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Obesity Paradox in Advanced Kidney Disease: From Bedside to the Bench.

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Abstract

While obesity is associated with a variety of complications including diabetes, hypertension, cardiovascular disease and premature death, observational studies have also found that obesity and increasing body mass index (BMI) can be linked with improved survival in certain patient populations, including those with conditions marked by protein-energy wasting and dysmetabolism that ultimately lead to cachexia. The latter observations have been reported in various clinical settings including end-stage renal disease (ESRD) and have been described as the “obesity paradox” or “reverse epidemiology”, engendering controversy. While some have attributed the obesity paradox to residual confounding in an effort to “debunk” these observations, recent experimental discoveries provide biologically plausible mechanisms in which higher BMI can be linked to longevity in certain groups of patients. In addition, sophisticated epidemiologic methods that extensively adjusted for confounding have found that the obesity paradox remains robust in ESRD. Furthermore, novel hypotheses suggest that weight loss and cachexia can be linked to adverse outcomes including cardiomyopathy, arrhythmias, sudden death and poor outcomes. Therefore, the survival benefit observed in obese ESRD patients can at least partly be

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derived from mechanisms that protect against inefficient energy utilization, cachexia and protein-energy wasting. Given that in ESRD patients, treatment of traditional risk factors has failed to alter outcomes, detailed translational studies of the obesity paradox may help identify innovative pathways that can be targeted to improve survival. We have reviewed recent clinical evidence detailing the association of BMI with outcomes in patients with chronic kidney disease, including ESRD, and discuss potential mechanisms underlying the obesity paradox with potential for clinical applicability.

Keywords

Obesity; mortality; body mass index; cachexia; obesity paradox; end stage renal disease; chronic kidney disease

INTRODUCTION

Obesity, as defined by a body mass index (BMI) ≥30 kg/m^2 (1), is a growing worldwide epidemic (2), which is associated with serious sequelae including higher risk of cardiovascular disease (CVD) and mortality (3-5). However, despite this markedly higher risk of adverse outcomes in the general population, elevated BMI may also be associated with improved survival in certain patient populations. This so-called “obesity paradox” has been observed in a variety of clinical settings including in patients suffering from obstructive pulmonary disease (6-8), chronic heart failure (HF) (9), acquired immunodeficiency disease syndrome (10, 11), advanced chronic kidney disease (CKD) and end-stage renal disease (ESRD) (12-39). Description of this phenomenon in patients with ESRD is particularly noteworthy given the disproportionately elevated risk of CVD and all-cause mortality in this patient population (5, 40-42). While treatment of traditional risk factors for CVD and mortality, such as hyperlipidemia, can be associated with improved outcomes in the general population, clinical trials targeting these pathways have failed to show a survival benefit in patients with ESRD. For instance, three large randomized clinical trials targeting serum low density lipoprotein (LDL) cholesterol levels have shown that treatment with 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase inhibitors, i.e. statins, which have proven effective in other patient populations, does not improve survival in patients on hemodialysis (43-45). Therefore, it has been postulated that nontraditional risk factors, such as protein energy wasting (PEW) and cachexia (46-48), uremic toxins (49), inflammation (48, 50-54) and oxidative stress (55, 56) may play a more significant role in CVD-related deaths in CKD and ESRD patients than traditional markers of risk. Moreover, the latter pathways are interrelated and the pathogenesis of one begets development and progression of others thereby creating a vicious cycle, ultimately leading to adverse outcomes. Accordingly, understanding and addressing the pathogenic role of these pathways in the setting of ESRD may be more effective in improving CVD and overall outcomes rather than strategies which focus on more traditional risk factors commonly targeted in other patient populations. Therefore, while the scientific exercise of scrutinizing all findings including the obesity paradox is of importance, it is also critical that we remain open to the possibility that the paradoxical associations observed between BMI and mortality in ESRD may also have biologic underlying mechanisms that need to be determined. Furthermore, investigating and

deciphering these mechanisms can provide important insights, which can be utilized to create novel therapies for risk factors such as cachexia and wasting. In the following sections, we will first describe the findings of prior studies which have assessed the association of BMI and body size with mortality in CKD and ESRD patients treated with hemodialysis (HD), peritoneal dialysis (PD), and kidney transplantation (KT). Subsequently, we will review some of the potential mechanisms, which may account for the paradoxical associations reported in these studies.

MEASUREMENTS OF BODY SIZE AND BODY COMPOSITION

Most definitions of obesity rely on BMI; however, BMI does not reliably account for body composition. The use of BMI to define obesity can have major clinical implications since individuals with the same height and weight, and thus same BMI, can have significant differences in their composition and distribution of their body fat and muscle (57, 58). Accurate measurement of body composition in patients with CKD and ESRD is relevant given frequent muscle wasting (59) and changes in the type and distribution of adiposity (60) observed in this population. Hence, more detailed methods of evaluating body mass and composition have been developed and demonstrated as more accurate predictors of outcome risk. For instance, a systematic review and meta-analysis reported that waist-to-height ratio and waist circumference (WC) seem to be more precise estimates of cardio-metabolic risk as compared to BMI (61). Bioelectrical impedance analysis/spectroscopy (BIA/S) (59) is another commonly cited method used to estimate body composition in CKD, although its accuracy may be altered given the fluid retention associated with renal disease (62). Estimates of lean body mass (LBM) could also be obtained using mid-arm muscle circumference measurements (63) or serum creatinine-based formulas which utilize creatinine as a marker of muscle mass (64). Body fat percentage can be estimated using near-infrared interactance (NIR) (65, 66) and this may be a practical and accessible tool for objective assessment of body fat content in HD patients. Furthermore, the amount of the adipose tissue can also be measured by dual energy x-ray absorptiometry (DEXA) (67-69), which is considered a more accurate and reliable reference method (70, 71). However, the most reliable methods for obtaining detailed body composition data might be computed tomography (CT) and magnetic resonance imaging (MRI) (72-74) given that they allow for the assessment of total body adipose tissue distribution and also distinguish between tissue edema, visceral and subcutaneous adipose tissue. The importance of body composition and its relevance to outcomes has been demonstrated in a number of studies, which have utilized the mentioned techniques in patients with CKD and ESRD. A study by Postorino et al. (75) examined a prospective cohort of 537 ESRD patients using WC as a surrogate of intra-abdominal/visceral fat and reported that each 10-cm increase in WC was associated with a 23% higher risk for all-cause and 37% higher risk for CVD mortality, while BMI was an inverse predictor of these outcomes. The effect of fat and LBM on survival of maintenance HD patients was also evaluated by Noori et al. (76) who concluded that higher fat mass in male and female patients and higher LBM only in female patients appeared to be protective. Therefore, in discussing the association of BMI and outcomes in CKD and ESRD patients, it is essential to keep in mind notable limitations of these measures as a marker of obesity and

body composition. Future studies will need to focus on delineating the impact of body composition on outcomes in patients with CKD and ESRD.

OBESITY AND MORTALITY IN CKD

While obesity and excess body fat are associated with a higher risk for development and progression of de novo CKD (77-79), a potential protective effect of higher BMI in terms of improved survival in CKD remains controversial **(**Table 1**)**. Madero et al. (80) analyzed data of 1,759 CKD patients with a mean estimated glomerular filtration rate (eGFR) ± standard deviation (SD) 39±21 mL/min/1.73m^2 and found no difference in all-cause mortality risk between higher BMI groups (BMI 25->40 kg/m^2) compared to those with normal weight (BMI 18.5-24.9 kg/m^2). Likewise, Dalrymple et al. (81) found that in 1,268 patients with eGFR <60 ml/min/1.73m^2, the BMI-mortality association was not significant for higher BMI groups. In contrast, lower BMI was associated with higher mortality when compared to the reference BMI of 18.5-24.9 kg/m^2 (Hazard Ratio [HR] 2.37, 95% confidence interval [95% CI] 1.37-4.10). In another study of individuals with eGFR<60 ml/min/1.73m^2 or presence of microalbuminuria, a BMI of 18.5-<22 kg/m^2 was associated with a higher risk of death (HR 1.30, 95% CI 1.03-1.64), while higher BMI was not significantly associated with mortality when compared to the reference group (BMI 22-<25 kg/m^2) (82). In a cohort of CKD and non-CKD patients undergoing a surgical procedure, obese (BMI ≥35 kg/m^2) patients with CKD (eGFR <60 mL/min/1.73 m^2) had higher odds of 30-day mortality than non-obese non-CKD patients in unadjusted and fully adjusted models (Odds Ratio (OR) 5.51, 95% CI 4.48-6.79 and OR 1.49 95% CI 1.18-1.87, respectively) (83). Obermayr et al. (84) analyzed data from the Vienna Health Screening Initiative study and Austrian Death Registry that included patients with stage I-III CKD. Although the results were not statistically significant, the study observed an inverse trend between BMI and mortality risk in patients with moderate CKD (eGFR 45 ml/min/1.73m^2). However, examining CVD risk as the primary outcome and BMI of 25 kg/m^2 as the reference, the authors reported that the risk of CVD death was higher in participants with both low (BMI level 20 kg/m^2, HR 1.35, 95% CI 0.82-2.20), and high BMI levels [BMI 30 kg/m^2 (HR 1.37, 95% CI 1.07-1.75) and BMI 35 kg/m^2 (HR 2.05, 95% CI 1.19-3.55)]. While most studies use all-cause mortality as the primary outcome, Navaneethan et al. (85) examined more refined causes of death (malignancy, non-CVD/non-malignancy-related death) to investigate the BMI-mortality association in 54,506 patients, the majority being in CKD stage III. They reported that CKD patients with BMI 25-39.9 kg/m^2 had lower risk for all three death outcomes compared to BMI of 18.5-24.9 kg/m^2.

