Association of obesity and muscle mass with risk of albuminuria in renal transplant recipients

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Abstract

Background Increased albuminuria is a predictor of graft loss in kidney graft recipients. It is unknown whether obesity is an independent risk factor for the development of increased albuminuria in this population. The aim of this study was to elucidate the association between obesity and albuminuria in renal transplant recipients.

Methods We enrolled 330 renal transplant recipients and prospectively collected demographic, anthropomorphic, clinical and laboratory variables susceptible to influence albumin excretion. The outcome was albuminuria, measured using accurately timed urine collections. Data from 201 patients were analyzed after exclusion of participants with missing data and patients enrolled less than 6 months since renal transplantation. Analysis was carried out for an early and a late period, defined according to the 2.4-year median follow-up time.

Results Body mass index (BMI), waist circumference and urinary creatinine excretion rate were independent predictors of albuminuria in the late post-transplant period, indicating that the predictive value of body mass index for albuminuria is related to both increased abdominal fat mass and increased muscle mass. BMI was an independent predictor of microalbuminuria. Waist circumference and urinary creatinine were independent predictors of microalbuminuria for values above certain cutoffs: 110% of the accepted thresholds defining abdominal obesity and 1500 mg/day, respectively.

Conclusions These associations, which have not previously been reported, suggest, but do not prove, that an imbalance between metabolic demand and nephron mass may be responsible for increased albuminuria in the renal transplant population.

Keywords Abdominal obesity · Glomerular hyperfiltration · Kidney transplant · Microalbuminuria · Muscle mass

Introduction

Renal transplant recipients have an increased risk of premature death due to cardiovascular and non-cardiovascular causes [1]. An increased urinary albumin excretion (UAE) rate is associated with increased risk for cardiovascular morbidity and mortality in both the general [2, 3] and the renal transplant populations [4, 5]. Obesity is an independent

risk factor for the development of microalbuminuria [6] and advanced stages of chronic kidney disease [CKD] [7] in the general population. Most studies in the renal transplant population [RTP] confirmed the role of obesity as a risk factor for graft failure [8, 9]. Considering the predictive power of albuminuria for graft loss [4, 5], we designed the present investigation to elucidate the relationship between obesity and albuminuria in this population, using prospectively collected data.

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Methods

Study population

The population investigated in this prospective cross-sectional study includes 330 adult kidney allograft recipients attending a renal transplant clinic in a tertiary care institution [Rabin Medical Center, Petah Tikva, Israel], who

were enrolled in 2008–2011. Data collected for the first 269 enrolled subjects were analyzed in order to define gender-specific cutoffs for urinary albumin/creatinine ratio for the detection of microalbuminuria in the RTP and were previously reported [10]. A secondary analysis was performed on the data collected for all 330 participants to determine the role of obesity as a predictor of albuminuria in the transplant population. This analysis is the subject of the present report. The study protocol was approved by the Rabin Medical Center Institutional Review Board. Participants gave their written informed consent. The study was conducted following the principles of the Declaration of Helsinki. The reported clinical and research activities are consistent with the Principles of the Declaration of Istanbul as outlined in the “Declaration of Istanbul on Organ Trafficking and Transplant Tourism”.

Inclusion criteria

Patients with functioning renal graft attending the renal transplant clinic at Rabin Medical Center who agreed to participate in the research study and signed an informed consent.

Exclusion criteria

Known proteinuria above 500 mg/day and/or known albuminuria above 300 mg/day; inability to perform accurate urine collection, as perceived by the investigators who followed the patients at the renal clinic; an infectious disease or use of nonsteroidal anti-inflammatory drugs during the 30 days

preceding enrollment; acute rejection during the 30 days preceding enrollment.

Figure 1 depicts the study flowchart. Out of 330 subjects, 38 were excluded because of missing data, 16 because of an albumin excretion rate higher than 300 mg/day, and 75 because of enrollment earlier than 6 months following transplantation. The latter subjects were excluded from the secondary analysis since temporary factors frequently affect renal function during this period. Thus, 201 subjects were included in the final analysis. Data were missing in one participant for age, in one for diabetes mellitus (DM) status, in nine for HbA1c measurements, in five for blood pressure measurements, in two for serum creatinine and in one for current smoking data.

