetes patients, Doehner et al. [16] reported higher all-cause mortality in adults in whose BMI was <22 or 22 to <25 as compared with those who were obese. Patterns were similar in the entire sample, but the positive hazard ratios among those in the lowest BMI group did not achieve statistical significance, likely due to small sample size in this group. In the REACH registry of diabetic patients with existing atherosclerosis, participants in the lowest BMI category (BMI <24.3) had significantly higher all-cause and cardiovascular mortality than patients whose BMI fell in the second quartile (BMI 24.3-26.9) [17]. Our research team [18••] assembled a cohort of 2625 men and women with newly-identified diabetes from across five longitudinal cohort studies, and reported a doubling in all-cause mortality in normal weight as compared with overweight or obese participants. While our findings were consistent in older (age>65 years) and younger adults, by gender, in non-white vs. white race groups and in smokers compared with non-smokers, other studies reported differences by these sociodemographic characteristics.

Sluick et al. [19] reported a significant interaction between gender and quintiles of BMI in relation to diabetes in the European Prospective Investigation into Cancer and Nutrition whereby the hazard ratios for mortality were significantly inversely associated with increasing BMI quintiles among

Table 1 Characteristics of studies investigating the association of weight status with mortality

Author	Sample description	Follow-up time	Outcomes (N events)
Inverse association			
Carnethon [18••]	2625 cohort participants with newly identified diabetes	27,125 P-Y	Total mortality (n= 449), CV mortality (n=178), Non-CV (n=253)
Dallongeville [17]	19,579 participants of the REACH registry of high risk diabetic patients	2 years of F-U	Total mortality (n= Not reported), CV mortality (n= Not reported)*
Doehner [16]	5202 patients from the PROActive clinical trial who had CVD at baseline	Max 34.5 months	Total mortality (n= 347)
Kokkinos [20]	4156 men from VA medical centers	33,112 P-Y	Total mortality (n=1,074)
McEwen [15]	8733 participants from the TRIAD study (a multicenter observational study of diabetes in managed care)	Mean f-u 3.7 Y	Total mortality (n=79), CV mortality (n=336), and non-CV mortality (n=455)
Sluik [19]	5435 participants in the European Prospective Investigation into Cancer and Nutrition with self-reported type 2 diabetes	Median f-u 9.3 Y	Total mortality (n=641)
Tseng [12••]	89,056 Taiwanese patients	598,747.75 P-Y	Total mortality (n=26,951), Cancer mortality, (n=4786)
Weiss [22]	122 hospitalized elderly Israeli patients with diabetes	Mean f-u of 3.7 years	Total mortality (n=69), CV mortality (n=31)
Zoppini [21]	3398 patients in Verona, Italy	Mean f-u 10 Y	Total mortality (n=1212), CV mortality (n=485), Cancer mortality (n= 298)
Direct association			
Cho [24]	5897 women from Nurse's Heath Study cohort (1310 with prevalent diabetes and 4587 with incident diabetes)	57,909 P-Y	Fatal and non-fatal CHD (n=418)
Eeg-Olofsson [23]	13,087 Swedish diabetes patients with no previous CHD or stroke	64,864 P-Y	Total mortality (n= 664)
U-shaped association			
Ross [25]	373 community dwelling adults	Max of 14 Y	Total mortality (n=124), CHD mortality=(62)
Yano [13]	507 Japanese medical school cohort participants with diabetes	Mean f-u 10.2 Y	Total mortality (n=65)
No association			
Church [27]	2196 men with prevalent diabetes in the Aerobics Center Longitudinal Study	32,161 P-Y	Total mortality (n=275)
Ford [26]	603 adults with diabetes in the National Health and Examination Epidemiologic Follow-Up Study	Mean 10 Y	Total mortality (n=233) and CHD mortality (n=92)
Landman [34]	1353 patients from the ZODIAC trial	9.8 F-U years	Cancer mortality (n=122)
McAuley [28]	831 male VA patients	Mean F-U 4.8 years	Total mortality (n=112)
Mulnier [35]	28,725 patients with diabetes from the UK General Practice Register	Mean F-U 7 years	Total Mortality (n=11,165)

F-U=Follow-up years; P-Y=Person-Years

*The authors did not report the number of events in the published manuscript

men, but there was no association between BMI and mortality among women. Although there were no women in the study, Kokkinos et al. [20] also reported that men with diabetes from VA medical centers who were normal weight had higher all-cause mortality than men who had class II obesity.

Zoppini et al. [21] observed that older Italians (age> 65 years) in a diabetes patient registry were likely to demonstrate the obesity paradox whereas younger adults were not. Italians aged<65 years in the uppermost BMI quintile experienced significantly higher mortality than participants in the lowest quartile. By contrast, patients aged>65 years in the uppermost BMI quartile experienced significantly lower mortality relative to participants in the lowest quartile. They reported a borderline inverse pattern in relation to cardiovascular mortality in adults aged ≥65, but no association in younger patients. Among adults with diabetes, there were no significant associations in relation to cancer mortality. Weiss and colleagues [22] conducted a study exclusively in Israeli adults aged >75 years who were hospitalized with diabetes and participants in the uppermost BMI quartile had significantly lower all-cause and cardiovascular mortality as compared with participants in the lowest quartile.