Among individuals with more advanced kidney disease (CKD stage III-IV [eGFR 15-60 ml/min/1.73m^2]), several reports found no significant association between higher BMI levels (per 5 kg/m^2) and all-cause mortality (86, 87). However, Babayev et al. (88) studied a cohort of 12,534 African American and Caucasian patients with CKD stage III-IV and reported that a BMI 30-34.9 kg/m^2 was associated with better survival (HR 0.74, 95% CI 0.62-0.87) compared to patients with BMI <30 kg/m^2. This effect was attenuated for CKD patients with a BMI >35 kg/m^2 (HR 1.08, 95% CI 0.89-1.30). In addition, a study using a cohort of patients with CKD stage III-IV in the United States (US) Veterans Administration (VA) system, found a U-shaped association between BMI and all-cause mortality where low and

high BMIs were both associated with worse outcomes (89). However, subsequent studies found that the latter findings may also be explained by gender differences given that the VA cohort was mostly comprised of male patients. Furthermore, a study from Taiwan found that in male patients with CKD, lower and higher BMI were associated with a higher risk of all-cause mortality, while in female patients, no association was observed (reference: BMI 27.6-30 kg/m^2) (90). These studies highlight the potential role of gender as a modifying factor in the association of BMI with outcomes.

As mentioned earlier, another modifier of the association of obesity with outcomes is body composition and shape. In a US cohort consisting of 5,805 CKD patients (50.3% with CKD stage I-II and 49.7% with CKD stage III-IV), BMI ≥40 kg/m^2 was associated with higher mortality risk after adjustment for age, sex and race (BMI reference group 25-29.9 kg/m^2). However, after accounting for WC, higher BMI categories trended towards lower mortality (91). Another study evaluating 13,324 CKD patients found that each SD increase in BMI was associated with a lower risk of the composite outcome of incident CKD and mortality (HR 0.94, 95% CI 0.90-0.99). However, when waist-to-hip ratio was used as a measurement of body mass, increasing body size was associated with higher risk of the composite outcome of incident CKD and mortality (HR 1.12, 95% CI 1.06-1.18) (92). Likewise, a study (93) using a body shape index formula (94), which accounted for height, weight and BMI, reported that an increase of 1 SD in body shape index was associated with a higher all-cause mortality risk (HR 1.16, 95%CI 1.01-1.34) in male CKD patients, whereas in female CKD patients, body shape index showed no significant association with all-cause mortality (93).

Another consideration was the role of metabolic health in obese and non-obese patients. Given that metabolic abnormalities might alter the association of the BMI with outcomes in CKD patients, in another study investigators grouped patients into metabolic healthy and unhealthy categories and stratified them by BMI (reference group: metabolic healthy normal weight study participants). While no statistically significant differences were observed in mortality risk among metabolically unhealthy overweight (BMI 25-29.9 kg/m^2) or obese (BMI ≥ 30 kg/m^2) CKD patients, metabolically healthy overweight CKD patients had a lower risk of all-cause mortality (HR 0.74, 95% CI 0.57-0.96) in the fully adjusted model (95).

OBESITY AND MORTALITY IN ESRD TREATED WITH HD

One of the first studies which provided evidence of an altered BMI-mortality association in HD patients was published in 1982 by Degoulet et al. (12) who found that higher BMI was not associated with higher mortality **(**Table 2**)**. Subsequently, Leavey et al. (13) also found no evidence of higher mortality risk among HD patients with higher BMI values using data from the US Renal Data System (USRDS). In addition, both investigators found that lower BMI was in fact associated with a higher risk of mortality (12, 13). Many subsequent studies have since observed similar findings. Fleischmann et al. (14) found that BMI >27.5 kg/m^2 was associated with improved survival in HD patients when compared to a reference BMI of 20-27.5 kg/m^2. In their study, each one-unit increase in BMI >27.5 kg/m^2 was associated with a 30% decrease in the relative risk (RR) of mortality, while with each unit decrease in

BMI below 20 kg/m^2, the RR of death was 1.6-fold higher. Likewise, using the body weight-to-height relationship as an alternative metric for body size measurement, Kopple et al. (15) found a progressive decrease in the risk of mortality with increasing body size in HD-treated ESRD patients. In addition, higher body weight or body volume was also associated with decreased risk of mortality (16). The association of higher BMI with lower mortality was also reported by Pifer et al. (19) in a study of US patients in the international Dialysis Outcomes and Practice Patterns Study (DOPPS). A higher risk of mortality was observed in patients with lower BMI, while a high BMI was associated with improved survival in HD patients. Similarly, in another cohort including patients from the US, it was found that BMI ≥30 kg/m^2 was associated with a higher survival rate in HD patients (HR 0.89, 95% CI 0.81-0.99) (96). Furthermore, Stack et al. (97) found that in a cohort of 117,309 HD patients, the adjusted RR of death was greatest for those with BMI ≤20.9 kg/m^2 (RR 1.40, 95% CI 1.32-1.50 for diabetics and RR 1.27, 95% CI 1.21-1.34 for non-diabetics) and lowest for patients with BMI >30.0 kg/m^2 (RR 0.97, 95% CI 0.96-0.99 for diabetic and RR 0.97, 95% CI 0.95-0.98 for non-diabetic patients) compared with the reference group (BMI 23.5-26.1 kg/m^2).

Finally, Doshi et al. (38) examined the obesity paradox with the application of causal modeling with a marginal structural model (MSM), which investigated the BMI-mortality relationship while controlling for time-varying confounders and informative censoring which may be influenced by prior BMI levels. The study assessed the association between BMI and all-cause mortality among 123,624 hemodialysis patients receiving treatment between 2001 and 2006. Compared with the reference (BMI 25 to <27.5 kg/m^2), a BMI of <18 kg/m^2 was associated with a 3.2-fold higher death risk (HR 3.17, 95% CI 3.05–3.29) and mortality risks declined with increasing BMI with the greatest survival advantage of a 31% lower risk (HR 0.69, 95% CI 0.64–0.75) observed for a BMI of 40 to <45 kg/m^2. For this review, using the same cohort, we herein show the BMI-mortality relationship using the World Health Organization categorizations of obesity (1), which similarly show an inverse linear pattern across all analytical models **(**Figure 1**).** Hence, the linear inverse relationship between BMI and mortality was considered as robust across multiple models including MSM analyses that more completely account for time-varying confounders and other statistical sources of biases.

The findings reported in US patients have been also been replicated globally. Leavey et al. (17) analyzed data from an international cohort including 9,714 HD patients from the US and Europe and again found a decrease in the relative mortality risk with increasing BMI. When using BMI of 23-24.9 kg/m^2 as the reference group, the RR of mortality was 0.84 in overweight (BMI 25-29.9 kg/m^2), 0.73 in mildly obese (BMI 30-34.9 kg/m^2), and 0.76 in moderately obese (BMI 35-39.9 kg/m^2) HD patients, while a BMI <20 kg/m^2 was associated with the highest risk of mortality. In another cohort of HD patients from Southern Europe, which was distinguished by a lower prevalence of diabetes mellitus, Chazot et al. (26) found a lower mortality risk for overweight and obese HD patients when compared to those with a normal BMI.

Additionally, the impact of race, ethnicity and place of origin on the association of obesity with outcomes has also been extensively studied in HD patients. In a study of 151,027

patients receiving either HD and PD using data from the USRDS, Glanton et al. (22) found that while obesity was independently associated with a reduced risk of mortality in the overall patient population (HR 0.75, 95% CI 0.72-0.78), this relationship was more pronounced in African Americans. Furthermore, Ricks et al. (31) examined a cohort of 109,605 maintenance HD patients that comprised of 39,090 African Americans, 17,417 Hispanics, and 53,098 non-Hispanic whites. Although higher BMI was associated with a survival benefit in Hispanic and African American patients when compared to non-Hispanic whites, African American patients showed the largest decrease in mortality risk with increasing BMI. Similarly, Wang et al. (98) sought to determine differences among racial/ethnic groups using LBM as predictor of mortality. Higher LBM was not only associated with lower mortality risk, but this association was also particularly evident among non-Hispanic white and African American HD patients. Hispanic HD patients, however, did not benefit from higher LBM, showing a U-shaped association with higher mortality in lower and higher LBM categories. Meanwhile, the association of obesity with survival in patients of Asian ancestry has been less consistent and less studied. Johansen et al. (23) found that high BMI was associated with higher survival in whites, African Americans, and Hispanics but not in Asians even after adjustment for LBM and estimates for adiposity using the Benn index. However, Park et al. (34) matched 20,818 HD patients from South Korea to 20,000 patients from the US (10,000 non-Hispanic whites and 10,000 African Americans) and found a consistent association between higher baseline BMI and lower mortality across all three racial groups. Finally, Hall et al. (29) reported that in a cohort of 21,492 Asian, Pacific Islander and non-Hispanic white dialysis patients, higher BMI was associated with better survival across almost all races and ethnicities.