Data collection

Enrolled participants were asked to provide a 24-h urine collection and given instructions on how to accurately time the urine collection. The times of beginning and end of collection were recorded. Urine was tested for albumin and creatinine excretion.

On the morning after completion of the urine collection, blood pressure was measured 3 times by a trained observer after 5 min of rest in the sitting position using an electronic oscillometric blood pressure measuring device. Blood pressure was calculated as the mean of the second and third readings. Gender, age, time of transplantation, past medical history [cardiovascular disease, DM] and medication use were recorded. Body weight, height and waist circumference were measured by a trained staff member. Blood was

Fig. 1 Investigation flowchart

drawn from a peripheral vein for serum creatinine, glucose and HbA1c measurement.

Analytical methods

The volume of each urine collection was accurately measured. Urine samples were kept at 4 °C and assayed within 5 days. Albumin and creatinine measurements were performed on each urine collection and each spot urine sample. The urinary albumin concentration was determined by a solid-phase, competitive chemiluminescence enzyme immunoassay [Immulite Analyzer, DPC] and the urinary creatinine concentration was determined by the Jaffe colorimetric assay. Hemoglobin A1c was determined by the turbidimetric inhibition immunoassay for hemolyzed whole blood [Cobas Integra 800, Roche, Basel, Switzerland].

Definitions

Microalbuminuria was defined as a urinary albumin excretion rate between 30 and 300 mg/day and abdominal obesity as waist circumference above 88 cm for women and above 102 cm for men [11]. DM was diagnosed if the HbA1c level was equal to or above 6.5% or if the patient received pharmacological treatment for DM. In case of missing data for HbA1c, DM was defined when the fasting blood glucose was equal to or above 126 mg/dl.

Calculations

Body mass index [BMI] was calculated as the body weight [kg] divided by the squared height [m²]. Adjusted waist circumference was calculated as the waist circumference [cm] divided by gender-specific cut-off points for obesity, 88 cm for women and 102 cm for men [11]. Solute excretion rate was calculated as solute concentration times urine collection volume. When the duration of the collection differed from 24 h, solute excretion rate was expressed per 24 h.

Statistical analysis

Results are expressed as mean and SD for normally distributed data, and median and interquartile range for non-normally distributed data. Differences between the means of different groups were analyzed using Student's *t* test for normally distributed and Mann–Whitney *U* test for non-normally distributed data. Differences in frequency distribution were estimated using the χ^2 test. For correlations between continuous variables, we used Pearson correlation test with a two-tailed significance level of 0.05. The primary independent variable of the study was BMI and its secondary variables were waist circumference and 24-h urinary creatinine excretion. We did not evaluate these variables

in the same model due to significant collinearity. We used single and multiple linear regression analysis for evaluating the correlation between the independent variables and log-transformed UAE. For multivariate analysis, we used a forward stepwise regression model with a *p* value of 0.05 for inclusion. The variables that were evaluated included: age, gender, time since transplantation, DM status, systolic and diastolic blood pressure, heart disease, treatment with mTOR inhibitors, blood pressure medications [renin-angiotensin inhibitors, calcium channel blockers and beta blockers], serum creatinine and current smoking. We also, introduced systolic blood pressure, DM status and use of mTOR inhibitors into the additional model regardless of significance level. The interaction with time was evaluated by multiplying BMI with time and its significance level was evaluated in addition to BMI. Furthermore, in order to evaluate the interaction of BMI with time, we performed analysis of variance (ANOVA) on log transformed albuminuria using BMI (divided into two groups with 30 kg/m² as cutoff value) and time since transplantation (divided into medians and quartiles) as a fixed effect and potential confounders as covariates. For evaluation of association between the independent variables and the risk of microalbuminuria, we used univariate and multivariate logistic regression analysis. For multivariate analysis, we used a forward stepwise regression model with a *p* value of 0.05 for inclusion using the variables detailed above. We introduced systolic blood pressure and DM status into the additional model regardless of significance level. For further evaluation of the interaction of the association between UAE and BMI with time, we divided the patients into early and long-term groups according to median time elapsed from transplantation and analyzed each group separately. Receiver operating characteristic (ROC) curve analysis was used as secondary analysis in order to identify potential cutoff values for two independent variables—adjusted waist circumference and urinary creatinine—as predictors of microalbuminuria. Youden's index was used to determine the optimal cut-offs. Statistical analysis was performed using SPSS version 25.

