Racial and Ethnic Disparities in the Obesity Paradox

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Obesity is a major risk factor for cardiovascular disease and worse survival in the general population. However, in patients with end-stage renal disease (ESRD), higher body mass index and indexes of body fat and muscle are associated with better survival. Furthermore, these associations, which some have described as the obesity paradox, are more consistent in African American patients being treated with hemodialysis when compared with other racial-ethnic groups. This is in view of data indicating that although the rate of progression to ESRD is faster in African American patients, they have a survival advantage after transition to ESRD when compared with their white counterparts. These observations indicate that there may be significant interaction between race/ethnicity and association of body mass index with outcomes in patients with ESRD. In addition, it is possible that mechanisms underlying improved survival in African American hemodialysis patients are partly related to the association of body mass index with outcomes observed in this patient population. Some of these potential mechanisms may include comparatively reduced risk for protein-energy wasting and malnutrition, possible salutary effects of factors that play a role in energy preservation, resistance to deleterious effects of inflammation, and enhanced muscle mass and body composition. Given that ESRD is associated with significantly increased risk for morbidity and mortality, understanding the pathophysiologic mechanisms responsible for the obesity paradox across race-ethnic populations might help identify potential therapeutic targets that can be used to improve survival in this patient population.

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Am J Kidney Dis. 72(5)(Suppl 1):S26-S32.

doi: 10.1053/j.ajkd.2018.06.024

Introduction

Obesity, as defined by body mass index (BMI) ≥ 30 kg/m^2, is a serious health care challenge given its association with significantly increased morbidity and mortality, especially from cardiovascular disease.[1] In contrast, numerous reports have indicated that in patients with end-stage renal disease (ESRD), obesity can be associated with better survival,[2-10] an observation that some have described as the obesity paradox. According to data from the US Renal Data System, ~20% of incident patients with ESRD have BMI ≥ 30 kg/m^2, with the highest rates being found among African Americans (25%).[11] One of the first studies to observe the obesity paradox was in a cohort consisting of 89% African American hemodialysis (HD) patients, which found that overweight HD patients (BMI > 27.5 kg/m^2) had higher survival rates than patients with normal BMI.[2] Although the obesity paradox has been consistently observed across racial-ethnic subgroups in additional large cohorts (Table 1), some studies have found racial differences in the strengths of these associations. These observations indicate that the underlying mechanisms responsible for the obesity paradox are complex, and patient-specific factors such as race, ethnicity, genetic, and environmental features may play a substantial role in the association of BMI with outcomes. Understanding these factors may be helpful in addressing increased ESRD-related mortality.

Impact of Race and Ethnicity on the Obesity Paradox

It has been reported that patients of African American and Hispanic background have 1.5 to 3.5 times higher incidence rates of ESRD.[12] However, published data suggest that when on dialysis therapy, African American and Hispanic patients have a survival advantage,[12] a phenomenon known as the racial paradox.[13] These findings have sparked a search for potential factors that may explain this survival benefit. Ricks et al[3] examined BMI-mortality associations across racial-ethnic subgroups and found that African Americans and Hispanics with BMI ≥ 40 kg/m^2 had the lowest death hazard ratio (HR) compared with non-Hispanics whites with BMI of 23 to <25 kg/m^2 (HRs of 0.63 [95% CI, 0.58-0.70] and 0.57 [95% Cl, 0.49-0.68], respectively). Additionally, Glanton et al[4] found that the association of BMI ≥ 30 kg/m^2 with lower death risk was strongest in African Americans. Doshi et al[5] tested the robustness of the obesity paradox using marginal structural model analyses, a technique that accounts for time-varying confounders, in a large cohort of HD patients. Although they found an inverse BMI-mortality association in all racial-ethnic subgroups, there was markedly lower risk for mortality among African Americans with BMI > 27.5 kg/m^2 compared with the other groups.

This greater benefit in African American patients is also a consistent observation when examining other metrics that account for body size, such as lean body mass (LBM). Wang et al[6] examined associations between calculated LBM and mortality across racial-ethnic subgroups and similarly found an inverse linear relationship between LBM and mortality even after adjustment for markers of malnutrition and inflammation, except in Hispanic patients. Moreover, these effects were found to be stronger in African Americans when compared with non-Hispanic whites.