A number of studies have attempted to evaluate the interaction between obesity, age and long-term survival in HD patients, but have reported conflicting results (32, 36, 37). Hoogeveen et al. (32) prospectively followed patients from a European cohort of HD patients and examined the association of age (<65 or ≥65 years) and baseline BMI (<20, 20-24 [reference], 25-29, and ≥30 kg/m^2) with mortality. They found that the age-standardized mortality rate was higher in younger obese patients than those with normal BMI (OR 1.70, 95% CI 1.10-2.90). Meanwhile, Calabia et al. (37) did not observe a survival benefit for higher BMI in young patients in a cohort of 6,290 adult incident HD patients. Finally, Vashistha et al. (36) analyzed the data of 123,383 maintenance HD patients in a US cohort and found that while higher BMI was associated with lower death risk across all age groups, the degree of this association was more pronounced in those younger than 65 years old.

There also have been studies conducted to account for the limitations of BMI as a surrogate for body size by using alternative metrics. This was done by using parameters of muscle mass as demonstrated by Beddhu et al. (21) who examined mortality risk in 70,028 HD patients using creatinine clearance as a proxy for muscle mass. They found that the association of elevated BMI with improved survival was limited to patients with normal or high serum creatinine (suggesting normal or higher muscle mass); and high BMI patients who have lower creatinine levels (suggesting lower muscle mass) had a higher mortality risk. Kalantar-Zadeh et al. (27) also examined 121,762 HD patients and found that higher BMI (up to 45 kg/m^2) and higher serum creatinine concentrations were progressively and

independently associated with better survival, even after multivariate adjustment for surrogates of nutritional status and inflammation. They also found evidence suggesting that muscle gain with loss of total body weight over time may be associated with better survival in contrast to weight gain while losing muscle mass. Using the same cohort in a separate study, Kalantar-Zadeh et al. (33) applied composite ranking scores to further clarify the BMI-mortality association and reported that a decrease in muscle mass (using serum creatinine as a surrogate) but an increase in weight (measured as BMI) was associated with higher mortality. The impact of weight loss, which is one of the key indicators of cachexia, has also been evaluated in patients on maintenance HD. Molnar et al. (30) found that unintentional weight loss was associated with a higher risk of mortality in a relatively healthy subset of HD patients who were waitlisted for a renal transplantation. These findings are also supported by another study by Kalantar-Zadeh et al. (25), who found that progressive weight loss over time was associated with higher CVD and all-cause mortality risk in HD patients. Cabezas-Rodriguez et al. (99) also sought to determine the effects of weight gain and loss (>1% or <1% of body weight) in HD patients and found that while weight gain was strongly associated with higher rates of survival, weight loss had the opposite effect. Interestingly, after stratification by BMI, this association was not observed in obese patients indicating a potential resistance to the development of cachexia in obese HD patients. Given that cachexia has been shown to be associated with a higher risk of mortality in numerous chronic conditions, it is possible that the association of improved survival with obesity may be at least partly related to mechanisms which prevent the development of wasting and its adverse effects in these patients.

OBESITY AND MORTALITY IN ESRD TREATED WITH PD

While it has been debated that obesity is a relative contraindication for initiation of PD therapy (100-103), the effect of obesity on survival rates among PD patients also remains controversial (104) **(**Table 3**)**. Comparison between the different studies done so far in this area has proven difficult given the heterogeneous methodology and BMI categories used in these studies. There are studies which found that obesity was associated with worse outcomes in patients undergoing PD. McDonald et al. (105) analyzed data from the Australia and New Zealand Dialysis and Transplant (ANZDATA) Registry that included 9,679 patients with ESRD who underwent PD treatment. In multivariate analyses, they found that BMI ≥30 kg/m^2 was associated with higher mortality (HR 1.36, 95% CI 1.14-1.54) and higher risk of technique failure (HR 1.17, 95% CI 1.07-1.26) in most patients, except in those of Maori/Pacific Islander origin. Furthermore, a J-shaped association was reported between BMI and mortality where BMI values close to 20 kg/m^2 were associated with the lowest risk of death. In addition, a study investigating 1,263 Chinese PD patients found that obesity was associated with a higher risk of CVD and all-cause mortality, in the unadjusted model (referent BMI, 18.5-22.9 kg/m^2) (106). However, in the multivariate model, this association only persisted for CVD, but not all-cause mortality.

There are also studies which found that lower BMI was associated with worse outcomes, but observed no association between mortality and obesity in patients being treated with PD. A study of 1,662 PD patients from the USRDS Dialysis Morbidity and Mortality Wave II Study (DMMS) found that BMI ≥30 kg/m^2 was not associated with a change in survival

(96). Furthermore, a cohort study of 900 prevalent PD patients from Korea showed that higher BMI was not associated with increased mortality (107). Meanwhile, in another investigation in patients on PD, Stack et al. (97) found that the RR of death for participants with BMI <20.9 kg/m^2 was higher (referent BMI 23.5-26.1 kg/m^2) but there was no association between higher BMI and improved survival. Data from the Canadian Organ Replacement Registry (CORR) also suggested that underweight incident PD patients (BMI <18.5 kg/m^2) suffered from a higher death risk (HR 1.3, 95% CI 1.1-1.6) when compared to the reference group of BMI 19-24.9 kg/m^2. The risk of mortality for incident PD patients with BMI >30 kg/m^2 compared to the reference group was null (HR 1.01, 95% CI 0.89-1.14) (108). Furthermore, in a prospective PD cohort from the Netherlands (Netherlands Co-operative Study on the Adequacy of Dialysis-2 (NECOSAD)), de Mutsert et al. (109) included 688 PD patients with a follow-up period of 5 years. After adjustment for age, sex, tobacco use, comorbidities and primary cause of CKD, PD patients with a BMI≥30 kg/m^2 did not have a statistically significant difference in mortality risk (HR 0.8, 95% CI 0.5-1.3) than those with a normal BMI (reference 18.5-25 kg/m^2); and the similar relationship was observed in time-dependent models (HR 0.7, 95% CI 0.4-1.2). In contrast, those patients who were underweight (BMI<18.5 kg/m^2) at the initiation of PD therapy suffered from a higher mortality risk than those with a normal BMI (HR 1.3, 95% CI 0.4-3.2). In a recent study using a large US cohort of PD patients, Obi et al. (110) found a U-shaped association between all-cause mortality and BMI, where the highest and lowest BMIs were associated with worse outcomes while patients with a BMI 30-<35 kg/m^2 had the lowest mortality risk.

Finally, there are also studies that have found that obesity is associated with improved outcomes in patients undergoing PD. Snyder et al. (111) performed a retrospective study of 41,197 PD patients and found that overweight and obese participants had a survival benefit compared to those with lower BMI. The adjusted mortality HR for overweight patients (BMI 25-29.9 kg/m^2), were 0.84, 0.89 and 0.98 for the first, second and third years of follow-up, respectively. For obese patients (BMI ≥30 kg/m^2), adjusted mortality HR for the first, second and third years of follow-up were 0.89, 0.99 and 1.00. Except for the higher mortality risk after three years of follow-up in obese patients, these findings remained robust after accounting for any modality switch to HD or transplantation. Moreover, Mehrotra et al. (112) analyzed data from the USRDS using multivariate piecewise exponential survival models to examine all-cause mortality and technique failure in 66,381 incident PD patients and concluded that higher BMI quartiles were related to lower mortality risk but higher technique failure risk compared to the reference BMI group <21.88 kg/m^2. Another study by Fernandes et al. (113) examined baseline BMI and weight change with all-cause mortality in 1,911 Brazilian incident PD patients and found that PD patients with BMI <18.5 kg/m^2 had a higher death risk while a BMI >30 kg/m^2 was associated with a survival benefit. Accordingly, in a study using time-varying analyses Badve and colleagues (35) found lower mortality risk in PD patients with BMI between 28.1-31 kg/m^2 (time-varying BMI reference group 25.1-28 kg/m^2) and a higher mortality risk in those with lower BMI (BMI <25 kg/m^2) values.

