Association of Body Mass Index with Outcomes in Patients with CKD

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ABSTRACT

Obesity is associated with higher mortality in the general population, but this association is reversed in patients on dialysis. The nature of the relationship of obesity with adverse clinical outcomes in nondialysis-dependent CKD and the putative interaction of the severity of disease with this association are unclear. We analyzed data from a nationally representative cohort of 453,946 United States veterans with eGFR < 60 ml/min per 1.73 m². The associations of body mass index categories (<20, 20 to <25, 25 to <30, 30 to <35, 35 to <40, 40 to <45, 45 to <50, and ≥50 kg/m²) with all-cause mortality and disease progression (using multiple definitions, including incidence of ESRD, doubling of serum creatinine, and the slopes of eGFR) were examined in Cox proportional hazards models and logistic regression models. Multivariable adjustments were made for age, race, comorbidities and medications, and baseline eGFR. Body mass index showed a relatively consistent U-shaped association with clinical outcomes, with the best outcomes observed in overweight and mildly obese patients. Body mass index levels <25 kg/m² were associated with worse outcomes in all patients, independent of severity of CKD. Body mass index levels ≥35 kg/m² were associated with worse outcomes in patients with earlier stages of CKD, but this association was attenuated in those patients with eGFR < 30 ml/min per 1.73 m². Thus, until clinical trials establish the ideal body mass index, a cautious approach to weight management is warranted in this patient population.


Obesity defined by elevated body mass index (BMI) has been regarded as a cardiovascular risk factor in the general population.1–4 Obesity is also associated with increased risk of incident CKD5–9 and ESRD.10–13 Negative effects of obesity include those effects mediated by conditions caused or worsened by it, such as diabetes mellitus (DM) or hypertension, and direct adverse metabolic effects, such as inflammation, increased synthesis of apolipoprotein B and very LDLs, increased production of insulin, and insulin resistance.14 Obesity also induces glomerular hyperfiltration,15 and weight loss in morbidly obese patients attenuates proteinuria.16 However, even in relatively healthy populations, very low BMI levels have been consistently associated with higher all-cause mortality,17 and the optimal BMI for survival has varied from study to study.18,19 Contrasting the unequivocally higher risk associated with elevated BMI in the general population, studies that examined patient groups with various chronic diseases have either found no association20 or described paradoxically lower mortality associated with high BMI levels.21,22 The reversal of the obesity–mortality association has been very robust in patients with ESRD,23,24 but there are limited studies showing conflicting results20,25,26 in patients with nondialysis–
dependent CKD (NDD-CKD). The heterogeneity of the NDD-CKD population, which encompasses patients with kidney function ranging from near-normal to near-nil, could make it difficult to determine the role that obesity plays as a risk factor in this group and the ideal therapeutic weight management goals.

We examined the association of BMI with all-cause mortality and progressive CKD in a large national cohort of United States veterans with eGFR<60 ml/min per 1.73 m².

RESULTS

The mean age of the cohort was 73.9±9.3 years, 87.0% \((n=394,763)\) were white, and 9.1% \((n=41,231)\) were African American. The mean BMI was 29.0±5.5 kg/m², and the mean eGFR was 47.8±9.9 ml/min per 1.73 m². Baseline characteristics of patients categorized by their baseline BMI are described in Table 1. Patients with higher BMI were younger, were more likely to be white, had higher BP and higher medication use, had higher prevalence of chronic heart failure (CHF), DM, and depression, and had lower prevalence of malignancies, dementia, and lung, liver, rheumatologic, and peptic ulcer diseases.

Mortality

In total, 148,276 patients died (mortality rate=73.9/1000 patient-years [PYs]; 95% confidence interval [95% CI], 73.5 to 74.3). Figure 1 describes associations of BMI with mortality in the overall cohort. Both higher and lower BMIs were associated with higher mortality, with the lowest adjusted mortality observed in the 30 to <35 kg/m² group. Similar U-shaped associations were present in all subgroups, except patients with eGFR<30 ml/min per 1.73 m², in whom higher BMI levels were not associated with significant increases in mortality (Supplemental Figure 1). The lack of significant association between higher BMI levels and mortality in patients with advanced CKD (CKD stages 4 and 5) was also apparent in analyses using a more granular CKD stage-based categorization (Figure 2). Additional adjustment for DM and BP in multivariable models did not attenuate the U-shaped association between BMI and mortality (Supplemental Figure 2).