The impact of race on the interaction between BMI and outcomes is also highlighted in patients of Asian ancestry. Johansen et al[7] found an association between obesity and improved survival in African American, Hispanic, and

Table 1. Summary of Studies Evaluating the Impact of Race/Ethnicity on the Association Between BMI and Outcomes

Study	N	Setting	Race/Ethnicity[a]	Modality	Results
Wong et al[8] (1999)	84,192	USA	Asian, white	HD/PD	In Asians, U-shaped association between BMI and mortality, with higher mortality risk (mortality risk ratio) in lowest and highest BMI groups
Glanton et al[4] (2003)	151,027	USA	African American, white	HD (87.9%)/PD	BMI ≥ 30 kg/m^2 correlated to reduced mortality; stronger association in African Americans
Johansen et al[7] (2004)	418,055	USA	African American, Asian (± Pacific Islanders), Hispanic, white	HD/PD	Higher BMI associated with lower mortality rate in African Americans, Hispanics, and whites but not Asians; adjustment for LBM (formula based) did not significantly alter results
Ricks et al[3] (2011)	109,605	USA	African American, non-Hispanic, white, Hispanic	HD	Higher BMI associated with survival benefit in African Americans, Hispanics, and whites; strongest association per kg BMI in African Americans
Hall et al[10] (2011)	21,492	USA/US territories/Mariana Islands	Asian (Asian Indian, Chinese, Filipino, Japanese, Korean, Vietnamese), Pacific Islander (Chamorro, Native Hawaiian, Samoan, other Pacific Islanders), non-Hispanic white	HD/PD	Higher BMI associated with lower mortality among Pacific Islanders, most Asians (exception: Filipinos), and whites
Park et al[9] (2013)	40,818	USA/South Korea	African American, Asian (South Korean), white	HD	Lower mortality risk across higher BMI levels in all 3 groups
Wang et al[6] (2016)	117,683	USA	African American, Hispanic, non-Hispanic white	HD	Higher LBM (Scr-based formula) associated with lower mortality risk in African Americans and non-Hispanic whites; in Hispanics, U-shaped association: lower and higher LBM not protective
Doshi et al[5] (2016)	123,624	USA	African American, Hispanic, non-Hispanic white (for subgroup analysis)	HD	Inverse relationship between BMI and mortality in African Americans, Hispanics, non-Hispanic whites; lower risk for mortality among African Americans with BMI > 27.5 kg/m^2

Abbreviations: BMI, body mass index; HD, hemodialysis; LBM, lean body mass; PD, peritoneal dialysis; Scr, serum creatinine.
[a]Race/ethnicity was determined by self-identification, except in Park et al (2013), who did not specify the method for South Korea participants.

white patients with ESRD, but not in Asian living in the US (reference group: BMI of 22-<25 kg/m^2). These results remained significant after adjustment for LBM. Wong et al[8] also found a U-shaped relationship between BMI and mortality in Asian American dialysis patients, with the lowest mortality risk observed in the middle BMI quintile of ~22.5 kg/m^2.

However, it should be noted that environment may also play a role in the interaction of obesity with race/ethnicity, and their association with outcomes. This is demonstrated in a study by Park et al,[9] who matched a large cohort of African American and white patients with ESRD being treated with HD in the US to a similar group of patients in South Korea and confirmed that mortality risk was lower across higher BMI levels in all 3 races (reference group: BMI > 25 kg/m^2). Hall et al[10] provided further details on body size associations across race by differentiating between US Asians (Asian Indian, Chinese, Filipino, Japanese, Korean, and Vietnamese) and Pacific Islanders (Chamorro, Native Hawaiian, Samoans, and other Pacific Islanders) given that inclusion of these groups into a single category may ignore relevant differences between these racial/ethnic backgrounds. Except for patients with Filipino ancestry, most US Asians and Pacific Islanders with greater BMI (vs the reference group of BMI < 18.5 kg/m^2) had lower risk for mortality. Therefore, racial-ethnic category classification alone may not be sufficient to explain these differences, and other factors such as country of origin and environment may also play an important role in these observations.