There are also numerous studies, which have attempted to account for muscle mass in the evaluation of the obesity and outcomes in PD patients. These investigations mostly relied on

serum and urinary creatinine concentrations as a surrogate of total body muscle mass. In a study of 10,140 incident PD patients, Ramkumar et al. (114) used urinary creatinine to estimate muscle mass and stratified patients into subgroups of BMI (BMI reference group 18.5-24.9 kg/m^2) and low vs. normal/high muscle mass, based on the 25th percentile of 24-hour urinary creatinine. PD patients classified with high BMI and high muscle mass had a 10% lower risk of all-cause mortality compared to those with normal BMI and normal/high muscle mass. In contrast, high BMI with low muscle mass was associated with a higher risk of all-cause (HR 1.29, 95% CI 1.17-1.42) and CV (HR 1.21, 95% CI 1.06-1.39) mortality. Also using creatinine as surrogate of LBM, the Canada-US (CANUSA) Peritoneal Dialysis Study Group reported that 1% lower LBM was associated with 3% higher RR for death (115, 116). Similarly, Park et al. (117) evaluated the association of change in baseline serum creatinine concentration during the first three months of treatment with all-cause mortality in a large cohort of patients undergoing PD therapy. They found that in the fully adjusted model, patients with serum creatinine <4 mg/dL and 4-5.9 mg/dL had a higher mortality risk (HR 1.36, 95% CI 1.19-1.55 and HR 1.19, 95% CI 1.08-1.31, respectively) when compared to PD patients with serum creatinine levels of 8-9.9 mg/dL. Accordingly, PD patients with serum creatinine levels of 10-11.9 mg/dL, 12-13.9 mg/dL and ≥14 mg/dL had lower mortality risk (HR 0.88 [95% CI 0.79-0.97], 0.71 [0.62-0.81] and 0.64 [0.55-0.75], respectively). While the authors concluded that muscle mass may partly explain these associations, they also noted the limitation that residual kidney function and delivered dialysis dose may also be confounders in these findings.

OBESITY AND MORTALITY IN ESRD TREATED WITH KT

Transplantation is the preferred method of treatment for ESRD since it is associated with a survival benefit in those who meet the eligibility criteria (118-121). While we have enumerated many studies, which indicate a paradoxical association between BMI and outcomes in most HD and PD patients, BMI is also a factor that may determine eligibility for receipt of a KT in ESRD patients. In fact, a survey conducted by the American Society of Transplant Surgeons (ASTS) indicated that 66 of 67 kidney transplant centers used a BMI cutoff value of 35-45 kg/m^2 in order to exclude those with obesity for potential KT evaluation (122). However, there are several studies, which have addressed the impact of pre-KT body size on post-KT outcomes, including graft and patient survival **(**Table 4**)**. In a US cohort of 10,090 HD patients, Streja et al. (123) evaluated the association between pre-KT three-month averaged BMI and three-month averaged serum creatinine, as a surrogate for muscle mass, with mortality. Pre-KT averaged serum creatinine levels of 12-<14 and ≥14 mg/dl in renal recipients were associated with 44% and 54% lower risks of mortality, respectively. However, pre-KT BMI neither as a continuous nor as a categorical parameter was significantly associated with mortality. Further adjustment for markers of malnutrition and inflammation did not alter these associations. Likewise, in a Spanish cohort of 3,365 KT recipients without graft loss in the first year after transplantation, pre-KT BMI measurement had no significant effect on post-KT mortality (124). Published data from Australia and New Zealand (BMI reference group 18.5-24.9 kg/m^2) (125), the Netherlands (BMI reference group 20.1-25 kg/m^2) (126) and Canada (BMI reference group 20-24.9 kg/m^2) (127) also reported no association between pre-KT BMI and post-KT mortality. Notably, morbid

obesity (BMI >35-40 kg/m^2) was not an independent predictor of post-KT mortality (128). However, Aalten et al. (129) did find that that pre-KT BMI as a continuous parameter was an independent predictor of post-KT CVD events (HR 1.03, 95% CI 1.00-1.05), although not all-cause mortality. Furthermore, Meier-Kriesche et al. (130) also reported a U-shaped association between BMI and post-KT mortality. Ahmadi et al. (131) conducted a meta-analysis including four studies (125-127, 132) and reported that compared to normal BMI (BMI, 18.5-24.9 kg/m^2), underweight (BMI <18.5 kg/m^2) (HR 1.09 95% CI 1.02-1.20), overweight (BMI 25-29.9 kg/m^2) (HR 1.07, 95% CI 1.04-1.12) and obese (BMI ≥30kg/m^2) (HR 1.20, 95% CI 1.14-1.23) categories were associated with higher mortality in KT recipients. Furthermore, Lafranca et al. (133) and Sood et al. (134) in two different meta-analyses concluded that obesity in KT recipients prior to surgery may be associated with worse outcomes after KT. Moreover, there is also evidence that age may impact the latter observations as elderly renal transplant recipients ≥75 years old might be more affected by negative sequela of obesity, since in these patients a pre-KT BMI >30 kg/m^2 (BMI reference group ≤30 kg/m^2) was associated with a 50% higher all-cause mortality risk (132). It should also be noted that analyzing data from the United Network for Organ Sharing (UNOS) database showed that a pre-KT BMI of 30-34.9 kg/m^2 might have a slightly reduced mortality risk (HR 0.92, 95% CI 0.86-0.99) in comparison to the referent group of non-obese patients with BMI <30 kg/m^2 (135). However, the findings of these studies have not been replicated in the other investigations mentioned. Therefore, future studies are needed to further assess the association of pre-KT BMI with post-transplant outcomes. Since net state of immunosuppression and chronic inflammatory state from chronic immunosuppression in kidney transplant recipients plays a role in several outcomes in kidney transplantation (136-138), potential confounders involving in the interplay between immunologic and non-immunologic factors need to be taken into account in these studies.

POTENTIAL MECHANISMS UNDERLYING THE OBESITY PARADOX

The observations that increased BMI and obesity can be associated with improved survival in patients with ESRD and especially those treated with HD have been met with some degree of skepticism. Some have attributed these observations to confounding and questioned the biologic plausibility of obesity being associated with protective mechanisms in this patient population. However, there is accumulating evidence that the observations collectively described as the obesity paradox remain robust even after extensive adjustment for various confounders. In addition, there is some evidence that obesity and increased body fat can provide potential protective mechanisms in the setting of inflammation and hemodynamic instability. More importantly, there is now a growing body of experimental and clinical evidence, which links cachexia and wasting to poor outcomes including CVD and mortality. The findings of these studies have shed light on underlying basic and molecular mechanisms which link cachexia and weight loss to worse outcomes thereby raising the possibility that patients with increasing BMI and obesity are resistant to these mechanisms and their deleterious sequelae. Nevertheless, the obesity-mortality associations and their underlying mechanisms remain complex and not yet fully understood. Here we will present some of the theories that have been proposed to contribute to the obesity paradox **(**Figure 2**)**.

CACHEXIA AND INEFFICENT ENERGY METABOLISIM

Cachexia is a metabolic syndrome characterized by an imbalance in energy storage and expenditure which commonly manifests clinically as weight loss and loss of muscle and fat tissue (139). The cachectic state has been described in numerous chronic inflammatory conditions including cancer, severe chronic obstructive pulmonary disease, chronic HF, rheumatologic disorders and advanced CKD and ESRD. It is well established that the presence of cachexia is associated with poor quality of life and higher risk of mortality (140). Although many factors including anorexia, malnutrition, oxidative stress and inflammation have been implicated in the pathogenesis of cachexia, it is recognized that ultimately this condition arises due to a severe alteration of energy balance (141). There is a large body of evidence which indicate that elevated resting energy expenditure (REE) is a major determinant in the development of energy wasting and consequently cachexia in patients at risk for this condition (47, 141). Further evidence supporting this mechanism is provided by data indicating that the complications associated with cachexia cannot be overcome by nutritional supplementation and appetite stimulants (142). Although the main tissues affected by cachexia are fat and skeletal muscle, several other organ systems including the liver, heart, and brain are also negatively impacted by this condition (143). In fact, there is now evidence describing the mechanisms by which cancer cachexia leads to cardiomyopathy and thereby cardiac dysfunction and higher mortality (144, 145). In addition, recent investigations in animal experimental models of cancer cachexia have indicated that preventing muscle and adipose tissue loss is effective in prolonging survival (146-148). Therefore, the biologic plausibility of a link between cachexia and development of multiorgan dysfunction leading to higher mortality and the potential efficacy of targeting this condition in order to improve survival is becoming more established.

Accordingly, patients with advanced CKD and ESRD have been found to have a significantly high prevalence of cachexia and its presence is associated with a higher risk of mortality (47). In addition, there is evidence that patients with ESRD have an increased REE (149-151). Furthermore, many of the risk factors identified in the causal pathway of poor energy metabolism and cachexia including PEW, inflammation, oxidative stress, insulin resistance and anorexia are also present in the CKD and ESRD population. More interestingly, there is also recent data indicating that CKD and ESRD are associated with browning of white adipose tissue which has been implicated in the inefficient expenditure of energy commonly found in many different patient populations with cachexia. In this regard, Cheung et al. (152) demonstrated that subtotally nephrectomized mice developed cachexia as indicated by an increased metabolic rate, loss of LBM, along with increased expression and abundance of uncoupling protein-1 (UCP1) in the fat tissue indicating a transition from energy preservation and storage to energy expenditure. Furthermore, it was noted that pair-feeding the animals in order to restore their energy intake to the level of control mice did not improve weight gain in the uremic animals, further confirming the role of abnormally elevated energy expenditure rather than poor energy intake in uremia-associated cachexia. More recently, Kir et al. demonstrated that the browning of white adipose tissue observed in uremia is at least partly mediated by the secondary hyperparathyroidism which is commonly encountered in this condition (153, 154). This is also consistent with the findings of a small

clinical study which showed that severe hyperparathyroidism in HD patients was associated with higher REE (150).