Results

The characteristics of the 201 patients included in the final analysis are presented in Table 1. The median time since transplantation was 2.44 years and its range 0.50–25 years.

BMI associations

BMI was 27.3 ± 5.1 [median 27, range 15.7–45.2] and 54 [26.7%] patients had a BMI of 30 or more. BMI was positively correlated with the presence of DM [29.7 ± 5.4 vs. 26.2 ± 4.5 , $p < 0.001$], high urinary creatinine excretion

Table 1 Characteristics of the study participants

Variable	
N	201
Age (years)	53.5 ± 12.4
Male gender N (%)	130 (65%)
Time since transplantation (years)	2.4 (1.0–6.5)
Diabetes mellitus N (%) ^a	77 (39%)
Heart disease N (%)	54 (27%)
Body mass index (kg/m ²)	27.3 ± 5.1
Waist circumference, male (cm)	99.7 ± 18.6
Waist circumference, female (cm)	92.1 ± 14.4
Systolic blood pressure (mm Hg) ^a	134 ± 19
Diastolic blood pressure (mm Hg) ^a	77 ± 10
Hemoglobin A1c (%) ^a	6.1 ± 1.0
Serum creatinine (mg/dl)	1.2 ± 0.6
Urinary creatinine (mg/24 h)	1276 ± 402
Urinary albumin (mg/24 h)	23 (8–58)
mTOR inhibitors N (%)	25 (12%)
Renin-angiotensin inhibitors N (%)	87 (43%)
Calcium blockers N (%)	74 (37%)
Beta blockers N (%)	72 (36%)
Diuretics N (%)	30 (15%)
Current smoking N (%) ^a	16 (8%)

^a Missing data: Age-1, DiabetesMellitus-1; Blood pressure-5; Serum creatinine-2; Hemoglobin A1c-9; Current smoking-1

[$r=0.316$, $p<0.001$], increased age [$r=0.145$, $p=0.035$], high serum glucose [$r=0.298$, $p=0.002$] and high systolic blood pressure [$r=0.177$, $p=0.012$].

Median UAE was 23 mg/24 hr [25–75 percentiles 8–58]. Eighty-five patients [42.1%] had microalbuminuria. By univariate linear regression analysis, there was a significant association between BMI and log UAE [$B=0.04$, 95% CI 0.007–0.073, $r=0.16$, $p=0.019$, Fig. 2a]. By multiple linear regression, serum creatinine, systolic blood pressure and treatment with mTOR inhibitors were associated with log UAE [$r=0.427$, $p<0.001$]. BMI was not associated with log UAE after adjustment for these variables [$B=0.027$, 95% CI – 0.006–0.060, $p=0.11$].

BMI was associated with microalbuminuria by univariate logistic regression analysis [OR 1.063 per kg/m², 95% CI 1.004–1.124, $p=0.035$]. By multivariate analysis, serum creatinine and treatment with mTOR inhibitors were associated with increased odds of microalbuminuria. There was a non-significant trend for increased odds of microalbuminuria with increased BMI [OR 1.059 per kg/m², 95% CI 0.996–1.126, $p=0.068$].

