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Body Mass Index, Waist Circumference and Mortality in Kidney Transplant Recipients

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Higher body mass index (BMI) appears paradoxically associated with better outcomes in patients with chronic kidney disease. Whereas higher BMI reflects both increased visceral and subcutaneous fat and/or muscle mass, a combined assessment of BMI and waist circumference may enable differentiation of visceral adiposity from muscle and/or nonvisceral fat mass. We examined the association of BMI and waist circumference with all-cause mortality in a prospective cohort of 993 kidney transplant recipients. Associations were examined in Cox models with adjustment for demographic and comorbid conditions and for inflammatory markers. Unadjusted death hazard ratios (95%CI) associated with one standard deviation higher BMI and waist circumference were 0.94 (0.78, 1.13), $p = 0.5$ and 1.20 (1.00, 1.45), $p = 0.05$, respectively. Higher BMI was associated with lower mortality after adjustment for waist circumference (0.48 [0.34, 0.69], $p < 0.001$), and higher waist circumference was more strongly associated with higher mortality after adjustment for BMI (2.18 [1.55–3.08], $p < 0.001$). The associations of waist circumference with mortality remained significant after additional multivariable adjustments. Higher BMI and waist circumference display opposite associations with mortality in kidney transplant recipients. Waist circumference appears to be a better prognostic marker for obesity than BMI.

Key words: body mass index, kidney transplant, mortality, waist circumference

Abbreviations: BMI, body mass index; CKD, chronic kidney disease; CI, confidence interval; CRP, C-reactive protein; DGF, delayed graft function; ESRD, end stage renal disease; SBP, systolic blood pressure.

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Introduction

An obesity epidemic in both developed and developing countries (1) has been implicated as a cause of various comorbidities including diabetes mellitus, atherosclerotic cardiovascular disease, cancer and chronic kidney disease (CKD) (2–5), and has been linked to higher mortality in the general population (6). Yet obesity, usually defined as a body mass index (BMI) >30 kg/m^2 (7), has been associated with better survival in various chronic disease states (8–10). Paradoxical associations between higher BMI and lower mortality have also been described in patients with end stage renal disease (ESRD) on hemodialysis (11–18) and in patients with nondialysis dependent CKD (19). Studies about the effects of obesity on outcomes in kidney transplant recipients are relatively scarce. Higher BMI has been associated with short-term adverse outcomes after kidney transplantation (20–23), likely as a result of cardiovascular, infectious and metabolic complications (24–29). The long-term outcomes associated with obesity in kidney transplant recipients are not that well characterized. Previous single center observational studies did not support an association of elevated BMI with all-cause mortality (25,30) or with graft loss (30).

The interpretation of observational studies is also made difficult by uncertainties surrounding BMI as a marker of obesity. It has been suggested that waist circumference may be a better predictor of outcomes than BMI (31), possibly because of its better reflection of visceral adiposity. The concomitant assessment of BMI and waist circumference has resulted in the uncovering of divergent associations with mortality for these two anthropometric measures (lower mortality in patients with elevated BMI but higher mortality in patients with elevated waist circumference) in elderly individuals (32) and in dialysis patients

(33), but the impact of various measures indicative of fat distribution and body composition on long term outcomes has not yet been studied in kidney transplant recipients. We examined all-cause mortality associated with BMI and with waist circumference in a prospective cohort of prevalent kidney transplant recipients. We hypothesized that the concomitant assessment of BMI and waist circumference would allow for the parallel assessment of the effects of visceral and general obesity on clinical outcomes in this patient population.

Materials and Methods

Study population and data collection

We examined all kidney transplant recipients 18 years of age or older (n = 1214) followed at the outpatient clinic of the Department of Transplantation and Surgery at the Semmelweis University, Budapest, as described in detail elsewhere (34). In brief, after excluding ineligible patients and those unwilling to participate, the final cohort consisted of 993 patients (Malnutrition and Inflammation in Transplant-Hungary [MINIT-HU] study). The study was approved by the Ethics Committee of the Semmelweis University. After informed consent baseline evaluations of all patients were conducted between February and August 2007, and included the recording of demographic and anthropometric characteristics (including BMI and waist circumference), comorbid conditions, medication usage (including the administration and the dose of corticosteroids, calcineurin inhibitors and antiproliferative agents) and laboratory measurements. Waist circumference was measured at the level of the iliac crest by using a tape measure. Transplant data included transplant 'vintage', defined as the duration post-transplant at the time of enrollment and history of delayed graft function, defined as the need for at least one hemodialysis session in the first week after transplantation. A modified Charlson comorbidity index, shown to better predict mortality in dialysis patients (35), was calculated for each individual. This index was computed by assessing the presence/absence or severity of 18 comorbid conditions (myocardial infarction, congestive heart failure, peripheral and cerebral vascular disease, dementia, chronic lung disease, rheumatological, peptic ulcer disease, mild, moderate or severe liver disease, diabetes with or without complications, hemiplegia, neoplasia, metastatic disease, leukemia, lymphoma and human immunodeficiency virus) (35). GFR was estimated using the abbreviated equation developed for the Modification of Diet in Renal Disease Study (36). Patients were followed until death or until June 27, 2010, with the recording of graft failures and return to dialysis. No patients were lost to follow-up. The outcome of interest was all cause mortality. Deaths were identified from a national vital status registry.