In regards to the potential impact of obesity in the pathogenesis and progression of cachexia, it can be postulated that obese patients may have underlying mechanisms (genetic or environmental) which allow them to be more resistant to the energy dysmetabolism and increased REE that is prevalent in chronic conditions such as ESRD. It is known that a major cause of obesity is increased energy surplus and decreased energy expenditure (155). Therefore, obese patients may have factors that protect them from inefficient energy loss and thereby cachexia and its complications. Furthermore, obese patients may have more energy reserves and hence more resilience against the deleterious impact of CKD and ESRD-associated REE. There is evidence, which indicates that fat tissue wasting can be the critical turning point in the cachectic process by stimulating skeletal muscle wasting (156). Therefore, patients with large adipose tissue reserves and underlying mechanisms that prevent lipolysis and loss of fat may be protected against the consequences of cachexia such as muscle loss. Future studies will need to examine the potential links between obesity, cachexia and mortality in the setting of CKD and ESRD.

INFLAMMATION

Chronic inflammation is commonly observed among CKD and ESRD patients, and may be a cause and consequence of CKD and its many different complications including cachexia (157, 158). Pro-inflammatory cytokines are linked to reduced appetite (159), but they can also facilitate muscle breakdown. For instance, tumor necrosis factor-α can induce muscle breakdown by inhibition of nuclear factor kappa-B kinase subunit beta/nuclear factor kappa-B pathway (160-164). In addition, inflammation can play a role in impaired insulin signaling and insulin resistance observed in ESRD (163). Furthermore, inflammation is considered a major contributor to CVD and mortality observed in patients with CKD and ESRD (41, 165-168). In this regard, there is evidence that adipose tissue may temper the deleterious effects of inflammatory mediators by sequestering them. For instance, it has been shown that adipose tissue can synthesize and release soluble tumor necrosis factor-α receptors which can bind tumor necrosis factor-α and prevent its proinflammatory activity (169).

THE IMPACT OF FAT DISTRIBUTION

Besides the total body mass of adipose tissue, the distribution of fat tissue might also influence survival. It has been shown that a pronounced central fat distribution may be associated with a higher risk of CVD, cancer and metabolic disorders (170-173). Moreover, the endocrine function of visceral and subcutaneous fat might markedly differ based on their distribution in the body. For instance, in HD patients it has been shown that waist circumference as a surrogate of visceral fat, directly correlated with C-reactive protein and interleukin-6 levels, whereas a proxy of subcutaneous fat inversely correlated with C-reactive protein and interleukin-6 (174). Therefore, regional fat distribution could impact the relationship between obesity and outcomes, details which may not be captured by evaluation of BMI alone.

On a side note, regional fat distribution, at least in the seemingly healthy population, varies between racial/ethnic groups, which could partly explain the racial/ethnic differences within the obesity paradox observed among HD patients. In a study of African American women, it was found that they had less visceral fat in comparison to Caucasian women, even though their BMI measurements were comparable (175). In addition, some Asian populations have been shown to be prone to higher visceral fat per total body fat content when compared to Europeans (176). Future studies will need to examine the role of fat distribution in the relationship between BMI and outcomes in patients with CKD and ESRD.

MORE STABLE HEMODYNAMICS

A study in patients with HF (177) reported that overweight and obese study participants had higher systolic blood pressure values, while there was no difference in pulmonary capillary wedge pressure and cardiac indices. Furthermore, obese hypertensive subjects in contrast to lean hypertensive individuals had lesser activation of the catecholamine and renin-angiotensin-aldosterone system when exposed to stress (178). These findings may also be relevant to patients with ESRD being treated with HD who are at risk for intra-dialytic hypotension and its deleterious consequences including cardiomyopathy (179-181) and higher mortality (182-184). Extrapolation of the evidence reported in the HF patients to the HD population would suggest that obese HD patients are more resistant to the deleterious hemodynamic effects of HD therapy. However, future studies are needed to assess these hypotheses and address the potential role of BMI in hemodynamic stability of HD patients.

EPIDEMIOLOGICAL LIMITATIONS WITHIN THE OBESITY PARADOX

It is possible that lower BMI is not a cause but rather a consequence of illness or poor health conditions, which leads to poor outcomes in ESRD patients. Illness and poor health may lead to loss of appetite and muscle wasting which promote a decrease in BMI and higher mortality risk. This opposition of general presumptions of the causal direction is known as reverse causation, and has been posited previously in a similar review by this group (185). However, if observational studies took full account of severity of illness and other clinical characteristics, reverse causation would not fully explain why higher BMI is associated with better outcomes in ESRD patients (41).

Another possible explanation for the obesity paradox is that the change of BMI is not in the causal pathway of the outcomes of ESRD patients, but rather an epiphenomenon that occurs when there is an alteration in a patient's health status (41). In this case, clinical studies would have limited ability to prove the causality of BMI and the survival rate in ESRD patients. However, the obesity paradox does not only occur in ESRD patients, but also exists in other chronic diseases with a preponderance of inflammation (41). Moreover, as shown in Tables 1-3, inverse associations between BMI and mortality were more likely observed in studies with longer follow up time, whereas associations were not as strong or did not exist under shorter follow up times. The long follow up time between BMI and the mortality may mitigate assumptions that the obesity paradox is an epiphenomenon derived from reverse causality. Recurring consistency and other emerging experimental evidence strengthen a potential causal biologic link between BMI and outcomes in ESRD.

The ESRD population represents a unique group of patients with a certain phenotype. It is possible that selection bias in the ESRD population may explain the difference in outcomes observed for obese patients in this population compared to the general population. Typically, CKD patients succumb to complications and mortality sooner than that of the general population. However, among CKD patients who reach ESRD, this group is considered more resilient than their counterparts, and thus may have a survival advantage. Additional studies are needed to more fully understand the obesity paradox in light of these selection biases.

Moreover, studies that have looked at the obesity paradox are observational in design, and thus, causality cannot be established between obesity and survival. Nevertheless, Kalantar-Zadeh et al. (41) used the Bradford Hill criteria as a framework to evaluate the association between obesity and outcomes in CKD patients. Applying Hill's criteria to the obesity paradox, the authors concluded that despite the observational nature of the studies on the obesity paradox, the increasing body of scientific evidence and considerations from Hill's criteria have contributed to a stronger picture of the association between higher body weight and outcomes.

Using a causal diagram or a directed acyclic graph (DAG), we sought to describe the underlying relations between the main exposures of obesity and PEW/cachexia and primary outcomes of survival and death, respectively. Based on existing literature, we accounted for potential confounders of the associations between obesity and survival and PEW/cachexia and death in the DAG models. Figure 3A-B shows the DAGs for the possible causal pathways between (A) obesity and survival and (B) PEW/cachexia and death and the potential confounders. These figures represent the complexity of the relationship between BMI and mortality and call for additional studies using causal modeling to further understand the obesity paradox.

CONCLUSION

While obesity is a well-established risk factor for the development of CVD and poor outcomes in the general population, there is also considerable evidence that its presence is associated with improved outcomes in select patient populations including some with CKD and ESRD. However, the limitations of the studies evaluating the obesity paradox including the use of BMI as a marker of body mass and the potential for residual confounding needs to be acknowledged. It is also important to recognize that obesity may be an indication of underlying mechanisms which are protective against some of the deleterious effects of CKD/ESRD including impaired energy utilization, cachexia and wasting. It is interesting to note that the association of obesity with improved outcomes is most consistent in patients with ESRD being treated with HD. It is also noteworthy that patients on maintenance HD have been shown to have an increased REE and are at great risk for cachexia and PEW. This is in light of mounting evidence linking cachexia to multiorgan dysfunction including cardiomyopathy and higher mortality. There is also experimental evidence, which indicates that treatment and prevention of cachexia can be associated with improved outcomes. Therefore, the findings described as the obesity paradox may be providing investigators with clues, which can be leveraged into novel therapies. The latter point is especially important in

the ESRD population where CVD remains the major cause of mortality, and currently there are no therapies, which have proven to be effective in improving survival.