In order to evaluate whether the association between BMI and UAE changed over time, we evaluated the association between the interaction of BMI and time since transplantation and UAE. The interaction was significantly

associated with UAE [$p=0.003$] and this association was still significant after adjustment for BMI and time since transplantation [$p=0.038$]. To further analyze this association, we performed ANOVA with time since transplantation divided into medians or quartiles evaluated, with BMI (below and above 30 kg/m²), serum creatinine, use of mTOR inhibitors and systolic blood pressure as covariates. We analyzed the interaction between time since transplantation and BMI. While the interaction between median time and BMI was significant ($p=0.04$), the interaction between time quartiles and BMI did not reach the significance level ($p=0.056$).

As these results suggest that the association between BMI and UAE changes over time, with median time since transplantation as a suitable cutoff, we evaluated the association between BMI and UAE separately for the early and long-term groups [defined as the follow-up period preceding and following the 2.44 years median time elapsed since transplantation, respectively].

Median UAE in the early group was 20 mg/24 hr [9–44]. Thirty-seven patients [37%] had microalbuminuria. By univariate linear regression analysis, there was no association between BMI and log UAE [$B=0.015$, 95% CI – 0.027–0.057, $r=0.071$, $p=0.48$, Fig. 2b]. By multiple linear regression, only serum creatinine was significantly associated with log UAE. There was no significant association between BMI and UAE when it was added into the model [$p=0.75$]. There was also no association between BMI and the odds of microalbuminuria [OR 1.018 per kg/m², 95% CI 0.94–1.1, $p=0.65$].

Median UAE in the long-term group was 23 mg/24 hr [7–94]. Forty-seven patients [46.5%] had microalbuminuria. By univariate linear regression analysis, there was a significant association between BMI and log UAE [$B=0.08$, 95% CI 0.026–0.133, $r=0.286$, $p=0.004$, Fig. 2c]. Using multiple linear regression analysis, mTOR inhibitor treatment, serum creatinine, systolic blood pressure and BMI [$B=0.057$, 95% CI 0.008–0.106, $p=0.023$] were associated with log UAE [$r=0.556$, $p<0.001$ for the model]. BMI was still significantly associated with log UAE after addition of DM status into the model [$B=0.057$, 95% CI 0.007–0.107, $p=0.027$, ($r=0.528$, $p<0.001$ for the model)]. The full model is presented in Table 2.

BMI was also associated with increased odds ratio [OR] for microalbuminuria using univariate logistic regression analysis [OR 1.15 per kg/m², 95% CI 1.04–1.26, $p=0.004$]. By multivariate logistic regression analysis, mTOR inhibitor treatment, systolic blood pressure, serum creatinine and BMI [OR 1.15 per kg/m², 95% CI 1.03–1.27, $p=0.012$] were associated with increased OR for microalbuminuria (Table 3). BMI was still significantly associated with increased rate of UAE after introducing DM status into the model [OR 1.15 per kg/m², 95% CI 1.04–1.28, $p=0.009$].

Fig. 2 Scatter plot of log-transformed urinary albumin excretion versus body mass index for the whole group [$n=201$] (a), the early group [less than 2.44 years after transplantation, $n=100$] (b) and the long-term group [2.44 years or more after transplantation, $n=101$] (c). BMI, body mass index

Table 2 Predictors of urinary albumin excretion in the long-term group: univariate and multivariate linear regression analysis for the model including BMI

Variable	Univariate analysis					Multivariate analysis				
	B	β	95% CI B		<i>p</i>	B	β	95% CI B		<i>p</i>
BMI	0.08	0.29	0.03	0.13	0.004	0.06	0.21	0.01	0.11	0.023
mTOR inhibitors	0.86	0.25	0.18	1.53	0.013	0.95	0.25	0.36	1.54	0.002
Systolic BP	0.02	0.33	0.01	0.04	0.001	0.01	0.24	0.001	0.02	0.026
Serum creatinine	0.64	0.32	0.26	1.02	0.001	0.63	0.29	0.23	0.97	0.001

BMI body mass index, CI confidence interval

Table 3 Odds ratio for microalbuminuria in the long-term group: univariate and multivariate logistic regression analysis for the model including BMI