Statistical analyses

Continuous variables were expressed as means ± SD or medians (interquartile range) and categorical variables were expressed as proportions. Skewed variables (Charlson index and transplant vintage) were log-transformed. Correlations between BMI, waist circumference and other relevant covariates were assessed by Pearson correlation coefficients. BMI and waist circumference were analyzed both as continuous measures and as categorical variables. The National Institutes of Health classifies nutritional status by BMI as under-nutrition (BMI < 18.5 kg/m^2), normal (BMI 18.5–24.9 kg/m^2), overweight (BMI 25–29.9 kg/m^2) and obese (BMI ≥30 kg/m^2) (7). Since only 21 patients in our cohort (2.1%) had a BMI <18.5 kg/m^2, we defined BMI categories as <25, 25–30 and >30 kg/m^2. Waist circumference was categorized according to median values separately in males (103 cm) and females (93 cm) in primary analyses and according to recommended standards (100 cm in males and 90 cm in females) in sensitivity analyses. Missing values for waist circumference (0.9% missing), blood pressure (1.3% missing) and for presence/absence of delayed graft function (2.3% missing) were not imputed; overall there were 948 patients (95%) with complete data for multivariable analyses.

Event rates were calculated using the person-years approach. Associations of BMI and waist circumference with mortality were assessed using the Kaplan–Meier method and the log rank test, and the effect of confounders was assessed in Cox proportional hazard models. The proportionality assumption for mortality risk was tested using Schoenfeld residuals. Survival models were built separately for both BMI and waist circumference with various levels of adjustments for confounders. We adjusted BMI models for waist circumference and vice versa in order to separate the effects of visceral and general (nonvisceral) obesity related components on outcomes. Other relevant confounders to be included in the fully adjusted multivariable models were determined based on theoretical considerations, and included age, gender, Charlson comorbidity index, diabetes mellitus, smoking status, blood pressure, transplant vintage, presence/absence of delayed graft function following transplantation and levels of estimated GFR, serum albumin and C-reactive protein. To further explore independent effects of BMI and waist circumference we repeated all analyses for BMI in subgroups of patients divided by waist circumference levels, and for waist circumference in subgroups divided by BMI levels. Interactions were explored by including interaction terms with age, gender, smoking status, Charlson comorbidity index, diabetes, estimated GFR, albumin and C-reactive protein and performing subgroups analyses if the interaction terms were significant. Due to the importance of diabetes mellitus as a potential confounder and effect modifier an interaction term for diabetes mellitus was included in all multivariable models. Sensitivity analyses were performed by considering only deaths that occurred prior to graft failure. Due to the competing nature of mortality and graft failure associations in these analyses were examined in semi-parametric competing risk regression models (STATA '*stcrreg*' see Refs. 37,38). p-Values of less than 0.05 were considered significant. Statistical analysis was carried out using Stata 11.0 software (StataCorp, College Station, TX, USA).

Results

The mean age of the 993 patients was 50.9 ± 12.8 years, 424 (43%) were females, 209 (21%) had diabetes mellitus and their mean estimated GFR was 50.9 ± 20.9 mL/min/1.73 m^2. Baseline characteristics for patient groups divided by categories of BMI and waist circumference are shown in Tables 1 and 2. Patients with a higher BMI and those with higher waist circumference were both older, were more likely to be diabetic and to have experienced delayed graft function, were less likely to be active smokers and had higher C reactive protein levels. Patients with higher waist circumference (but not those with higher BMI) also had significantly higher Charlson comorbidy indexes (Table 2). Table 3 shows the correlation of BMI with waist circumference, and of both with various potential confounders. Higher BMI and higher waist circumference were both significantly correlated with each other and with older age, higher Charlson comorbidity index, diabetes mellitus, smoking, history of delayed graft function, higher systolic blood pressure and higher C-reactive protein. Higher waist circumference (but not higher BMI) was also significantly correlated with female gender. One hundred and twenty-two patients died

Table 1: Baseline characteristics in patients grouped according to body mass index