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Abbreviations:

95% CI	95% Confidence Interval
ANZDATA Registry	Australia and New Zealand Dialysis and Transplant Registry
ASTS	American Society of Transplant Surgeons
BIA/S	bioelectrical impedance analysis/spectroscopy
BMI	body mass index
CANUSA	Canada-US Peritoneal Dialysis Study Group
CKD	chronic kidney disease
CORR	Canadian Organ Replacement Register
CT	computed tomography
CVD	cardiovascular disease
DAG	directed acyclic graph
DEXA	dual energy x-ray absorptiometry
DMMS	Dialysis Morbidity and Mortality Wave II Study
DOPPS	Dialysis Outcomes and Practice Patterns Study
eGFR	estimated glomerular filtration rate
ESRD	end-stage renal disease
HD	hemodialysis
HF	heart failure
HMG-CoA	3-hydroxy-3-methyl-glutaryl-coenzyme A
HR	Hazard Ratio

KT	kidney transplant
LBM	lean body mass
LDL	low density lipoprotein
MRI	magnetic resonance imaging
MSM	Marginal Structural Model
NECOSAD	Co-operative Study on the Adequacy of Dialysis-2
NIR	near-infrared interactance
OR	Odds Ratio
PD	peritoneal dialysis
PEW	protein energy wasting
REE	resting energy expenditure
RR	Relative Risk
SD	standard deviation
UCP1	uncoupling protein-1
UNOS database	United Network for Organ Sharing
US	United States of America
USRDS	United States Renal Data System
VA	Veterans Administration
WC	waist circumference

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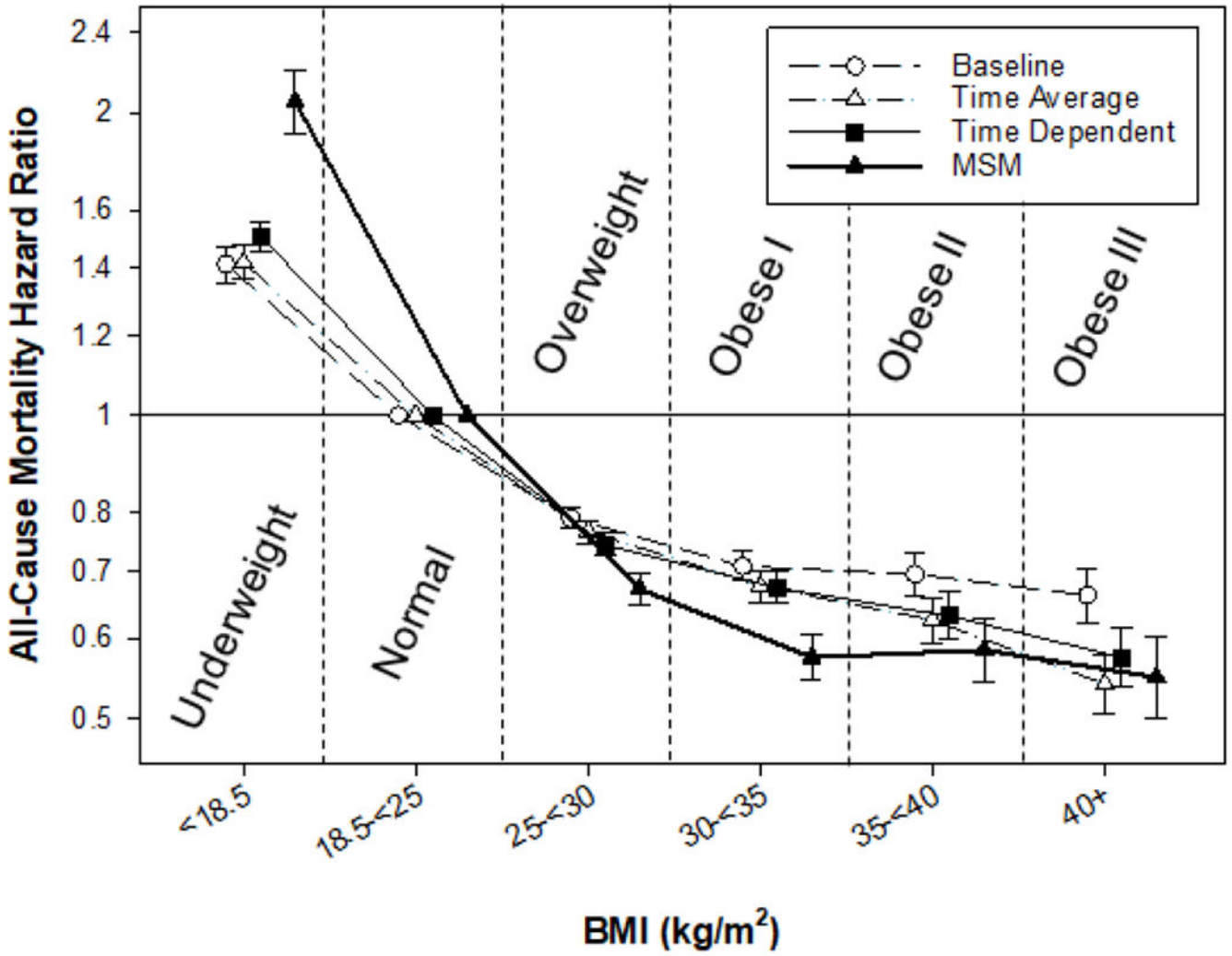

Figure 1.

Associations of body mass index categories with all-cause mortality from baseline, time-average, time-varying and marginal structural models in a cohort of 123,624 hemodialysis patients. Models adjusted for case-mix covariates and markers of malnutrition and inflammation.

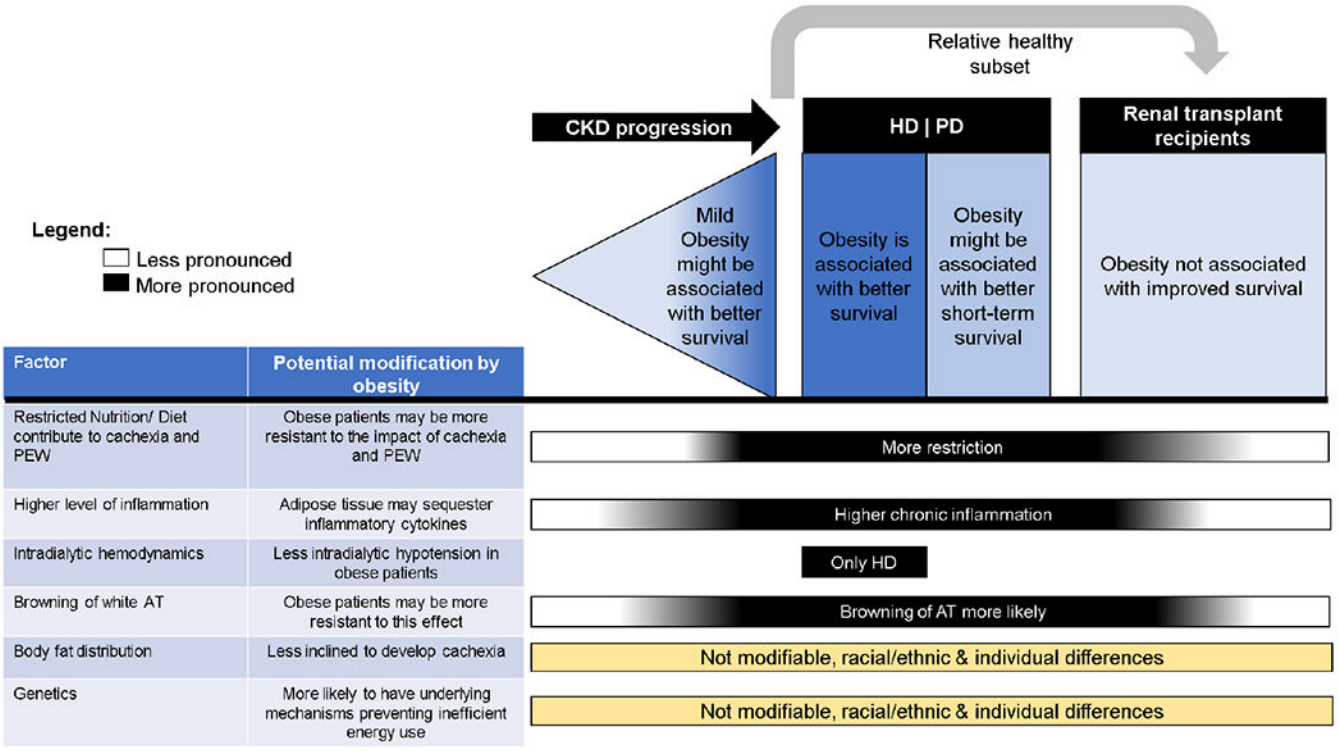

Figure 2.

Changes in the obesity-mortality association and possible underlying mechanisms (factors) in different stages of CKD/ESRD.