Table 1. Baseline characteristics of 453,946 United States veterans with NDD-CKD categorized by their baseline BMI

<table>
<thead>
<tr>
<th>Variables</th>
<th>BMI (kg/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;20 (n=9916)</td>
</tr>
<tr>
<td>Age, yr</td>
<td>77.5±9.5</td>
</tr>
<tr>
<td>Sex, men</td>
<td>93.9</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>79.4</td>
</tr>
<tr>
<td>Black</td>
<td>17.1</td>
</tr>
<tr>
<td>Hispanic</td>
<td>1.8</td>
</tr>
<tr>
<td>Other</td>
<td>1.8</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>132±20</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>70±11</td>
</tr>
<tr>
<td>CVD</td>
<td>38.1</td>
</tr>
<tr>
<td>CHF</td>
<td>17.2</td>
</tr>
<tr>
<td>Diabetes</td>
<td>17.9</td>
</tr>
<tr>
<td>Cancer</td>
<td>23.1</td>
</tr>
<tr>
<td>Lung disease</td>
<td>42.2</td>
</tr>
<tr>
<td>Rheumatologic</td>
<td>2.8</td>
</tr>
<tr>
<td>PUD</td>
<td>5.1</td>
</tr>
<tr>
<td>Liver disease</td>
<td>1.1</td>
</tr>
<tr>
<td>Depression</td>
<td>5.6</td>
</tr>
<tr>
<td>Dementia</td>
<td>5.0</td>
</tr>
<tr>
<td>eGFR (ml/min per 1.73 m²)</td>
<td>46.6±10.6</td>
</tr>
<tr>
<td>Loop diuretics</td>
<td>19.0</td>
</tr>
<tr>
<td>Thiazide diuretics</td>
<td>21.0</td>
</tr>
<tr>
<td>ACEI/ARB</td>
<td>41.9</td>
</tr>
<tr>
<td>α-Blockers</td>
<td>20.6</td>
</tr>
<tr>
<td>β-Blockers</td>
<td>41.9</td>
</tr>
<tr>
<td>Ca channel blockers</td>
<td>32.8</td>
</tr>
<tr>
<td>Statins</td>
<td>45.8</td>
</tr>
</tbody>
</table>

Values expressed as percent or mean±SD. CVD, cardiovascular disease; PUD, peptic ulcer disease; ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker.
Progression of CKD

ESRD developed in 9117 patients (5.6 events/1000 PYs; 95% CI, 5.5 to 5.7), the combined end point of doubling of serum creatinine or ESRD developed in 21,688 patients (12.2/1000 PYs; 95% CI, 12.0 to 12.3), and 40,696 patients had a projected eGFR 10 ml/min per 1.73 m² or ESRD assuming no deaths during the follow-up period (14.9/1000 PYs; 95% CI, 14.8 to 15.1). The median slope was 2.0.84 ml/min per 1.73 m² per year (interquartile range=2.3.14 to 1.25), and 18.8% of patients had a slope steeper than 24ml/min per 1.73 m² per year. The multivariable-adjusted associations between BMI and the various outcomes of CKD progression were U-shaped (Figure 3, A–C), except for the incidence of ESRD (Figure 3D), which showed a linearly incremental association. The lowest CKD progression for the end points showing U-shaped associations was observed with BMI corresponding to overweight/mild obesity (25–35 kg/m²). A U-shaped association of BMI with progressive CKD was also apparent in subgroup analyses, except for patients with more advanced CKD (Supplemental Figure 3). In analyses categorizing patients by CKD stages, the association of higher BMI with progression of CKD diminished in patients with CKD stage 4 (Figure 4). Adjustment for DM and hypertension significantly attenuated the association between BMI and progressive CKD (Supplemental Figure 4).