This important point is also relevant when evaluating African American or Hispanic HD patients of different ancestry. For instance, among African American patients, the frequency of apolipoprotein L1 (APOL1) genetic variants, which can be related to the place of origin in their African ancestry, can have an impact on progression of

chronic kidney disease (CKD) and survival.[14] Moreover, Moradi et al[15] found differences in the association of serum lipid levels with outcomes in HD patients of Hispanic origin depending on whether they resided on the West or East Coast of the US. These differences may be reflective of the fact that patients classified as Hispanic on the East Coast have more individuals of Afro Caribbean ancestry, whereas those on the West Coast are more likely to be Mexican American. Therefore, self-reported racial and ethnic classification of patients may not account for important genetic and environmental differences that exist within each racial and ethnic group. These differences can introduce unmeasured confounding, which will need to be carefully considered when evaluating the association of obesity with outcomes in the ESRD population.

Potential Mechanisms Underlying the Obesity Paradox

The potential mechanisms that may play a role in the ESRD-related obesity paradox may be linked to physiologic characteristics or pathways counteracting the many deleterious complications of ESRD/HD. Select potential mechanisms are summarized in Table 2 and are further discussed here.

Browning of White Adipose Tissue

Type of adipose tissue might play a crucial role in the obesity paradox. Whereas white adipose tissue is known for energy preservation and associated with obesity, brown adipose tissue has been implicated in inefficient energy use and a lean body phenotype. Although there has not been a study to date that has evaluated and compared the total-body content of brown adipose tissue in patients with ESRD, there is some indirect evidence that browning of adipose tissue is occurring in this condition. This is suggested through studies showing increased energy expenditure in patients with ESRD, which is associated with increased mortality and cardiovascular disease.[16,17] Furthermore, browning of white adipose tissue has been shown to occur in a mouse model of CKD, thereby leading to inefficient energy expenditure and increased risk for cachexia/wasting.[18,19]

Therefore, it is possible that patients with higher BMI have mechanisms in place that prevent inefficient energy expenditure and browning of white adipose tissue, thereby reducing their risk for cachexia. For instance, overactivity of the endocannabinoid system, a key player in physiologic energy preservation, can increase the risk for obesity while also preventing brown adipose tissue formation and pathogenesis of wasting/cachexia.[20] Future studies are needed to elucidate the potential role and possible interaction of race/ethnicity with these pathways.

Protein-Energy Wasting and Inflammation

Protein-energy wasting (PEW) refers to the loss of body protein and other nutritional factors leading to reduced muscle and fat mass and is frequently observed in patients with CKD.[21] The pathophysiology of PEW is complex and can be related to a variety of factors, including malnutrition, uremia, and inflammation.[21] Many of these factors can be interrelated, with one causing and being caused by the other. For instance, in maintenance HD patients, inflammation, as indicated by higher C-reactive protein

Table 2. Selected Possible Mechanisms Underlying the Obesity Paradox

Hypothesis	Summary of Mechanism	Race/Ethnical Disparities in CKD/ESRD
Obesity may indicate less browning of white adipose tissue	Browning of white adipose tissue may result in inefficient energy use and increased risk for wasting/cachexia[18,19]; possible mechanisms may involve the endocannabinoid system, which plays a role in energy preservation[20]	To be determined
Adipose tissue may moderate inflammation by synthesis of pro- and anti-inflammatory cytokines and hormones	Adipose tissue synthesis of pro- and anti-inflammatory cytokines and hormones[24]; soluble TNF-α receptor produced by adipose tissue might neutralize negative effects of TNF-α[27]; good nutrition status may affect survival more strongly than obesity-associated oxidative stress, inflammation, and atherosclerosis[34]	Inflammation status might differ between racial/ethnic groups[35-37]; further research needed
Regional fat distribution might affect outcomes	Central fat has been linked to higher cardiovascular risk and metabolic complications[20]; in the non-CKD population, differences in fat distribution across racial/ethnical groups have been described[38,39]	To be determined
Higher levels of fetuin A might promote obesity and reduce mortality	Low fetuin A levels are associated with malnutrition, inflammation, atherosclerosis, and mortality[41]; high fetuin A levels are associated with obesity in CKD[40]; inflammation might reduce fetuin A synthesis[44]	Association of fetuin A levels and mortality might differ between racial/ethnic groups,[41,43] but further research is warranted
Obese patients could have more stable hemodynamics attenuating hemodynamic stress	Obese non-CKD patients have a mitigated neuroendocrine response to hemodynamic stress[30]; extrapolation of data could suggest that obese hemodialysis patients are more resistant to hemodynamic instability, such as dialysis-mediated fluid removal	To be determined