Abbreviations:

AT – adipose tissue, CKD – chronic kidney disease, ESRD – end-stage renal disease, HD – hemodialysis, PD – peritoneal dialysis, PEW – protein-energy wasting

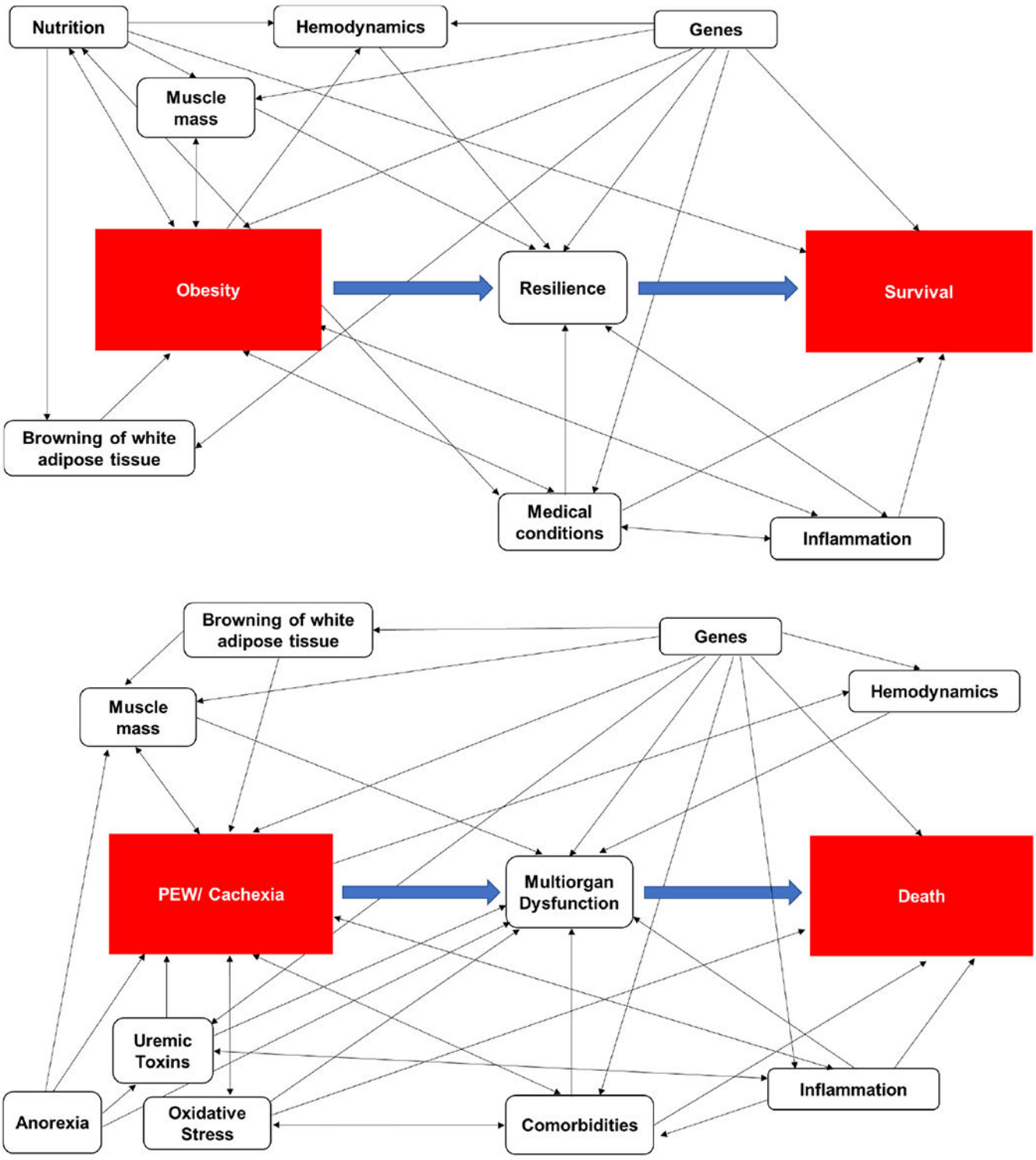

Figure 3.

(A) Directed acyclic graph (DAG) explaining the relationship between obesity (exposure) and survival (outcome). A head-to-tail arrow indicates a possible association from one variable to another. A bidirectional arrow represents an association between two variables

with an unknown common cause. Variables (i.e., nutrition, muscle mass, hemodynamics, genes, resilience, browning of white adipose tissue, medical conditions and inflammation) in the DAG are potential confounders.

(B) Directed acyclic graph (DAG) explaining the relationship between PEW/cachexia (exposure) and death (outcome). A head-to-tail arrow indicates a possible association from one variable to another. A bidirectional arrow represents an association between two variables with an unknown common cause. Variables (i.e., muscle mass, anorexia, uremic toxins, oxidative stress, medical conditions, inflammation, multiorgan dysfunction, browning of white adipose tissue, genes and hemodynamics) in the DAG are potential confounders.

Table 1.

Summary of studies with large sample size (>1,000 individuals) evaluating the association between BMI and mortality outcomes in CKD patients

Study	Patients (n)	F/U* (y)	Results
Madero et al, 2007 (80)	1,759	10	No significant difference in all-cause mortality risk between higher BMI groups (BMI 25->40) compared to normal weight group (BMI 18.5-24.9 kg/m^2)
Weiner et al, 2008 (86)	1,678	9	No significant association between increase in BMI (per 5 kg/m^2) and all-cause mortality
Elsayed et al, 2008 (92)	13,324	up to 9.3	Each SD increase in BMI reduced the risk of the composite outcome (HR 0.94, 95% CI 0.90-0.99)
Obermayr et al, 2009 (84)	49,398 (392 Moderate CKD)	5.5	Compared to the BMI of 25 kg/m^2, a higher risk of cardiovascular death in participants with BMI 20 kg/m^2 (HR, 1.35), BMI 30 kg/m^2 (HR, 1.37) and BMI 35 kg/m^2 (HR, 2.05)
Kramer et al, 2011 (91)	5,805	4	Every 1-kg/m^2 increase in BMI was related to a 3% reduction in mortality risk (95% CI, 0.94-0.99) and each 1-cm increase in waist circumference was associated with a 2% higher mortality risk (95% CI, 1.01-1.04)
Dalrymple et al, 2011 (81)	1,268	9.7	BMI <18.5 kg/m^2 was associated with higher mortality, but higher BMI groups had similar mortality risk of the reference group (18.5-24.9 kg/m^2)
De Nicola et al, 2012 (87)	1,248	5.2	No significant association between BMI (continuous parameter) and mortality
Bello et al, 2013 (83)	393,659 (54,403 CKD patients)	up to 30 days	Higher odds for 30-day mortality following an eligible procedure in obese CKD (BMI ≥35 kg/m^2 and eGFR <60 mL/min/1.73 m^2) when compared to non-obese non-CKD patients in unadjusted and adjusted models (OR 5.51, 95% CI 4.48-6.79 and OR 1.49, 95%CI 1.18-1.87, respectively)
Babayev et al, 2013 (88)	12,534	up to 8	BMI between 30-34.9 kg/m^2 was associated with improved survival (HR, 0.74) when compared to CKD patients with BMI <30 kg/m^2
Ricardo et al, 2013 (82)	2,288	13	Participants with BMI 18.5-<22 kg/m^2 had a higher mortality hazard rate (HR, 1.3). In contrast higher BMI was not associated with a significant different mortality risk when compared to BMI 22-<25 kg/m^2
Hanks et al, 2013 (95)	4,374	4.5	Metabolic healthy overweight (BMI 25-29.9 kg/m^2) CKD patients had statistical significant lower all-cause mortality (HR, 0.74) in the fully adjusted model compared to metabolic healthy normal weight (BMI 18.5-24.9 kg/m^2)
Lu et al, 2014 (89)	453,946	-	BMI had an U-shaped association (higher mortality in the lower and higher BMI groups) with all-cause mortality (reference group 30-<35 kg/m^2)
Huang et al, 2015 (90)	3,320	2.9	Male participants with BMI <22.5 kg/m^2 and BMI of 30.1-35 kg/m^2 had higher risk of all-cause mortality (reference BMI 27.6-30 kg/m^2) but not in females
Navaneetha n et al, 2016 (85)	54,506	3.7	CKD patients (mostly CKD stage III) with 25<BMI<39.9 kg/m^2 had lower risk of cardiovascular, malignancy, non-cardiovascular/ non-malignancy related death compared to the BMI of 18.5-24.9 kg/m^2
Sato et al, 2017 (93)	27,978	up to 4	Increase of 1 SD in a body shape index associated with a higher risk for all-cause mortality in male CKD patients but not in females

*Duration of follow-up as reported by the authors. If not indicated mean or median reported.

Table 2.

Summary of studies with large sample size (>1,000 individuals) evaluating the association between BMI and mortality outcomes in HD patients