	BMI (kg/m^2)			p-Value for trend
	<25 N = 367 (37%)	25–30 N = 365 (37%)	>30 N = 261 (26%)	
Age (years)	47.3 ± 14.1	53.1 ± 12.0	53.1 ± 10.8	<0.001
Gender (females)	179 (49)	130 (36)	115 (44)	0.13
Charlson comorbidity index	2.0 (2.0, 3.0)	2.0 (2.0, 4.0)	2.0 (2.0, 4.0)	0.2
Diabetes mellitus	47 (13)	81 (22)	81 (31)	<0.001
SBP (mmHg)	139 ± 19	143 ± 19	144 ± 20	0.002
Waist circumference (cm)	86 ± 10	101 ± 9	113 ± 10	<0.001
Transplant vintage (months)	75 (43, 121)	66 (38, 113)	71 (39, 108)	0.11
History of DGF	80 (22)	94 (26)	79 (31)	0.02
Active smoking	84 (23)	67 (18)	34 (13)	0.002
Estimated GFR (mL/min/1.73m^2)	50.7 ± 22.6	51.5 ± 20.1	50.2 ± 19.6	0.8
Albumin (g/L)	40.1 ± 4.3	40.4 ± 4.2	40.3 ± 3.8	0.5
CRP (mg/L)	2.3 (1.1, 4.9)	3.2 (1.6, 6.6)	4.6 (2.7, 9.7)	<0.001

Data presented as means ± SD, number (percent) or median (interquartile range). SBP = systolic blood pressure; DGF = delayed graft function; CRP = C-reactive protein. Comparisons were made by Chi-square test for linear trend. To convert GFR in mL/min/1.73m^2 to mL/s/1.73m^2, multiply by 0.01667.

Table 2: Baseline characteristics in patients grouped according to waist circumference

	Waist circumference		
	Lower (<103 cm males, <93 cm females) N = 494 (50%)	Higher (≥103 cm males, ≥93 cm females) N = 490 (50%)	p-Value
Age (years)	47.4 ± 13.5	54.6 ± 10.8	<0.001
Gender (females)	220 (45)	200 (41)	0.2
Charlson comorbidity index	2.0 (2.0, 3.0)	2.5 (2.0, 4.0)	<0.001
Diabetes mellitus	74 (15)	133 (27)	<0.001
SBP (mmHg)	139 ± 19	145 ± 19	<0.001
Body mass index (kg/m^2)	23.8 ± 3.5	30.2 ± 3.9	<0.001
Transplant vintage (months)	72 (40, 116)	71 (39, 113)	0.3
History of DGF	106 (22)	143 (30)	0.007
Active smoking	111 (22)	70 (14)	0.001
Estimated GFR (mL/min/1,73m^2)	51.0 ± 21.6	50.8 ± 20.3	0.8
Albumin (g/L)	40.3 ± 4.3	40.2 ± 4.0	0.6
CRP (mg/dL)	2.3 (1.2, 4.9)	4.2 (2.0, 8.5)	<0.001

Categories of waist circumference were established based on median values in males and females. Data presented as means ± SD, number (percent) or median (interquartile range). SBP = systolic blood pressure; DGF = delayed graft function; CRP = C-reactive protein. Comparisons were made by t-test, rank sum test or Chi-square test. To convert GFR in mL/min/1.73m^2 to mL/s/1.73m^2, multiply by 0.01667.

Table 3: Pair-wise correlations of body mass index and waist circumference with each other and with various other variables

	BMI	p-Value	Waist circumference	p-Value
BMI			0.81	<0.001
Waist circumference	0.81	<0.001		
Age	0.23	<0.001	0.30	<0.001
Gender	−0.05	0.09	−0.34	<0.001
Charlson index	0.09	0.003	0.13	<0.001
DM	0.17	<0.001	0.19	<0.001
Smoking	0.10	<0.001	0.10	0.001
Transplant vintage	−0.03	0.3	0.01	0.7
Delayed graft function	0.08	0.02	0.14	<0.001
SBP	0.13	<0.001	0.19	<0.001
Estimated GFR	−0.02	0.5	−0.01	0.6
Albumin	−0.002	0.9	−0.01	0.8
CRP	0.09	0.03	0.12	<0.001

BMI = body mass index; DM = diabetes mellitus; SBP = systolic blood pressure; eGFR = estimated glomerular filtration rate; CRP = C-reactive protein. To convert GFR in mL/min/1.73m^2 to mL/s/1.73m^2, multiply by 0.01667.

Table 4: Hazard ratios (95% confidence intervals) of mortality associated with BMI and waist circumference

	Model 0	Model 1	Model 2	Model 3
BMI (5 kg/m^2 higher)	0.94 (0.78, 1.13) p = 0.5	0.48 (0.34, 0.69) p < 0.001	0.67 (0.45, 1.01) p = 0.053	0.69 (0.46, 1.03) p = 0.067
Waist circumference (15 cm higher)	1.20 (1.00, 1.45) p = 0.05	2.18 (1.55, 3.08) p < 0.001	1.64 (1.08, 2.47) p = 0.019	1.61 (1.07, 2.44) p = 0.023

BMI, body mass index.
Associations were examined in Cox proportional hazard models.
Model 0: unadjusted.
Model 1: adjusted for waist circumference (for BMI) and for BMI (waist circumference).
Model 2: Model 1 + age, gender, comorbidity index, diabetes mellitus, smoking, transplant vintage, presence/absence of delayed graft function, SBP, estimated GFR and an interaction term for diabetes mellitus.
Model 3: Model 2 + albumin, CRP.

