

Obesity Paradox in Type 2 Diabetic People: the Evidence Suggests that is the Results of Studies' Biases

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Article Information

Received date: Jan 18, 2016

Accepted date: Feb 12, 2016

Published date: Feb 17, 2016

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Keywords Diabetes Mellitus; All-Cause Mortality; Survival; Epidemiology; Obesity Paradox

Abstract

There is growing evidence that overweight or obese patients with cardiovascular disease survive longer than their normal-weight counterparts, an effect called the "Obesity paradox". Similar effect might exist in patients with Type 2 Diabetes Mellitus (T2DM), however, results conflict; some studies confirm such effect while others observed negative associations between higher BMI and mortality rates. A brief review of the more powerful studied suggest that obesity paradox in T2DM people is rather product of studies biases than a real biological phenomenon.

Introduction

The relationship between obesity and increased risk for Cardiovascular Disease (CVD) is well-established in the general population [1,2], however, once CVD occurs, paradoxically, obesity seems to confer a survival advantage, this effect was called "obesity paradox or reverse epidemiology" [3]. This effect has been observed in other chronic diseases such as heart failure, hypertension and chronic kidney disease.

Several studies seem to indicate that similar obesity paradox might exist in patients with Type 2 Diabetes Mellitus (T2DM). However, results conflict, with studies reported both positive and negative associations between higher BMI or other weight indices and CVD [4-12]. It is very important to clarify whether overweight or obese confer lower risk of mortality in T2DM people, because it may imply thoroughly review the mainstays of treatment of these patients were obtained a healthy weight is an important point.

The present brief review aimed to summarize current findings on the relationship between BMI all-cause mortality in patients with T2DM and to draw conclusions from them.

Search Strategy for Identification and Selection of Studies

MEDLINE and PUBMED databases were systematically searched for studies which reported all-cause mortality rates in relation to BMI in patients with T2DM from 2010 to 2015. Keywords Body Mass Index (BMI), mortality, T2DM and obesity paradox or reverse epidemiology were used to identify studies investigating the afore mentioned relationship. Studies with big sample of subjects prospectively followed at least 4.5 years were included.

What Are Possible Explanations For Obesity Paradox In Type 2 Diabetes Patients?

Possible explanations for obesity paradox are: (A) Normal weight diabetics might have a different genetic profile than overweight or obese diabetics, if such genetic variants that predispose to diabetes are associated with other diseases, normal-weight diabetics may be genetically loaded towards higher mortality. (B) Patients with T2DM and a low BMI might have higher tobacco and/or alcohol consumption. (C) Being overweight might provide a metabolic reserve in older patients, protecting against osteoporosis, malnutrition and frailty. (D) It is conceivable that patients with established diseases may garner protective effects from increased "good adiposity" or fewer harmful effects by having less "bad adiposity". The potential benefits of good adiposity may be attributed to higher fuel reserve and/or presence of protective factors [13,14], (E) High levels of circulating lipoproteins in obese subjects can bind lipopolysaccharides, decreasing inflammatory cytokine secretion is also used to explain the obesity paradox.

Studies Reviewed

Of the 7,788 participants with chronic mild to moderate Heart Failure (HF) in the Digitalis Investigation Group trial, 7379 had BMI ≥ 20 kg/m² at baseline [15]. Of these, 29% had Diabetes

Mellitus (DM), of whom 37% were BMI ≥ 30 kg/m². Of the 5,226 patients without DM, 22% were obese. Propensity scores for obesity were used to separately assemble 636 pairs of obese and non-obese patients with DM and 770 pairs of obese and non-obese patients without DM, who were balanced on 32 baseline characteristics. Among matched patients with DM, all-cause mortality occurred in 38 and 39% of obese and non-obese patients, respectively [Hazard Ratio (HR) when obesity was compared with no obesity 0.99; 95% Confidence Interval (CI) 0.80-1.22; P = 0.915]. Among matched patients without DM, all-cause mortality occurred in 23 and 27% obese and non-obese patients, respectively (HR associated with obesity 0.77; 95% CI 0.61-0.97; P = 0.025). They concluded that in patients with chronic mild to moderate HF and DM, obesity confers no paradoxical survival benefit.

McEwen, et al. [16], survey and medical record information was obtained from 8,334 participants in Translating Research into Action for Diabetes (TRIAD), a multicentre prospective observational study of diabetes care in managed care. The National Death Index was searched annually to obtain data on deaths over an 8-year follow-up period (2000-2007). Predictors examined included age, sex, race, education, income, smoking, age at diagnosis of diabetes, duration and treatment of diabetes, BMI, complications, comorbidities, and medication use. The authors observed highest all-cause mortality in patients under 25 of BMI.

Logue, et al. [11], using records of 106,640 patients in Scotland investigated the association between BMI recorded around the diagnosis of T2DM and mortality using Cox proportional hazards regression adjusted for age and smoking status, with BMI 25 to 30 kg/m² as a referent group. Deaths within 2 years of BMI determination were excluded. Mean follow-up to death or the end of 2007 was 4.7 years. They found lowest mortality in type 2 diabetic patients with BMI 25 to 29.9, being U-shape relationship between both variables.

Carnethon, et al. [7], pooled analysis of 5 longitudinal cohort studies: Atherosclerosis Risk in Communities Study, Cardiovascular Health Study, Coronary Artery Risk Development in Young Adults, Framingham Offspring Study and Multi-Ethnic Study of Atherosclerosis. Being 2,625 participants with incident diabetes mellitus, main outcome measures: total, cardiovascular, and non-cardiovascular mortality. The authors concluded that adults who are normal weight at the time of incident diabetes have a higher mortality than those who are overweight or obese.