Abbreviations: CKD, chronic kidney disease; ESRD, end-stage renal disease; TNF-α, tumor necrosis factor α.

and tumor necrosis factor α (TNF-α) levels, has been shown to be associated with malnutrition and increased mortality.[22] Meanwhile, inflammation is a crucial contributor to the development of PEW and can be caused by malnutrition and depletion of body antioxidants due to uremia or the dialysis procedure.[23] Therefore, the PEW complex is the result of many interlinked factors, for which the interaction ultimately can result in increased risk for mortality.

The role of obesity and adipose tissue in these processes can be complex. Although adipose tissue is thought to be a source of hormones and cytokines that can be associated with inflammation and cardiovascular disease, in patients with ESRD, this can be more complicated.[24] For instance, in patients on HD therapy, lower leptin and higher adiponectin levels have been observed to be paradoxically associated with PEW, and the latter, with higher risk for death.[25,26] In addition, adipose tissue may also generate soluble TNF-α receptors, which may neutralize the adverse effects of the proinflammatory cytokine TNF-α.[27] Given that inflammation can induce muscle proteolysis and sarcopenia through various mechanisms,[28] loss of body fat, which can counteract some of these mechanisms, can increase the risk for mortality.[29-31] This is especially important in a condition such as ESRD, which is marked by a proinflammatory state.

Additionally, it is possible that in patients with ESRD, decreased body mass and fat content are manifestations of malnutrition that can be linked to inflammation[32,33] and PEW and thereby worse outcomes. Accordingly, patients with higher BMI may have better nutritional and energy reserves, leading to decreased risk for PEW/cachexia and hence a survival advantage. Beddhu[34] postulated that the protective effect of good nutritional and energy reserves could be stronger than the negative effects of adipose tissue–associated inflammation, oxidative stress, and atherosclerosis. In this regard, a study by Streja et al[35] found that race-mortality associations (African American and Hispanic as compared to non-Hispanic white) were attenuated or reversed after adjustment for markers of the malnutrition-inflammation complex, including BMI. Other data in HD patients suggest that there might be differences in inflammatory characteristics across racial/ethnic groups.[36,37]

Regional Fat Distribution

Accumulating evidence suggests that distribution of body fat plays a key role in its association with outcomes; namely, central fat distribution has been shown to be associated with higher risk for cardiovascular disease and metabolic complications.[20] In the general population, regional fat distribution differs based on racial/ethnic groups,[38,39] and a more favorable body composition at higher BMI (ie, higher LBM index[6]) may partly explain the consistently better survival observed in obese African American patients with ESRD. However, further research is needed to determine whether racial/ethnic differences in regional fat distribution in CKD and ESRD might be contributing to the obesity paradox.

Obesity and Fetuin A

Another potential mechanism underlying the obesity paradox may be related to fetuin A. Elevated levels of this protein (also known as α2-Heremans-schmid glycoprotein [AHSG]) have been shown to be associated with increased obesity in stage 5 CKD.[40] Low fetuin A levels have been found to be associated with malnutrition, inflammation, atherosclerosis, and increased mortality in a cohort of mainly white patients with ESRD.[41] A study that examined a small cohort of 17 African American patients on long-term HD therapy found a strong inverse correlation between serum fetuin A levels and coronary artery calcium scores.[42] Additionally, Wang et al[43] found a significant inverse association between fetuin A level and mortality in a cohort of 238 Chinese peritoneal dialysis patients, but associations were attenuated in models adjusted for cardiovascular comorbid conditions, inflammation, and malnutrition. Furthermore, there are studies in maintenance dialysis patients that indicate that low circulating fetuin A levels may be partly driven by proinflammatory cytokines, thereby linking this protein to ESRD-related inflammation and malnutrition.[44] Future studies will need to clarify the potential interaction between race/ethnicity and serum fetuin A levels and their impact on the obesity paradox.