(mortality rate 40.6/1000 patient-years (95% confidence interval [CI]: 34.0–48.5) over a median follow up of 3.2 years; 87 of these deaths occurred before graft failure (31.4/1000 patient-years (95%CI: 25.5–38.8) and 102 patients developed graft failure (graft failure rate 36.8/1000 patient-years (95%CI): 30.3–44.7).

Table 4 shows hazard ratios of mortality associated with a one standard deviation higher BMI and waist circumference, unadjusted and after adjustment for waist circumference/BMI and for various other covariates. In unadjusted models BMI was not associated and waist circumference showed a modest association with higher mortality; after adjustment for waist circumference/BMI higher BMI was associated with significantly lower mortality, and higher waist circumference was more strongly associated with significantly higher mortality. These associations remained significant after further adjustment in the case of waist circumference (Tables 4 and 5), and showed a trend towards significance in the case of BMI. Figure 1 shows unadjusted (A) and waist circumference-adjusted (B) cumulative incidences of mortality in patients categorized by their BMI level, indicating lower mortality associated with higher BMI only after adjustment for waist circumference. The lower mortality associated with higher BMI was present in both subgroups of patients with higher and lower waist circumference, but was more pronounced in patients with lower waist circumference: waist circumference-adjusted hazard ratios (95%CI) of mortality associated with one standard deviation higher BMI in patients with waist circumferences above and below median were 0.65 (0.42–1.01), p = 0.055 and 0.28 (0.15–0.56), p < 0.001, respectively. Figure 2 shows unadjusted (A) and BMI-adjusted (B) cumulative incidences of mortality in patients categorized by their level of waist circumference, indicating a trend towards higher mortality associated with increased waist circumference only after adjustment for BMI. The higher mortality associated with increased waist circumference was present in all BMI subgroups: BMI-adjusted hazard ratios (95%CI) of mortality associated with one standard deviation higher waist circumference in patients with BMI levels of <25, 25–30 and >30 kg/m^2 were 2.61 (1.45–4.71, p < 0.001), 2.31 (1.34–3.99, p = 0.003) and 1.91 (0.98–3.71, p = 0.06), respectively. There were no interactions with age, gender, smoking status, Charlson comorbidity index, diabetes mellitus and levels of estimated GFR, serum albumin and C reactive protein (data not shown). Results remained consistent in competing risk analyses that considered only

Table 5: Hazard ratios (95% confidence intervals) of mortality associated with waist circumference and with other covariates in unadjusted and in multivariable adjusted models.

Variable		Unadjusted model	Multivariable adjusted model
Waist circumference	15 cm higher	1.20 (1.00, 1.45)	1.64 (1.08, 2.47)
BMI	5 kg/m^2 higher		0.61 (0.42, 0.88)
Age	1 year older		1.05 (1.03, 1.07)
Gender	Female vs. male		0.86 (0.55, 1.33)
Charlson index	1 log-unit higher		4.30 (2.62, 7.06)
DM	vs. no DM		3.78 (0.16, 86.77)
DM∗waist circumference	Interaction term		0.79 (0.50, 1.24)
Smoking	vs. nonsmoking		1.63 (0.97, 2.75)
Transplant vintage	1 log-unit higher		1.96 (1.42, 2.70)
Delayed graft function	vs. no delayed graft function		0.72 (0.46, 1.10)
SBP	1 mmHg higher		1.013 (1.003, 1.021)
eGFR	1 mL/min/1.73m^2 higher		0.97 (0.96, 0.98)

BMI = body mass index; DM = diabetes mellitus; SBP = systolic blood pressure; eGFR = estimated glomerular filtration rate.
Multivariable adjusted model corresponds to Model 2 from Table 4.
To convert GFR in mL/min/1.73m^2 to mL/s/1.73m^2, multiply by 0.01667.