DISCUSSION

We examined the association of BMI with mortality and progression of CKD in a large cohort of NDD-CKD patients and detected optimal outcomes associated with overweight/mild obesity status. BMI levels below 30 kg/m² were linearly associated with higher mortality. Conversely, BMI levels above 35 kg/m² were also associated with higher mortality, except in patients with advanced CKD (eGFR<30 ml/min per 1.73 m²), in whom the association was attenuated and nonsignificant. Our study adds to the findings of prior studies showing a paradoxical benefit of obesity in the setting of comorbid conditions, such as CHF,27,28 DM,22,29 chronic obstructive pulmonary disease,30 rheumatoid arthritis,31 NDD-CKD,26 and ESRD.14,24 Contrary to the discrepant and controversial association of high BMI levels with mortality in many studies, an association of low BMI with higher mortality has been described in numerous previous studies of various patient populations, including several studies performed in the general population.3,18,32,33 In the latter studies, the BMI levels associated with ideal survival varied significantly, including those levels corresponding to normal up to mild obesity status (BMI=30 to <35 kg/m²), with BMI levels above these nadirs typically showing associations with increased mortality.
Similar to associations with mortality, we also detected U-shaped associations of BMI with progression of CKD, except when we defined progression as the incidence of ESRD. In the latter case, we described a linear association of higher progression associated with higher BMI, which is similar to two previous studies using the same end point. This discrepancy may have been because of different population characteristics and much longer follow-up duration in general population-based studies or competing risk by the very high mortality experienced in patients with the lowest BMI levels, especially because deaths significantly outnumbered ESRD events in our cohort and alternative definitions of progressive CKD (which attenuated the competing risk related to deaths) uniformly indicated U-shaped associations. A U-shaped association and a trend to increased risk of progressive CKD associated with the lowest BMI levels were also recently described in a large population-based cohort of 1.2 million individuals from Israel, although the very low number of ESRD events seen in those individuals with low BMI precluded precise risk estimates. Similar to the mortality end point, we also observed effect modification by severity of kidney disease for the association of higher BMI with progressive CKD, with BMI losing predictive value at eGFR levels $<30$ ml/min per 1.73 m$^2$.

Figure 3. BMI categories showing a U-shaped association with progression of chronic kidney disease in 453,946 United States veterans with eGFR $<60$ ml/min per 1.73 m$^2$. Association of BMI categories with four different outcomes representing progression of CKD: (A) steeper slopes of eGFR versus time (defined as slopes $<-4$ ml/min per 1.73 m$^2$ per year), (B) doubling of serum creatinine or ESRD, (C) projected eGFR $<10$ ml/min per 1.73 m$^2$ or ESRD, and (D) ESRD. Estimates were calculated from a logistic regression model (for steeper slopes) and Cox models (for all other outcomes) adjusted for age, race, comorbidities, medications, and baseline eGFR.
Obesity can exert negative effects through various mechanisms, which include mediation by comorbidities caused by obesity (such as DM and hypertension) and also direct metabolic effects of increased adiposity.\textsuperscript{14,15} Indeed, in our study, the association of higher BMI with progressive CKD was attenuated by adjustment for DM and BP. In light of such well defined adverse effects of obesity, it seems controversial that, in our study and other studies, BMI levels in the overweight/mildly obese range were associated with the best outcomes and that, in patients with advanced CKD, even morbid obesity was not associated with adverse outcomes at all.

Several potential explanations have been offered for this so-called obesity paradox. The short lifespan of patients with more advanced CKD and significant comorbid conditions may not allow the full fruition of the adverse metabolic effects of obesity, which could, in turn, have short-term protective effects in these patients by virtue of better nutritional reserves.\textsuperscript{34} Another possible explanation for the high adverse event rates seen in patients with low BMI could be the high prevalence of metabolically obese normal weight individuals in patient groups with high comorbidity burden,\textsuperscript{35} in whom adverse metabolic effects of obesity may be manifest despite low BMI levels. Other possible explanations for the obesity paradox include the presence of lower metabolic rates in obese individuals, leading to lower production of uremic waste products and hence, better tolerance of CKD-related morbidity, the presence of short-term protective cytokine profiles in obese individuals,\textsuperscript{36–38} and protective effects of either higher muscle mass\textsuperscript{39–42} and/or higher body fat\textsuperscript{43} typically present in patients with higher BMI. The latter two conditions could offer short-term advantages under conditions of duress, such as better nutritional reserves, enhanced antioxidant capacity,\textsuperscript{39} or lower circulating actin and higher plasma gelsolin levels,\textsuperscript{44} thus predisposing to better outcomes. These putative advantages could be magnified in patients with the most advanced stages of CKD (who also suffer from a higher comorbidity burden and have shorter life expectancy) and thus, result in a gradual attenuation of the negative effects seen in those patients with normal kidney function or milder stages of CKD.