Variable	Univariate analysis				Multivariate analysis			
	OR	95% CI OR		<i>p</i>	OR	95% CI OR		<i>p</i>
BMI (per kg/m ²)	1.15	1.04	1.26	0.004	1.15	1.03	1.27	0.012
mTOR inhibitors	2.74	0.94	8	0.065	3.56	1.1	12.35	0.042
Systolic BP (per mm Hg)	1.04	1.01	1.06	0.005	1.03	1.002	1.06	0.038
Serum creatinine (per mg/dl)	5.25	1.52	18.16	0.009	4.68	1.36	16.11	0.015

BMI body mass index, BP blood pressure, CI confidence interval, OR odds ratio

Changes in BMI may reflect changes in both fat and lean body mass. In order to evaluate the role of these determinants in the association between BMI and UAE in the long-term group, we used waist circumference as an indicator of visceral fat mass [8] and urinary creatinine as an indicator of muscle mass [9].

Waist circumference association with UAE—long-term group

Waist circumference was significantly associated with log UAE by simple linear regression [$B=0.017$ per cm, 95% CI 0.001–0.033, $r=0.203$, $p=0.037$]. By multiple linear regression analysis, mTOR inhibitor treatment, serum creatinine, systolic blood pressure and waist circumference [$B=0.014$ per cm, 95% CI 0.000–0.028, $p=0.05$] were associated with log UAE [$r=0.518$, $p<0.001$, for the model]. However, addition of DM status to the model rendered this association not significant [$B=0.014$ per cm, 95% CI – 0.001–0.029, $p=0.061$, ($r=0.518$, $p<0.001$) for the model]. The relationship between adjusted waist circumference and log UAE as a continuous variable was not significant [$B=0.014$ per percent, 95% CI – 0.002–0.029, $r=0.173$, $p=0.083$] and [$B=0.011$ per percent, 95% CI – 0.004–0.033, $p=0.145$] for univariate and multivariate analyses, respectively.

Adjusted waist circumference was not significantly associated with the odds of microalbuminuria [OR 1.023 per cm, 95% CI 0.997–1.049, $p=0.084$]. By multivariate analysis mTOR inhibitor treatment, serum creatinine and systolic blood pressure were associated with odds of microalbuminuria. Waist circumference was not significantly associated with odds of microalbuminuria when added to this model [OR 1.023 per cm, 95% CI 0.994–1.053, $p=0.116$] and to

the model after addition of DM status [OR 1.026 per cm, 95% CI 0.997–1.057, $p=0.08$].

By ROC curve analysis the optimal cutoff point for adjusted waist circumference as a predictor of microalbuminuria was 1.10, i.e. a circumference 10% above the reference value (Supplementary Material 1 Fig S1). Detailed results of this analysis are provided as supplementary material (Supplementary Material 2).

Urinary creatinine association with UAE—long-term group

Urinary creatinine was significantly associated with log UAE by simple linear regression [$B=0.753$ per gr, 95% CI 0.088–1.417, $r=0.221$, $p=0.027$]. By multiple linear regression analysis, mTOR inhibitor treatment, serum creatinine, systolic blood pressure and urinary creatinine [$B=0.691$ per gr, 95% CI 0.107–1.274, $p=0.021$] were associated with log UAE [$r=0.537$, $p<0.001$, for the model]. The addition of DM into the model gave comparable results [$B=0.706$ per gr, 95% CI 0.116–1.296, $p=0.019$, ($r=0.533$, $p<0.001$ for the model)]. Normalization of urinary creatinine to height did not change the results: [$B=0.137$ per mg/cm, 95% CI 0.014–0.267, $r=0.221$, $p=0.029$] and [$B=0.125$ per mg/cm, 95% CI 0.015–0.235, $p=0.027$, ($r=0.529$, $p<0.001$ for the model)] for univariate and multivariate, respectively.