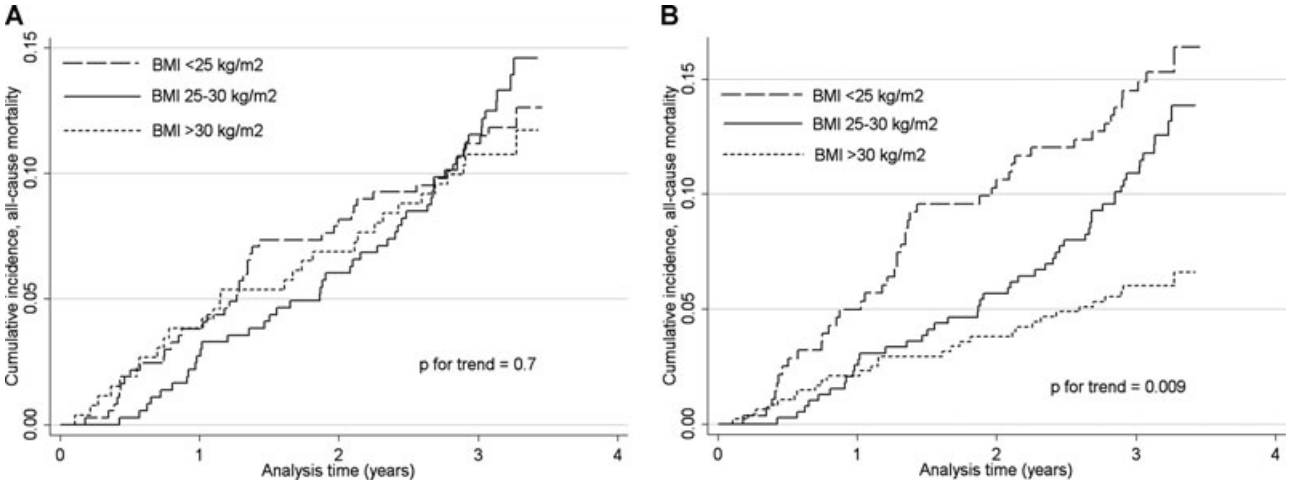

Figure 1: Kaplan–Meier curves of unadjusted (A) and waist circumference-adjusted (B) cumulative incidence of all-cause mortality in kidney transplant recipients grouped according to their body mass index.

deaths before graft failure and when repeating analyses using different cutoffs for the definition of elevated waist circumference (data not shown).

Discussion

We describe increased all-cause mortality associated with higher waist circumference, but lower mortality associated with higher BMI in kidney transplant recipients. These associations were independent of age, gender, degree of comorbidity and smoking status, and were present in patients with higher and lower levels of BMI and waist circumference. Obesity is still most often defined as a BMI level >30 kg/m^2 (7), and in the general population is thought to be responsible for a variety of complications including diabetes mellitus, atherosclerotic cardiovascular disease, cancer, CKD (2–5) and higher mortality (6). In a seemingly paradoxical manner higher BMI has been associated with better survival in various chronic disease states (8–10) and also in ESRD (11–18) and in nondialysis dependent CKD (19). Due to observations suggesting short-term poor outcomes (20–23) related to cardiovascular, infectious and metabolic complications (24–29) in patients with higher BMI in the immediate posttransplant period obesity as defined by elevated BMI is in general deemed undesirable in kidney transplant recipients. Furthermore, it is currently not recommended for patients deemed extremely obese (BMI > 35 kg/m^2) to undergo kidney transplantation (39) unless they are able to loose weight (40). Earlier studies

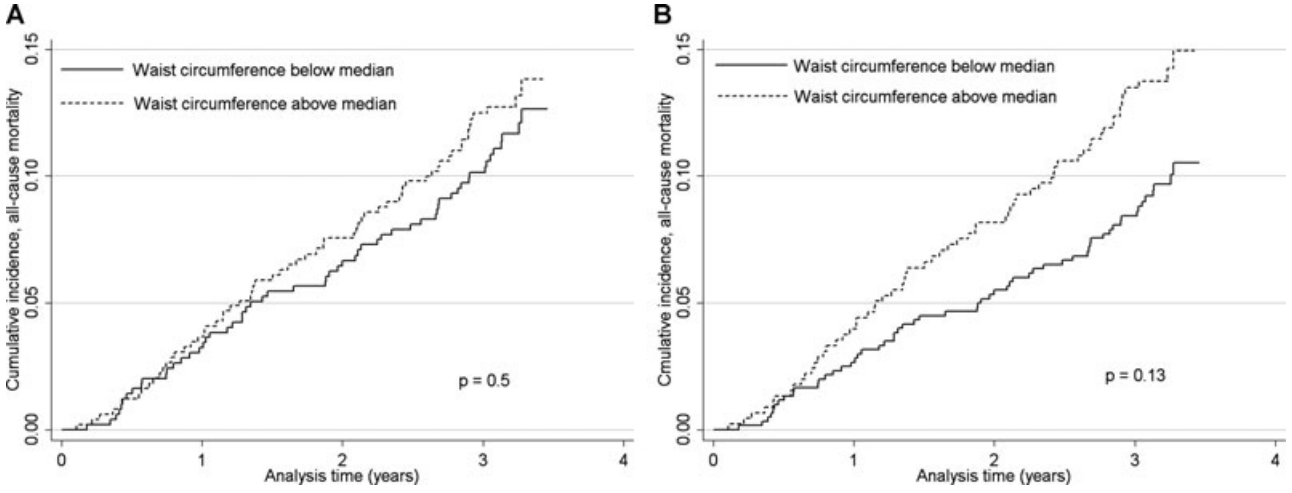

Figure 2: Kaplan–Meier curves of unadjusted (A) and body mass index-adjusted (B) cumulative incidence of all-cause mortality in kidney transplant recipients grouped according to their waist circumference. Median waist circumference was 103 cm in males and 93 cm in females.