The observed association of BMI with outcomes in our study could also have been affected by certain other characteristics of our cohort other than different levels of kidney function. The mean age in our cohort was $>70$ years, which is at least 20 years older than general population cohorts, and could be specifically related to certain characteristics, like functional decline, cognitive impairment, and frailty, which may be particularly relevant in underweight individuals.\textsuperscript{45}
is, thus, possible that the association of BMI with outcomes could be different in this older age group compared with younger people, which has suggested by other studies.\textsuperscript{46–48} Patients in our cohort also suffered from a high prevalence of comorbid conditions, which could themselves have had an impact on the observed associations as shown by previous studies.\textsuperscript{22–24,26–31} Our subgroup analyses did not detect significant effect modification by these various characteristics, but we cannot rule out potential effects by unmeasured conditions or some individual combinations of measured characteristics (e.g., associations may be different in young patients with no comorbidities even at more advanced stages of CKD). The main purpose of our study was to examine BMI as a risk factor in the overall CKD population, and a detailed assessment of the roles of various clinical characteristics will have to be performed in future dedicated studies.

Our study has limitations that need to be acknowledged. Our study was observational, and hence, its results cannot be used to infer causality. Our data do not allow us to glean the effects of interventions that intentionally lower or increase BMI, and it is, therefore, important to emphasize that our observations cannot be used to advocate weight gain in patients with a BMI < 30 kg/m\(^2\) or suggest that therapeutic weight loss would worsen outcomes. Most of our patients were men and United States veterans; hence, the results may not apply to women or the general United States population. We examined a prevalent cohort of CKD patients, and thus, we could not examine effects that obesity might have had on incident CKD. The competing risk of death\textsuperscript{1,2} versus kidney disease\textsuperscript{1,2} caused by higher BMI in patients with no CKD may have affected the composition of our cohort, which was suggested by the markedly lower baseline age of those patients with the highest BMI levels. Studies in the general population would have to clarify how BMI affects clinical characteristics of patients with incident CKD and how they may impact on future outcomes, such as mortality and progression of kidney disease. BMI may not be an ideal marker of obesity, because high BMI does not differentiate patients with relatively high muscle mass or bone mass who are not truly obese, and other indices, such as waist circumference or waist-to-height ratio, have been suggested to be better markers of obesity.\textsuperscript{49–51} Nevertheless, BMI remains the predominant index to establish obesity in clinical practice; hence, our results have direct clinical relevance. We did not examine cause-specific mortality, which could have informed about different effects of low and high BMI on various outcomes. We adjusted for a number of potential confounders, but residual confounding remains possible, especially because comorbidities in our study were only identified by International Classification of Diseases, Ninth Revision codes and we did not have sufficient information on levels of proteinuria, another potentially important mediator of the adverse effects of obesity.

In conclusion, the association between BMI and adverse outcomes in patients with NDD-CKD is U-shaped, especially in those patients with earlier stages of CKD. The best outcomes were associated with BMI levels consistent with overweight/mild obesity status. Traditional weight management strategies may, thus, not be appropriate in patients with all stages of NDD-CKD. The ideal BMI and the best ways to achieve this BMI need to be established from randomized controlled clinical trials. Before such information becomes available, a cautious approach to BMI-based weight management in CKD is warranted.

**CONCISE METHODS**

**Study Population**

The creation of this NDD-CKD cohort was previously described.\textsuperscript{52–54} Briefly, study subjects were identified by using measurements of serum creatinine in the Veterans Affairs (VA) Decision Support System National Data Extracts Laboratory Results file\textsuperscript{55} from October 1, 2004 to September 30, 2006. eGFR was calculated by using the Chronic Kidney Disease Epidemiology Collaboration equation.\textsuperscript{56} Patients with eGFR < 60 ml/min per 1.73 m\(^2\) on at least two occasions no less than 3 months apart and available BMI measurements within this period were included in the study. Cohort entry was defined as the date of the first baseline eGFR used to define CKD status. Patients with ESRD, defined as either receiving maintenance dialysis during this period or the presence of a kidney transplant based on records obtained from the US Renal Data System (USRDS),\textsuperscript{57} were excluded from the cohort. The final cohort included 453,946 patients.