In contrast, urinary creatinine was not significantly associated with the odds for microalbuminuria [OR 2.47 per gr, 95% CI 0.88–6.98, $p=0.087$]. By multivariate logistic regression analysis mTOR inhibitor treatment, serum creatinine and systolic blood pressure were associated with odds of microalbuminuria. Urinary creatinine was not significantly associated with odds of microalbuminuria when

added to this model [OR 2.39 per gr, 95% CI 0.74–7.68, $p=0.145$]. Addition of DM status into the model gave similar results [OR 2.46 per gram, 95% CI 0.76–7.95, $p=0.134$].

By ROC curve analysis the optimal cutoff for urinary creatinine as a predictor of microalbuminuria was 1500 mg per 24 h (Supplementary Material 1 Fig S1). Detailed results of this analysis are provided as supplementary material (Supplementary Material 2).

Discussion

This study reveals that BMI, waist circumference and urinary creatinine excretion are independent predictors of albuminuria in the late period following renal transplantation.

Albuminuria is a predictor of advanced CKD and mortality in the general population [2, 3] and in the RTP [4, 5]. While the role of obesity as an independent risk factor for albuminuria in the general population is well established, its predictive role for albuminuria has not been examined in renal transplant recipients. In the present cross-sectional study, we evaluated the relationship between obesity and albuminuria in the RTP, using data collected for research purposes on demographic, anthropomorphic, clinical and laboratory variables susceptible to influence albumin excretion.

Whole group analysis showed that BMI is not an independent predictor of albuminuria. Following renal transplantation, the engrafted kidney is immersed in a new milieu provided by the recipient's metabolic and adiposity state. The influence of adiposity on albuminuria, if it occurs, is expected to be time-related and to develop after prolonged exposure to an obese environment provided by the recipient. A separate statistical analysis was thus performed for an early and a late period. These periods were defined according to the 2.4-year median time elapsed at the time of data collection since transplantation. This analysis revealed that in the late period, BMI is an independent predictor of albuminuria and microalbuminuria after adjustment, amongst others, for arterial pressure and the presence of DM.

BMI is used as an indicator of body adiposity [11]. However, body weight, one of the determinants of BMI, is itself determined by both adiposity and lean body mass. We questioned whether fat mass, lean body mass or both account for the predictive role of BMI for albuminuria. Since abdominal fat excess is responsible for the increased rate of cardiovascular morbidity and of overall mortality associated with obesity in the general population [11], we evaluated the power of abdominal obesity and lean body mass, in addition to that of BMI, as predictors of albuminuria and microalbuminuria in the RTP. Waist circumference and urinary creatinine excretion rate were used as markers of abdominal obesity [11] and lean body mass [12], respectively. Both variables

were found to be independent predictors of albuminuria. The primary statistical analysis showed that these variables were not predictors of microalbuminuria. We were surprised by the fact that waist circumference was associated with albuminuria and not with microalbuminuria in the late group, while BMI predicted microalbuminuria in this same group. Four factors may account for this discrepancy: the intrinsic variability of 24-h urinary albumin excretion, a type B statistical error, an additive or synergistic effect of 2 of the BMI components—adiposity and lean body mass—on the predictive effect of BMI on microalbuminuria and the presence of a threshold effect. The latter hypothesis was tested using ROC curve analysis aimed at detecting the presence of a threshold value above which these variables may be associated with microalbuminuria. It revealed that urinary creatinine above 1500 mg/day and waist circumference above 110% of the accepted thresholds defining abdominal obesity (11) predict microalbuminuria. Thus, in the late period following transplantation, increased abdominal fat and increased muscle mass are associated with albuminuria and, above certain levels of these variables, with microalbuminuria. These predictive effects are independent of confounding factors, as arterial pressure, DM, serum creatinine and treatment with mTOR inhibitors. Abdominal obesity is an established independent risk factor for the development of increased albuminuria in the general population [6]. The present findings demonstrate that the independent relationship between abdominal adiposity and albuminuria also occurs in the RTP.