have, however, suggested that kidney transplant recipients with elevated BMI may not have increased mortality (25), indicating a need to critically reassess the role of BMI in the risk stratification of this population. Importantly, BMI is a complex marker of visceral and nonvisceral adiposity and also of nutritional status including muscle mass (41). This may be a potential reason why elevated BMI has shown seemingly paradoxical associations with mortality in many observational studies (11–19), as the better outcomes associated with higher BMI may be related to differential benefits portended by one or more of these components (18,42).

It has been suggested that waist circumference may be a better marker to capture the adverse effects of obesity (31), possibly because of its reflection of visceral adiposity. Studies concomitantly assessing outcomes associated with BMI and with waist circumference in elderly individuals (32) and in dialysis patients (33) have indicated that higher waist circumference was associated with increased mortality, but higher waist circumference-adjusted BMI (in this context possibly a marker of increased muscle mass and/or increased nonvisceral adiposity [see Ref. 41]) was associated with lower mortality.

To our knowledge our study is the first to examine the concomitant effects of waist circumference and BMI in kidney transplant recipients. The increase in mortality seen in association with higher waist circumference may be explained by the differential negative metabolic effects of visceral adipose tissue, which include the influx of portal fatty acids, cytokines, and hormones into the liver from omental adipocytes with a subsequent increased synthesis of apolipoprotein B and VLDL and increased production of insulin (43). The elevated cytokine levels also promote peripheral insulin resistance and the increase in lipids promotes proliferation of the vasa vasorum and apoptosis by medial macrophages (43). Conversely, the mechanism of action behind the lower mortality seen in patients with elevated waist circumference-adjusted BMI is not entirely clear, but may involve mechanisms related to both higher muscle mass and higher nonvisceral adiposity. Observational studies in dialysis patients suggested that in patients with elevated BMI both higher muscle mass (18) and higher overall adiposity (14) are associated with better survival. Increased muscle mass may lead to improved skeletal, respiratory and cardiac muscle function and it may also improve muscle-based oxidative metabolism and thus lead to increased antioxidant defense (44). Skeletal muscle also produces gelsolin which could have various protective effects (45–47), and higher levels of which have been associated with better survival in dialysis patients (48). Studies in patients with exclusive subcutaneous (as opposed to visceral) fat excess (such as symmetric lipomatosis) indicated minimal lipid accumulation in the liver, muscle and visceral adipose tissue and a normal metabolic state in spite of a clinically obese state (49). These results suggest that nonvisceral adipocytes may limit the deposition of fat at sites where it could have a more deleterious metabolic impact (50,51). Similar studies measuring the effects of body composition and fat distribution are not available in kidney transplant recipients, hence we can only speculate about the plausibility of similar mechanisms of action in them.

Our findings could have several practical implications. These results, along with the findings of studies in different patient populations (32,33) suggest that a definition of obesity that differentiates between visceral adiposity, nonvisceral adiposity and higher muscle mass may improve risk stratification in kidney transplant recipients. It may also be possible to design weight management strategies specifically aimed at reducing visceral adiposity without the reduction (or with the concomitant increase) in muscle mass and/or nonvisceral adiposity in order to optimize outcomes in kidney transplant recipients or in dialysis patients wait listed for kidney transplantation. The optimal approach towards such goals (which could include various dietary and exercise-based strategies) will have to be tested in clinical trials.

Our study has a number of limitations. We examined exclusively Caucasian patients from a single medical center; hence our results may not apply to the transplant population at large. The observational nature of our study does not allow us to make inferences about causation, but merely the description of associations. Hence, the association of the examined predictors with the studied outcomes should be viewed as primarily prognostic, rather than etiologic. We attempted to correct for major confounders including comorbid conditions and specific measures of inflammation, but we cannot rule out the effect of residual confounding by additional factors such socio-economic status, alcohol consumption, exercise tolerance or various life style and dietary habits.

Elevated waist circumference is associated with higher mortality, but high BMI is associated with lower mortality in kidney transplant recipients. Incorporating measures of visceral adiposity in the definition of obesity may improve the risk stratification of kidney transplant recipients and of dialysis patients wait-listed for kidney transplantation. The combined assessment of waist circumference and BMI could also be useful as part of an overall assessment of nutritional status, and should help to determine individualized intervention goals (which could vary from weight loss strategies to lower visceral adiposity to exercise programs to bolster strength and muscularity).