Patients’ age, sex, race, and BP were obtained from the VA Corporate Data Warehouse. Information on race was cross-referenced with data obtained from Medicare through the VA–Medicare data merge project.\textsuperscript{58} Information on prevalent comorbidities was extracted from the VA Inpatient and Outpatient Medical SAS Datasets\textsuperscript{59} using International Classification of Diseases, Ninth Revision Diagnostic and Procedure Codes and Current Procedural Terminology Codes recorded from October 1, 2004, to September 30, 2006. Cardiovascular disease was defined based on diagnostic codes for coronary artery disease, angina, or myocardial infarction or procedure codes for percutaneous coronary interventions or coronary artery bypass grafting. Data related to baseline (first 90 days after cohort entry) medication exposure were collected from VA Pharmacy dispensation records.\textsuperscript{60} To minimize random variation, we used the respective means of all the BMI, BP, and laboratory measurements from the first 90 days after cohort entry as baseline values for these variables in our analyses. Incident ESRD was defined as initiation of maintenance dialysis or preemptive renal transplantation occurring between the cohort entry date and September 30, 2009, as provided by the USRDS. Information about all-cause mortality was obtained from the VA Vital Status Files.\textsuperscript{38}

We collected information on all weight and height measurements obtained on cohort participants and calculated BMI as the weight in kilograms divided by the height in meters squared. To detect nonlinear associations and better characterize the effects of very low and very high BMI categories, we divided BMI into eight a priori-defined categories: < 20, 20 to < 25, 25 to < 30, 30 to < 35, 35 to < 40, 40 to < 45, 45 to < 50, and ≥ 50 kg/m\(^2\); we used the 30 to < 35 kg/m\(^2\) category
as referent in all analyses based on the hypothesis that BMI has a U-shaped association with outcomes. We favored this categorization as opposed to the BMI categories advocated by the World Health Organization because of this large cohort population size allowing more precise effect estimates in all BMI ranges and recent studies suggesting a steady elevation in mean BMI levels in both men and women worldwide.

Missingness for variables used in multivariable models was small, with 99% of patients contributing to the main fully adjusted models; therefore, missing data were not imputed.

Statistical Analyses
Descriptive analyses were performed using means±SDs, medians (interquartile ranges), and proportions as appropriate. Event rates were calculated using the PY approach. The association of baseline BMI with all-cause mortality was examined in Cox proportional hazards models. Patients were followed in survival analyses from the date of the baseline BMI measurement to death or April 1, 2012. The association of BMI with progression of CKD was examined in patients with baseline eGFR=15 to <60 ml/min per 1.73 m² by using both slopes of eGFR in patients with at least three available serum creatinine measurements and time-to-event analyses with ESRD and the composite of doubling of serum creatinine or ESRD as the event of interest (censored for pre-ESRD deaths or on September 30, 2009).

To mitigate the competing risk effect of pre-ESRD mortality in time-to-event analyses, we also examined the incidence of the composite outcome of ESRD or an eGFR<10 ml/min per 1.73 m² generated using measured slopes of eGFR assuming that no deaths occurred until the end of the follow-up period (April 1, 2012). The association of BMI with the slopes of eGFR was examined in logistic regression models after categorizing eGFR slopes as progressive (decrease in eGFR by more than 4 ml/min per 1.73 m² per year) and nonprogressive (decrease in eGFR by 4 ml/min per 1.73 m² per year or less). Time-to-event analyses of CKD progression were performed using Cox proportional hazards models.

The effect of potential confounders was analyzed by constructing models with incremental adjustments: unadjusted (model 1); age (model 2); age, sex, and race (model 3); model 3 plus comorbid conditions (dementia, rheumatologic disease, malignancy, depression, cardiovascular disease, CHF, peptic ulcer disease, and chronic lung disease) and medications (angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, α-blockers, β-blockers, calcium channel blockers, loop diuretics, thiazide diuretics, and statins; model 4); and model 4 plus baseline eGFR adjusted (model 5). Multivariable models analyzing slopes of eGFR and the incidence of an eGFR<10 ml/min per 1.73 m² were also adjusted for the presence or absence of deaths. Our main multivariable models did not include DM and BP, because they are likely effect mediators of obesity rather than confounders. To examine whether DM and/or BP mediate the effects of obesity on outcomes, we constructed additional models adjusting for these two variables in addition to all other variables in the main fully adjusted model.

Effect modification by key patient characteristics was examined in subgroup analyses after categorizing patients according to prespecified cutoffs of various key characteristics. Baseline kidney function was categorized as both an eGFR<30 and ≥30 ml/minute per 1.73 m² and according to the Kidney Disease: Improving Global Outcomes classification (stages 3A–5 for analyses of mortality and stages 3A–4 for analyses of progressive CKD).

Statistical analyses were performed using Stata MP version 11 (Stata Corporation, College Station, TX).

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DISCLOSURES
None.

REFERENCES


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