Muscle mass was found to independently predict albuminuria in the RTP. This finding is novel. No studies have previously examined the relationship between muscle mass and albuminuria in transplant recipients. Studies in the general population [13] and in type 2 diabetic subjects [14] showed the opposite, i.e. that sarcopenia is independently associated with albuminuria. The sarcopenia-associated risk for albuminuria is further increased when obesity is associated with sarcopenia [15]. Decreased muscle mass is a frequent finding in renal transplant recipients [16, 17]. Two groups [18, 19] previously evaluated the relationship between sarcopenia and outcome in the RTP. Chan et al. [18] investigated the associations of muscle strength, muscle mass, sarcopenia, and sarcopenic obesity with a composite endpoint of all-cause mortality and acute hospitalization. They found that low muscle strength was associated with negative outcomes. The association between low muscle mass and poor outcomes was present in a partially adjusted model, but not after further adjustment for confounding variables. In contrast, Oterdoom et al. [19], using urinary creatinine excretion as a marker of muscle mass in an RTP showed that low muscle mass predicts mortality. In addition, low muscle mass predicted graft loss in patients with a protein excretion rate of more than 400 mg/day but not in a subgroup without

proteinuria, which is the population included in our study. Our present findings are not in line with these 2 investigations. It could be argued that the studied outcomes are different, albuminuria in the present study vs. mortality and graft survival in the previous ones. However, considering the known predictive value of albuminuria on mortality and graft survival in the RTP [4, 5] we have to recognize that there is a discrepancy between the positive relationship linking muscle mass and albuminuria found in the present study and the findings of the previous studies showing a negative relationship or no relationship between muscle mass and hard outcomes. The reason for this discrepancy is unclear and could be related to differences related to methodology and population.

The singularity of the independent association of muscle mass with albuminuria found in the present study in the RTP suggests that albuminuria results from an imbalance between the recipient body mass and nephron supply. It has been shown that transplantation of a low functioning nephron mass relative to the recipient body mass is associated with a high risk of renal graft failure [20]. This occurs in various circumstances, such as kidney transplantation from old or very young donors to young adult recipients [21], a more than 10 kg excess in recipient's body weight as compared to donor's weight [22] and a low ratio of donated kidney weight to recipient's body weight [23–30]. Thus, it is reasonable to hypothesize that the marked independent relationship between muscle mass and albuminuria revealed by the present investigation arises from an adaptive hyperfiltration nephropathy [31], consequent to the co-occurrence of a relatively low engrafted nephron mass and a relatively high muscle mass [23, 31]. Brenner's group showed more than 3 decades ago that a reduced nephron mass leads to glomerular hypertension and single-nephron hyperfiltration in remnant glomeruli, resulting in glomerulosclerosis and renal insufficiency [32].

This adaptive glomerular hyperfiltration and the related mechanical stress applied on nephron structures form a central mechanism underlying the progression of CKD following nephron injury [33]. It also accounts for the increased prevalence of progressive kidney disease in subjects with congenital dysplastic kidney [34] and those who underwent nephrectomy [35, 36]. Single-nephron glomerular hyperfiltration may also occur independently of decreased nephron mass, as in obesity, where hyperfiltration is adaptive to the increased metabolic requirements. The association between obesity and renal hyperfiltration, known for more than 4 decades [37], led to the assumption by inference that obesity is associated with hyperfiltration at the single-nephron level [38–40]. This link between obesity and single-nephron hyperfiltration was recently confirmed by a study combining physiological and stereologic measurements on kidney biopsies [41].

Despite the elevated risk associated with low nephron mass and obesity, most individuals born with a single kidney and most obese people do not develop advanced CKD. By contrast, Praga's group [31, 34] demonstrated that the risk for progressive kidney disease in obese patients with reduced nephron mass is markedly increased, suggesting a synergistic effect between low nephron mass-induced hyperfiltration and obesity-induced hyperfiltration. Subsequent studies showed that BMI above 30 is an independent risk factor for CKD 5 following kidney donation [35, 36]. Likewise, studies on IgA nephropathy [42] demonstrated that obesity is an independent predictor of progression of the disease. This effect probably reflects the interaction between obesity and low nephron mass, the latter resulting from initial inflammatory and sclerotic injury occurring in IGA nephropathy. These studies suggest that the interaction between 2 factors prompting hyperfiltration brings about accelerated CKD progression.