Direct Association of Weight Status with Mortality

Two studies reported a direct relationship between BMI and morality in patients with diabetes. Eeg-Olofsson et al. [23] reported higher relative all-cause, CHD and CVD (combination

of CHD and stroke) mortality in Swedish diabetes patients who were obese as compared with those who are normal weight. Overweight was associated with a non-significant trend toward higher mortality. In the Nurse's Health Study, Cho et al. [24] reported a positive association between BMI and mortality in 1310 women with prevalent diabetes and 4587 with incident diabetes.

U-shaped Association

Among community dwelling men and women who had diabetes in the US, Ross et al. [25] identified higher mortality among men and women with the lowest and the highest BMIs, relative to rates from participants in the middle (BMI 22.7-27.9 in men and BMI 21.2-27.3 in women). When Yano and colleagues [13] examined Japanese who did not have diabetes and whose BMI ranged from 211–25.0, there was a significant U-shaped association in participants aged<65 years as evidenced by higher hazards in the leaner BMI group and the higher BMI group compared with the middle range. Among participants aged ≥65 years, mortality was only significantly elevated in the leanest participants, with a trend toward an elevation among those with the highest BMI.

No Association of Obesity with Mortality

In one of the earliest studies carried out in 1991, Ford et al. [26] reported no association of obesity with total mortality in 602 participants with diabetes in the NHANES epidemiologic follow up study; however, they did observe a direct association between weight status and CHD mortality. While Church et al. [27] identified a positive association between BMI categories and mortality among men with diabetes in the Aerobics Center Longitudinal study in unadjusted models, those effects attenuated to non-significance once cardiorespiratory fitness was taken into account. The authors concluded that the adverse effect of BMI on mortality in persons with diabetes was attributed to poor fitness. Few other studies have included this physiologic measure in order to quantify its role as a confounder. However, even with adjustments for a limited set of clinical factors, Landman et al. reported no association of weight status with cancer mortality in patients from the ZODIAC trial of outpatient diabetes care conducted in the Netherlands [17]. Similarly, McAuley et al. [28] reported no difference in total mortality with increasing BMI (per unit) in men with diabetes from a VA population.

Limitations of Existing Research

The majority (13 of 18) studies we identified reported an inverse association between obesity and mortality in persons with diabetes, providing evidence of an obesity paradox. Conflicting findings may have been due to a number of factors. The majority of studies were unable to determine whether participants had type 2 diabetes or one of the less common forms of diabetes in adults (e.g., type 1, latent autoimmune diabetes in adults). However, because the studies were conducted in adults where over 95 % of diabetes can be assumed to be type 2, the findings should apply to persons with type 2 diabetes. Some studies relied on self-reported BMI and/or diabetes whereas others included standardized measurements. Despite the potential for misclassification, we did not observe differential findings based on how the exposures were captured. BMI is a crude estimate of overall adiposity and does not take into account body fat distribution or composition. Despite the known association of waist circumference with direct measures of visceral and subcutaneous fat, ours was the only study that presented estimates for the relationship of waist circumference with mortality in persons with diabetes [18••]. We reported in a sensitivity analysis that mortality was positively associated with waist circumference (HR=1.14, 95 % CI: 1.02-1.28 per SD higher). The "obesity paradox" was not present as determined by central adiposity. One challenge of using estimates of central adiposity is that there are a number of different protocols for measuring waist circumference and any observed magnitude of association could vary based on measurement error. Further, waist circumference is not a standard clinical measure, due in some degree because of the difficulty standardizing the measurement, and so the utility of the findings for clinical practice if waist circumference is used is limited. All but two of the studies (Carnethon [18••] and Cho [24]), used prevalent diabetes to determine disease status. Prevalent diabetes presents a challenge for a number of reasons. One, some patients successfully lose weight following a diagnosis of diabetes and so these patients are not actually "normal weight diabetics" and their mortality experience may reflect a combination of their previous and current weight. Two, duration of diabetes can be difficult to accurately determine. Patients with longstanding diabetes may experience weight loss as a result of pharmacotherapy or behavioral therapy (i.e., diet and physical activity changes) or comorbidities, again obscuring the true association of normal weight diabetes with mortality. Additional research is needed in incident diabetes cohorts to overcome these limitations and to provide more evidence given the conflicting findings between our research team [18••] and Cho et al. [24].

Biological Plausibility of an Obesity Paradox

Although prior studies that reported a finding of an obesity paradox in persons with diabetes hypothesized mechanisms to explain elevated mortality, empirical data are needed to test these hypotheses. One piece of evidence for differences between lean and obese persons with diabetes comes from a large GWAS in those of European ancestry examining common genetic variants in lean (BMI<25 kg/m^2) T2D cases vs.

obese (BMI≥30 kg/m^2) T2D cases [29••]. This study identified two novel SNPs associated with T2D in the subset of lean cases; and also demonstrated that 29 of 36 SNPs previously identified in T2D GWAS appeared more strongly associated with T2D in the lean subset as compared to the obese [29••]. For these genetic differences to plausibly account for the elevated mortality in this subgroup, those genetic variants must also be associated with other harmful traits or a more malignant or treatment-resistant form of the disease. Future studies should investigate this possibility.