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Disclosure

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation*.

References

1. Kuczmarski RJ, Flegal KM, Campbell SM, Johnson CL. Increasing prevalence of overweight among US adults. The National Health and Nutrition Examination Surveys, 1960 to 1991. JAMA 1994; 272: 205–211.
2. Byers T. Body weight and mortality. N Engl J Med 1995; 333: 723–724.
3. Hsu C, McCulloch C, Iribarren C, Darbinian J, Go A. Body mass index and risk for end-stage renal disease. Ann Intern Med 2006; 144: 21–28.
4. Lew EA, Garfinkel L. Variations in mortality by weight among 750,000 men and women. J Chronic Dis 1979; 32: 563–576.
5. Manson JE, Willett WC, Stampfer MJ et al. Body weight and mortality among women. N Engl J Med 1995; 333: 677–685.
6. Pischon T, Boeing H, Hoffmann K et al. General and abdominal adiposity and risk of death in Europe. N Engl J Med 2008; 359: 2105–2120.
7. National Institutes of Health. Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults—The Evidence Report. National Institutes of Health. Obes Res 1998; 6(Suppl 2):51S–209S.
8. Curtis JP, Selter JG, Wang Y et al. The obesity paradox: Body mass index and outcomes in patients with heart failure. Arch Intern Med 2005; 165: 55–61.
9. Wilson DO, Rogers RM, Wright EC, Anthonisen NR. Body weight in chronic obstructive pulmonary disease. The National Institutes of Health Intermittent Positive-Pressure Breathing Trial. Am Rev Respir Dis 1989; 139: 1435–1438.
10. Escalante A, Haas RW, del R, I. Paradoxical effect of body mass index on survival in rheumatoid arthritis: Role of comorbidity and systemic inflammation. Arch Intern Med 2005; 165: 1624–1629.
11. Leavey SF, Strawderman RL, Jones CA, Port FK, Held PJ. Simple nutritional indicators as independent predictors of mortality in hemodialysis patients. Am J Kidney Dis 1998; 31: 997–1006.
12. Glanton CW, Hypolite IO, Hshieh PB, Agodoa LY, Yuan CM, Abbott KC. Factors associated with improved short term survival in obese end stage renal disease patients. Ann Epidemiol 2003; 13: 136–143.
13. Johansen KL, Kutner NG, Young B, Chertow GM. Association of body size with health status in patients beginning dialysis. Am J Clin Nutr 2006; 83: 543–549.
14. Kalantar-Zadeh K, Kuwae N, Wu DY et al. Associations of body fat and its changes over time with quality of life and prospective mortality in hemodialysis patients. Am J Clin Nutr 2006; 83: 202–210.
15. Leavey SF, McCullough K, Hecking E, Goodkin D, Port FK, Young EW. Body mass index and mortality in 'healthier' as compared with 'sicker' haemodialysis patients: Results from the Dialysis Outcomes and Practice Patterns Study (DOPPS). Nephrol Dial Transplant 2001; 16: 2386–2394.
16. Port FK, Ashby VB, Dhingra RK, Roys EC, Wolfe RA. Dialysis dose and body mass index are strongly associated with survival in hemodialysis patients. J Am Soc Nephrol 2002; 13: 1061–1066.
17. Wolfe RA, Ashby VB, Daugirdas JT, Agodoa LY, Jones CA, Port FK. Body size, dose of hemodialysis, and mortality. Am J Kidney Dis 2000; 35: 80–88.
18. Beddhu S, Pappas LM, Ramkumar N, Samore M. Effects of body size and body composition on survival in hemodialysis patients. J Am Soc Nephrol 2003; 14: 2366–2372.
19. Kovesdy CP, Anderson JE, Kalantar-Zadeh K. Paradoxical association between body mass index and mortality in men with CKD not yet on dialysis. Am J Kidney Dis 2007; 49: 581–591.
20. Holley JL, Shapiro R, Lopatin WB, Tzakis AG, Hakala TR, Starzl TE. Obesity as a risk factor following cadaveric renal transplantation. Transplantation 1990; 49: 387–389.
21. Pirsch JD, Armbrust MJ, Knechtle SJ et al. Obesity as a risk factor following renal transplantation. Transplantation 1995; 59: 631–633.
22. Pischon T, Sharma AM. Obesity as a risk factor in renal transplant patients. Nephrol Dial Transplant 2001; 16: 14–17.
23. Ghahramani N, Reeves WB, Hollenbeak C. Association between increased body mass index, calcineurin inhibitor use, and renal graft survival. Exp Clin Transplant 2008; 6: 199–202.
24. Howard RJ, Thai VB, Patton PR et al. Obesity does not portend a bad outcome for kidney transplant recipients. Transplantation 2002; 73: 53–55.
25. Lentine KL, Rocca-Rey LA, Bacchi G et al. Obesity and cardiac risk after kidney transplantation: Experience at one center and comprehensive literature review. Transplantation 2008; 86: 303–312.
26. Johnson DW, Isbel NM, Brown AM et al. The effect of obesity on renal transplant outcomes. Transplantation 2002; 74: 675–681.
27. Massarweh NN, Clayton JL, Mangum CA, Florman SS, Slakey DP. High body mass index and short- and long-term renal allograft survival in adults. Transplantation 2005; 80: 1430–1434.
28. Lynch RJ, Ranney DN, Shijie C, Lee DS, Samala N, Englesbe MJ. Obesity, surgical site infection, and outcome following renal transplantation. Ann Surg 2009; 250: 1014–1020.
29. Bennett WM, McEvoy KM, Henell KR, Valente JF, Douzdjian V. Morbid obesity does not preclude successful renal transplantation. Clin Transplant 2004; 18: 89–93.
30. Marks WH, Florence LS, Chapman PH, Precht AF, Perkinson DT. Morbid obesity is not a contraindication to kidney transplantation. Am J Surg 2004; 187: 635–638.
31. Yusuf S, Hawken S, Ounpuu S et al. Obesity and the risk of myocardial infarction in 27,000 participants from 52 countries: A case-control study. Lancet 2005; 366: 1640–1649.
32. Guallar-Castillon P, Balboa-Castillo T, Lopez-Garcia E et al. BMI, waist circumference, and mortality according to health status in the older adult population of Spain. Obesity (Silver Spring) 2009; 17: 2232–2238.
33. Postorino M, Marino C, Tripepi G, Zoccali C. Abdominal obesity and all-cause and cardiovascular mortality in end-stage renal disease. J Am Coll Cardiol 2009; 53: 1265–1272.
34. Molnar MZ, Keszei A, Czira ME et al. Evaluation of the malnutrition-inflammation score in kidney transplant recipients. Am J Kidney Dis 2010.