More Stable Hemodynamics in Obese ESRD Patients

Progression of ESRD is often accompanied by decreased urine output and anuria. Hence, patients being treated with HD often have fluid overload. Treatment of this condition involves ultrafiltration, which is associated with intradialytic hypotension and adverse hemodynamic effects, including myocardial stunning.[45] Furthermore, intradialytic hypotension has been linked to increased risk for mortality.[45] It has been shown that neuroendocrine response to hemodynamic stress is attenuated in obese patients without CKD.[30] Extrapolation of these data could indicate that obese HD patients may be more resistant to the hemodynamic effects of dialysis-related ultrafiltration. Future studies will need to evaluate this mechanism in obesity-related racial/ethnical outcomes in patients with ESRD.

Potential Limitations of the Obesity Paradox

Although the obesity paradox has been found in a number of large epidemiologic studies, critics of this phenomenon believe that the observed associations may be related to epidemiology modeling, such as reverse causation, selection bias (survivor bias), competing death risk, and residual confounding.[30] An important

confounder might be the utility of BMI as a surrogate for estimating body adipose tissue content given that BMI does not discriminate between body fluid, adipose tissue, or muscle tissue.[30] However, despite these limitations, repeated analyses examining the relationship between BMI and mortality using several different epidemiologic models (including a marginal structural model) accounting for many confounders in large cohorts robustly show similar associations of improved survival for patients with higher BMI.[5,46-48] It should also be noted that associations between BMI and mortality are less consistent in peritoneal dialysis cohorts,[49,50] indicating that these observations may be partly related to factors unique to HD therapy. Furthermore, differences in these associations across all racial-ethnic subgroups have not been fully examined using advanced causal models, and future studies are needed to address these important considerations.

Brief Perspective

The obesity paradox has been reported in a large portion of patients with ESRD on HD therapy across racial and ethnic backgrounds. However, these findings appear to be most consistent in African American patients on maintenance HD therapy. Although limitations of epidemiologic studies will need to be acknowledged, it is also likely that these associations may be related to important underlying pathophysiologic mechanisms that affect the pathogenesis of cachexia, PEW, malnutrition, and inflammation. In this regard, future areas of research should include further evaluation of browning of white adipose tissue in ESRD, genetic characteristics associated with obesity such as fetuin A, and the association between obesity and inflammation. In addition, the role of regional fat distribution and its impact on hemodynamics across racial-ethnic populations will need to be further delineated. Identifying the unique racial/ethnic features of the obesity paradox can help us better understand these mechanisms/pathways and not only provide new markers of risk, but also serve as novel therapeutic targets to improve survival in the ESRD population.

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Support: This article is part of a supplement that arose from the Frank M. Norfleet Forum for Advancement of Health: African Americans and Kidney Disease in the 21st Century, held March 24, 2017, in Memphis, TN. The Forum and the publication of this supplement were funded by the Frank M. Norfleet Forum for Advancement of Health, the Community Foundation of Greater Memphis, and the University of Tennessee Health Science Center. The work described in this article was supported by National Institutes of Health (NIH)/National Institute of Diabetes and Digestive and Kidney Diseases grant K24-DK091419 (Dr Kalantar-Zadeh), philanthropic grants from Mr. Harold Simmons (Dr Kalantar-Zadeh), and by career development award 1 IK CX 001043-01A2 from the Office of Research and Development of the Department of Veterans Affairs (VA ORD; Dr Moradi).

Financial Disclosure: Dr Kalantar-Zadeh has received honoraria and/or support from Abbott, Abbvie, Alexion, Amgen, American Society of Nephrology, Astra-Zeneca, AVEO, Chugai, DaVita, Fresenius, Genetech, Haymarket Media, Hospira, Kabi, Keryx, NIH, National Kidney Foundation, Relypsa, Resverlogix, Sanofi, Shire, Vifor, and ZS-Pharma. Dr Moradi has received grant funding from the NIH, VA ORD, and Novartis. Dr Streja has received grant funding from the VA. The remaining authors declare that they have no relevant financial interests.

Peer Review: Received January 31, 2018, as part of a supplement invited by the journal. Evaluated by 3 external peer reviewers, with direct editorial input from the Health Equity Editor and a Deputy Editor. Accepted in revised form June 25, 2018.

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