Two other commonly cited alternative explanations for the obesity paradox in diabetes are: 1) the presence of undetected comorbid illness; and 2) sarcopenic obesity. Weight loss due to pre-existing illness has been hypothesized as an explanation of the obesity paradox in healthy populations and in populations with pre-existing illness [30••]. In the setting of diabetes, the argument for reverse causality is made by assuming that illnesses that often co-occur with diabetes such as chronic kidney disease and heart failure are associated with muscle wasting and consequent lower body weight. Additionally, correlates such as hypertension, cerebrovascular disease and cardiovascular disease can independently hasten mortality. Ideally, these comorbidities would be measured and the association of weight status with mortality should be studied in the absence of these conditions (i.e., tests for statistical interaction). However, not all studies include a comprehensive set of confounders or they may only have them available at a single point in time and not updated throughout follow up. One alternative is to exclude participants who died early during the follow-up period because they may have already been ill at the time of their BMI measurement. A methodologic paper by Flegal et al. [30••] examined the issue of reverse causality and concluded that the influence of the potential bias was minimal based on her team's observation that there were few appreciable differences after either adjustment or exclusion for deaths that occurred early in the follow up period. Similarly, findings from the reports in the present review did not change when these strategies were applied.

A related issue is the change in body composition that accompanies aging. With aging, muscle and bone mass decline while overall fat mass and fatty infiltration of muscles becomes more common. The result is a net loss in weight and lower BMI, but a less metabolically favorable body composition and body fat distribution. Dual x-ray absorptiometry scans describe higher fat mass and less muscle mass with greater deposits of fat in the central region in older adults (a shift to "android" obesity). Within the central region, highly metabolically active visceral adipose tissue is more common than more benign subcutaneous fat. These changes, referred to as sarcopenic obesity, are a key component underlying frailty—a condition that predisposes older adults to higher mortality [31]. As a result, the prevalence of normal weight diabetes is higher in older adults [10, 11, 18••, 32]. Lending support for this hypothesis, two studies reported that the obesity paradox was observed in older, but not younger, adults [13, 21]. Future studies that include imaging for body composition and body fat distribution can determine the contribution of these factors to the "obesity paradox."

In summary, it seems implausible that elevated mortality in adults with diabetes is due solely to preexisting illness and aging-related sarcopenic obesity, given the consistency of findings across study populations with a range of ages and varying health status. Additional research should explore plausible mechanisms that both contribute to the onset of normal weight diabetes, and that independently convey an elevated mortality risk.

Management Strategies for Normal Weight Diabetes

Although normal weight diabetes remains relatively uncommon, research suggests that the demographic groups most likely to experience normal weight diabetes (i.e., older adults, non-white race/ethnic minorities) are growing as a proportion of the total population. In response, management strategies are warranted that may differ from recommendations targeted to overweight or obese persons with diabetes. The most obvious difference is for recommendations for weight loss through a combination of dietary modification and physical activity. While the behaviors themselves may result in positive changes in glycemic control, the goal in the normal weight patient may not be weight loss. Evidence from the Aerobics Center Longitudinal Study suggests that cardiorespiratory fitness is an even stronger determinant of mortality than weight status when the two are included in the same multivariable model [27]. Thus, improving cardiorespiratory fitness through aerobic activities may be a recommended therapy for normal weight persons with diabetes with the added recommendation to maintain, rather than lose, weight by increasing calorie consumption accordingly. Recent findings from a randomized trial conducted by Church et al. [33••] indicate that a combination of aerobic training and resistance training was superior to placebo for reducing HbA1c in persons with diabetes. There was no significant change in participants who were randomized to aerobic exercise alone or resistance training alone. Participants in that trial were, on average, obese at baseline. Research is needed to determine whether a similar strategy would be effective in adults who are normal weight, and whether lowered hemoglobin A1c translates into lowered mortality in these adults.

Conclusion

The preponderance of the evidence from longitudinal observational studies suggests the presence of an obesity paradox in

adults who have diabetes. These findings are consistent across different research settings from cohort studies to patient registries and persist following adjustment for known confounders and after using strategies to mitigate the influence of reverse causality. Mechanisms that could account for this association including inflammation, body fat distribution and adipose tissue action have been hypothesized but not tested empirically. Additional research is needed to identify mechanisms that are associated both with normal weight diabetes and, independently, with an increase in mortality. Finally, emerging evidence suggest that there may be appropriate management strategies including resistance training that can improve glycemic control. It is not known whether such behavioral changes can also lower mortality in persons who are normal weight with diabetes.

Compliance with Ethics Guidelines

Conflict of Interest Mercedes R. Carnethon has received honoraria from the American Diabetes Association for a talk on metabolically obese normal weight and mortality.

Laura J. Rasmussen-Torvik declares that she has no conflict of interest.

Latha Palaniappan declares that she has no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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