Tobias, et al. [17], the study includes incident cases of DM from Nurses' Health Study (8,970 participants) and Health Professionals Follow-up Study (2,457 participants). Being the mean period of 15.8 years of follow-up, they observed a J-shaped association between BMI and all-cause mortality, compared with participants with a BMI of 22.5 to 24.9 those in the lowest BMI categories, 18.5 to 22.4 had a significant elevated mortality risk as did those in the highest BMI categories, 30 to 34.9 and >35 . The authors found no evidence of lower mortality among patients with diabetes who were overweight or obese at diagnosis.

Costanzo, et al. [18] in a prospective cohort From National Health Service, England, 10,568 patients with DM was followed a median of 10.6 years. Data about cause of death were not available. The authors found that overweight but not obese was associated with lower risk of all-cause mortality.

Finally, Chang and co-workers [19] in a recent report performed a systemic review and meta-analysis select articles from MEDLINE, EMBASE and The Cochrane databases. They used BMI, mortality, diabetes and obesity paradox or reverse epidemiology as key-words. Sixteen studies with 385,925 patients were included, patients were divided into 5 groups based on BMI (Kg/m²): Underweight (<18.5), normal weight (18.5-24.9), overweight (25-29.9) mild obesity (30-34.9) and morbid obesity (>35). A random effect meta-analysis was performed by inverse variance method. Heterogeneity was examining using Higgins I² test. The authors observed a U-shape association between BMI and all-cause mortality in male but no in females with DM. They are also highlighting the significant heterogeneity in most of group's comparisons.

Comments

The present review showed that 5 out of 7 studies observed data support the obesity paradox. However, the relationship between all-cause mortality and BMI had different shapes, Table 1, this may be explained for methodological differences such as: differences in BMI categories used, no identified patients with Latent Autoimmune Diabetes in Adults (LADA, self-reported weight measures, use of prevalent cases with different durations of disease, lack of information on ethnicity, medications taken, and difficulties to assess tobacco and alcohol consumption. Other important aspect is that T2DM is a disease of older people and is well-known that they have a high prevalence of coexisting chronic diseases which increases the potential for reverse-causation bias. Despite that BMI is still conventionally accepted as a measure of adiposity, in older people decreased validity of BMI as a measure of adiposity owing to age-related declines in muscle mass and wasting [20], and we should hold in mind that obesity paradox was mostly reported in elderly.

In line with this is the recent report by Stokes and Preston [21], studied the association between weight status and mortality in the US population, data from the National Health and Nutrition Examination Survey 1988-2010, included 30,462 individuals of whom 3,388 reported a prior diagnosis of cardiovascular disease. To minimize biases resulting from illness-induced weight loss, a reference category consisting of individuals who have always maintained a normal weight are used. Age-standardized mortality rates and Cox models were estimated, comparing overweight/obesity (BMI ≥ 25), to normal weight (BMI 18.5-24.9). At the time of survey overweight/obese paradox exists, however, when the reference category was limited to the always-normal-weight, the paradox disappeared. They concluded that obesity paradox is a product of biases involving reverse causation and confounding by smoking. A recent report by the same group

Table 1: Resume of results of recent major studies showed BMI and all-cause mortality relationship.

Studies, year, reference	< 18.5	18.5-24.9	25-29.9	30-34.9	> 35
McEwen et al, 2012 [14]		HRM			
Carnethon et al, 2012 [7]	NS	HRM			
Logue et al, 2013 [11]	HRM	HRM			HRM
Costanzo et al, 2015 [16]			RRM		
Chang et al, 2015 SR, MA [13]		HRMm			HRMm

HRM: High Risk Mortality; HRMm: High Risk Mortality in Males; RM: Reduced Risk Mortality; NS: Not Studied; SR: Sytemic Review; MA: Meta-Analysis.

concluded that Categorization of BMI and self-report bias combine to produce substantial error in the estimated hazard ratios and percent of deaths attributable to obesity. Future studies should use caution when estimating the association between obesity and mortality using categorical self-reported data [22].

Furthermore, explanations on the obesity paradox such as: (a) that patients with established diseases may garner protective effects from increased “good adiposity” or fewer harmful effects by having less “bad adiposity”. The potential benefits of good adiposity have been attributed to higher fuel reserve, and/or the presence of other protective factors. For instance, in heart failure, adipose tissue secretes soluble tumor necrosis factor- α receptors that neutralize the adverse biological effects of tumor necrosis factor- α . (b) Higher levels of circulating lipoproteins in obese patients can bind lipopolysaccharides, decreasing inflammatory cytokine secretion, also used as an explanation for the paradox. (c) Obese patients may be diagnosed earlier and treated more aggressively than non-obese patients, may be valid but none is well established

All these mechanisms supporting the obesity paradox found in clinical studies may be valid, but none is well established. In Goyal, et al. [23] opinion, a true paradox doesn't exist. Instead, we may simply be observing heterogeneous populations that have been poorly characterized into obese and non-obese groups by measurements of BMI alone, without factoring-in the type of adiposity, level of inflammation and the metabolic health. Death is another confounding factor as in non-prospective epidemiological observational studies; individuals with high death rate are not part of the analysis. Thus, the obesity paradox as characterized by BMI alone, without consideration of other confounders, should not be accepted as a true paradox [23].

Conclusion

In view of the results of recent studies, obesity paradox is a product of biases in the studies; subsequently the maintenance of a healthy body weight remains the cornerstone of T2DM treatment.

Supportive foundations

South Galicia Biomedical Foundation

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