The present investigation reveals muscle mass as a new independent factor predicting glomerular dysfunction in the RTP. Lean body mass is associated with glomerular hyperfiltration [43–47], suggesting that a high lean body mass is associated with increased single-nephron glomerular filtration rate. The findings of the present study suggest that muscle mass emerges as a risk factor for glomerular dysfunction when increased lean body mass is associated with reduced nephron mass.

The present study shows that albuminuria is associated with BMI and 2 of its determinants—fat mass and lean body mass. Considering the known causal relationship between BMI and hyperfiltration, as demonstrated by a decrease in glomerular filtration rate following bariatric surgery [48, 49] and between hyperfiltration and glomerular injury [32, 33, 50, 51], it is tempting to assume a cause-to-effect relationship between elevated BMI and albuminuria. This hypothetical cause-to-effect relationship is illustrated in Fig. 3. However, a dependence between these 2 variables does not imply a cause-and-effect relationship. The present study, as most non-interventional studies, cannot prove or disprove causality and we cannot rule out that unknown factors associated with body mass are the cause of albuminuria.

The fact that BMI, waist circumference and muscle mass emerge as predictors of albuminuria in the late period following transplantation and not in the early period reflects the time needed for factors associated with obesity and lean body mass to trigger changes in glomerular permeability leading to albuminuria. This lag-time is less than 2.5 years. To the best of our knowledge, no data are available regarding the time needed for body mass to emerge as a predictor of albuminuria in the general population. However, considering the low nephron mass of the renal graft, this time lag is probably much shorter in the RTP than in the general population.

Fig. 3 Hypothetical explanation for the increased risk of albuminuria associated with obesity and increased muscle mass in the renal transplant recipient. Renal grafts have reduced nephron mass. Abdominal obesity and increased muscle mass concur to induce single-nephron

The strength of this study comes from the prospective data collection carried out for research purposes, with blood pressure and anthropometric measurements made by trained team members and accurate information obtained regarding urine collection timing. The main study weaknesses are the relatively small number of participants recruited in a single center and its cross-sectional nature.

In conclusion, BMI, abdominal obesity and muscle mass predict albuminuria in the late period following renal transplantation. Considering the importance of albuminuria as a predictor of mortality, screening for albuminuria in the RTP may allow identification of obese renal transplant recipients at risk for progressive CKD and premature death.

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Author contributions BZ: data collection; discussion on results and contribution to the manuscript. AE: study design, laboratory analysis; discussion on results and contribution to the manuscript. TM: data collection; discussion on results and contribution to the final manuscript. AC: study design; data analysis; discussion on results and contribution to the final manuscript; BRZ: data analysis, statistical analysis, discussion on results and contribution to the final manuscript. RR: study design; data collection; discussion on results and contribution to the final manuscript. All authors reviewed and approved the final manuscript.

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Data availability Datasets analyzed during the current study will be made available upon publication in a public repository. All individual participant data will be de-identified.

Compliance with ethical standards

Conflicts of interest The authors have no conflict of interest to declare.

Ethics approval The study protocol was approved by the Rabin Medical Center Institutional Review Board. The study was conducted following the principles of the Declaration of Helsinki. The reported clinical and research activities are consistent with the Principles of the Declaration

hyperfiltration and increased albuminuria. Glomerular hyperfiltration occurring in the presence of reduced nephron mass raises the risk for increased urinary albumin excretion. *BMI* body mass index, *SNGFR* single-nephron glomerular filtration rate

of Istanbul as outlined in the “Declaration of Istanbul on Organ Trafficking and Transplant Tourism”.

Consent to participate Informed consent was obtained from all individual participants included in the study.

Consent to publish The signed informed consent to participate in the research study included a statement that published data will be de-identified.

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