35. Hemmelgarn BR, Manns BJ, Quan H, Ghali WA. Adapting the charlson comorbidity index for use in patients with ESRD. Am J Kidney Dis 2003; 42: 125–132.
36. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: A new prediction equation. Ann Intern Med 1999; 130: 461–470.
37. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of competing risk. J Am Stat Assoc 1999; 94: 496–509.
38. Fine JP. Regression modeling of competing crude failure probabilities. Biostatistics 2001; 2: 85–97.
39. Holley JL, Monaghan J, Byer B, Bronsther O. An examination of the renal transplant evaluation process focusing on cost and the reasons for patient exclusion. Am J Kidney Dis 1998; 32: 567–574.
40. Scandling JD. Kidney transplant candidate evaluation. Semin Dial 2005; 18: 487–494.
41. Kuk JL, Janiszewski PM, Ross R. Body mass index and hip and thigh circumferences are negatively associated with visceral adipose tissue after control for waist circumference. Am J Clin Nutr 2007; 85: 1540–1544.
42. Kovesdy CP, Kalantar-Zadeh K. Why is protein-energy wasting associated with mortality in chronic kidney disease? Semin Nephrol 2009; 29: 3–14.
43. Haslam DW, James WP. Obesity. Lancet 2005; 366: 1197–11209.
44. Argiles JM. Cancer-associated malnutrition. Eur J Oncol Nurs 2005; 9(Suppl 2):S39–S50.
45. Lee PS, Waxman AB, Cotich KL, Chung SW, Perrella MA, Stossel TP. Plasma gelsolin is a marker and therapeutic agent in animal sepsis. Crit Care Med 2007; 35: 849–855.
46. Rothenbach PA, Dahl B, Schwartz JJ et al. Recombinant plasma gelsolin infusion attenuates burn-induced pulmonary microvascular dysfunction. J Appl Physiol 2004; 96: 25–31.
47. Christofidou-Solomidou M, Scherpereel A, Solomides CC et al. Recombinant plasma gelsolin diminishes the acute inflammatory response to hyperoxia in mice. J Investig Med 2002; 50: 54–60.
48. Lee PS, Sampath K, Karumanchi SA et al. Plasma gelsolin and circulating actin correlate with hemodialysis mortality. J Am Soc Nephrol 2009; 20: 1140–1148.
49. Haap M, Siewecke C, Thamer C et al. Multiple symmetric lipomatosis: A paradigm of metabolically innocent obesity? Diabetes Care 2004; 27: 794–795.
50. Lemieux I. Energy partitioning in gluteal-femoral fat: Does the metabolic fate of triglycerides affect coronary heart disease risk? Arterioscler Thromb Vasc Biol 2004; 24: 795–797.
51. Snijder MB, Dekker JM, Visser M et al. Trunk fat and leg fat have independent and opposite associations with fasting and postload glucose levels: The Hoorn study. Diabetes Care 2004; 27: 372–377.