Study	Patients (n)	F/U* (y)	Results
Degoulet et al, 1982 (12)	1,453	2,063 person-years	A high BMI was not found to be associated with significantly higher all-cause and CV mortality
Leavey et al, 1998 (13)	3,607	up to 5	Lower BMI was associated with higher mortality risk as an independent risk factor; whereas higher BMI was not associated with higher mortality risk
Fleischmann et al, 1999 (14)	1,346	up to 1	With every one unit increase in BMI over 27.5 kg/m^2 the relative risk of mortality was decreased by 30% , and with every one unit of BMI lower than 20 kg/m^2, the relative risk was higher by 1.6-fold
Kopple et al, 1999 (15)	12,965	up to 1	A progressive decrease in mortality with an increase in weight to height ratio
Wolfe et al, 2000 (16)	9,165	up to 2	Larger body size was associated with lower mortality risk
Leavey et al. 2001 (17)	9,714	up to 4	Increasing body size associated with a decreased mortality risk even in the healthier subgroups with mild to moderate obesity
Lowrie et al. 2002 (18)	43,334	-	There was a reversed J-shape association between mortality and weight to height ratio and BMI.
Pifer et al, 2002 (19)	7,719	up to 0.5	A significantly higher risk of mortality was observed in patients with lower BMI and a high BMI seemed to have protective effect
Port et al, 2002 (20)	45,967	up to 2	Mortality risk was 42% higher in group with the lowest BMI than the highest tertile. Higher dialysis dose; above the dialysis outcomes quality initiative guidelines (Urea Reduction Ratio >65%), was associated with lower mortality in all body-size groups
Beddhu et al, 2003 (21)	70,028	105,042 person-years	Protective effect of high BMI was limited to those patients with normal or high muscle mass and high BMI patients with inferred high body fat had higher and not lower mortality
Glanton et al, 2003 (22)	151,027	1.7	Obesity was independently associated with reduced risk of mortality, particularly in African Americans
Johansen et al, 2004 (23)	418,055	2	High BMI was associated with greater survival even at extremely high BMI after adjustment for demographic, laboratory, and comorbidity data in all ethnic groups except Asian Americans
Abbott et al, 2004 (96)	1,675	up to 5.8	5-year survival for patients with BMI ≥ 30 kg/m^2 was 39.8% vs. 32.3% for lower BMI
Stack et al, 2004 (97)	117,309	1	The adjusted RR of death was greatest for patients with BMI ≤ 20.9 kg/m^{2}and lowest for patients with BMI >30.0 kg/m^2 in HD patients compared with the reference (BMI 23.5-26.1 kg/m^2)
Kalantar-Zadeh et al, 2005 (25)	54,535	up to 2	Obesity, including morbid obesity, and progressive weight gain were associated with improved survival even after adjusting for variation in BMI and laboratory values over time
Johansen et al, 2006 [156]	2,467	-	Although higher BMI was associated with enhanced survival, physical function impairment by obesity adversely affected health status
Chazot et al, 2009 (26)	5,592	2	Confirmed existence of obesity paradox and showed reduced survival in those who were in the lower quintile of body weight variation
Kalantar-Zadeh et al, 2010 (27)	121,762	up to 5	Higher BMI (up to 45 kg/m^2) and higher serum creatinine concentration were progressively and independently associated with improved survival and muscle gain with weight loss over time may be associated with better survival in contrast to weight gain while losing muscle
Yen, et al, 2010 (28)	959	up to 3	A higher mortality risk in HD patients who were underweight

Study	Patients (n)	F/U* (y)	Results
Hall et al, 2011 (29)	21,492	up to 13	Asians, Pacific Islanders and non-Hispanic Whites showed improved survival with higher BMI and HD patients waiting for kidney transplantation have better survival due to less severe co-morbidities
Molnar et al, 2011 (30)	14,632	2.5	Better survival in higher (>25 kg/m^2) than lower (<22 kg/m^2) BMI in transplant-waitlisted hemodialysis patients and higher risk of mortality in those with unintentional weight or muscle loss
Ricks et al, 2011 (31)	109,605	up to 6	Higher BMI was associated with higher survival in all three racial/ethnic groups – non-Hispanic white, Hispanic, and African American. Hispanic and African American patients experienced greater survival than non-Hispanic whites across higher BMI categories and African American HD patients showing the largest consistent decrease in death HR with increasing BMI
Kalantar-Zadeh et al, 2012 (33)	121,762	up to 5	A considerable proportion of the obesity paradox in dialysis patients might be explained by the amount of decline in muscle mass
Hoogeveen et al, 2012 (32)	1,749 (1,087 HD)	up to 7	Age-standardized mortality rate was higher in obese younger patients than those with normal BMI (OR 1.7, 95% CI 1.1-2.9)
Park et al 2013 (34)	40,818	5.9	Race (Asian, white, African American) does not affect the protective effect of larger body size and muscle mass in HD patients
Cabezas-Rodriguez et al, 2013 (99)	6,797	up to 3	Weight loss or gain (<1% or >1% of body weight) was strongly associated with higher rates of mortality or survival, respectively. In obese patients, the association between weight loss and mortality was attenuated, no survival benefit of gaining weight was seen
Vashistha et al, 2014 (36)	123,383	up to 8	Higher BMI was associated with lower death risk across all age groups and was more pronounced in those younger than 65 years
Calabia et al, 2015 (37)	6,290	up to 8	No survival benefit for higher BMI values in young patients
Doshi et al, 2016 (38)	123,624	up to 6	A BMI of <18 kg/m^2 was associated with a 3.2-fold higher death risk; mortality risks declined with increasing BMI with the greatest survival advantage of 31% lower risk at a BMI of 40 to <45 kg/m^2

*Duration of follow-up as reported by the authors. If not indicated mean or median reported.

Table 3.

Summary of studies with large sample size (>500 individuals) evaluating the association between BMI and mortality outcomes in PD patients

Study	Patients (n)	F/U* (y)	Results
McDonald et al, 2003 (105)	9,679	17,973 person-years	BMI≥30 kg/m^2 was associated with higher mortality and technique failure; there was a J-shaped association between BMI and mortality with lowest mortality risk for patients with BMI close to 20 kg/m^2
Snyder et al, 2003 (111)	41,197	up to 3	Overweight and obese participants had a survival benefit compared to those with lower BMI
Abbott et al, 2004 (96)	1,662	up to 5.8	BMI ≥30 kg/m^2 was not related to improved 5-year survival
Stack et al, 2004 (97)	17,419	1	No survival advantage with higher BMI values
Ramkumar et al, 2005 (114)	10,140	17,500 patient-years	Patients with a BMI≥ 25 kg/m^2 and high muscle mass, had a 10% lower hazard ratio of all-cause mortality
Pliakogiannis et al, 2007 (108)	4,054	4.3	BMI >30 kg/m^2 had neither higher nor lower mortality risk than the reference group (BMI 19-24.9 kg/m^2)
de Mutsert et al, 2009 (109)	688	up to 5	BMI≥30 kg/m^2 did not have statistically significant difference in mortality risk than normal BMI (18.5-25 kg/m^2)
Mehrotra et al, 2009 (112)	66,381	up to 10	Higher BMI quartiles were related to lower mortality but higher technique failure (reference BMI<21.88 kg/m^2)
Fernandes et al, 2013 (113)	1,911	up to 2.8	BMI <18.5 kg/m^2 had a higher death risk while a BMI >30 kg/m^2 was associated with a survival benefit, also weight reduction in the first year of dialysis of <−3.1% was associated with significant higher mortality
Park et al, 2013 (117)	10,896	5.9	Patients with serum creatinine levels≥ 10 mg/dL had lower mortality risk compared to serum creatinine levels of 8-9.9 mg/dL, accordingly higher muscle mass might be associated with better survival
Kim et al, 2014 (107)	900	2	Increased BMI was not associated with higher mortality
Badve et al, 2014 (35)	6,162	2.3	Survival advantage was seen only for patients with time-varying BMI between 28.1-31 kg/m2 (reference group time-varying BMI 25.1-28 kg/m^2)
Xiong et al, 2015 (106)	1,263	2.1	Obesity was associated with a higher cardiovascular mortality risk in multivariate analysis in Chinese patients and BMI decline >0.8% during the first year after PD initiation had higher cardiovascular and all-cause mortality hazard ratios (reference group Δ −0.8% to 2.69%)
Obi et al, 2017 (110)	15,573	up to 2	U-shaped association between BMI and mortality with best survival in 30-<35 kg/m^2 strata

*Duration of follow-up as reported by the authors. If not indicated mean or median reported.

Table 4.

Summary of studies with large sample size (>1,000 subjects) evaluating the association between BMI and mortality outcomes in kidney transplant patients

Study	Patients (n)	F/U* (y)	Results
Meier-Kriesche et al, 2002 (130)	51,927	-	BMI was strongly associated with renal post-transplant outcomes. BMI<18 or>36 kg/m^2 were associated with worse patient and graft survival
Gonzales-Posada et al, 2006 (124)	3,365	up to 3	Pre-KT BMI had no significant effect on post-transplant mortality
Aalten et al, 2006 (186)	2,067	2	Pre-KT BMI greater than 28 kg/m^2 was associated with increased mortality risk
Chang et al, 2007 (125)	5,684	up to 5	Obesity was not associated with higher risk of graft loss or patient death in multivariate model
Aalten et al, 2008 (129)	2,187	8	Pre-KT BMI was an independent predictor for post-transplantation cardiovascular events but not for all-cause mortality
Hoogeveen et al, 2011 (126)	1,810	8.3	One year post-transplant obesity and BMI increment had higher relative risk of death and death censored graft failure (reference BMI 20.1-25 kg/m^2) but no association between pre-KT BMI and death
Streja et al, 2011 (123)	10,090	up to 5	Higher pre-KT serum creatinine level (larger muscle mass) was associated with better graft and patient survival; whereas BMI was not significantly associated with higher or lower mortality
Cannon et al, 2013 (135)	74,983	5	30≤BMI<35 kg/m^2 was associated with reduced hazard of death (reference BMI<30 kg/m^2)
Hatamizadeh et al, 2013 (132)	145,470 (15,667 >65y)	3.9	Pre-KT BMI>30 kg/m^2 in elderly (≥75y) was associated with higher all-cause mortality (reference BMI≤30 kg/m^2)
Curran et al, 2014 (127)	1,151	4405 patient-years	BMI>35 kg/m^2 was associated with higher all cause graft failure (reference BMI 20-24.9 kg/m^2) but not significantly associated with death with graft function
Pieloch et al, 2014(128)	30,132	up to 3	Morbid obesity (BMI 35-40 kg/m^2) did not independently predict higher graft failure or mortality rates

*Duration of follow-up as reported by the authors. If not indicated mean or median reported.