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ORIGINAL ARTICLE

Prevalence of abdominal aortic calcifications in older living renal donors and its effect on graft function and histology

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Summary

We assessed the prevalence of abdominal aortic calcification (AAC) in older living kidney donors and its effect on recipient eGFR and graft histology. A total of 292 consecutive living pairs with donor age ≥50 from 2003 to 2013 were identified (mean age 56; range 50–78; F/M: 1.8). Donor AAC was determined by prenephrectomy unenhanced CT. Recipient eGFR and spot urine protein: creatinine ratios (UPCRs) were recorded. A total of 180 recipients had 6-month protocol biopsies. AAC was present in 40.7% of donors, and they were older (58.6 versus 54.7 years old, $P < 0.0001$) and more likely to be male (77.6% vs. 37.3%, $P = 0.004$). There was no significant difference in eGFR or spot UPCR up to 36 months in recipients of allografts from donors with versus without AAC. At 6-month biopsy, there was a higher percentage of allografts with vascular fibrous intimal thickening and arteriolar hyaline thickening from donors with versus without AAC (vascular fibrous intimal thickening: 38.8% vs. 7.1% and arteriolar hyaline thickening: 35.8% vs. 7.1%; $P < 0.001$ for both). The presence of donor AAC predicts the presence of vascular disease [vascular fibrous intimal thickening (OR: 7.2; CI:2.9–17.9) and arteriolar hyaline thickening (OR:5.7; CI:2.3–14.1)] in allografts at 6 months. Donor AAC is predictive of renal vascular disease and may help to improve the screening of potential donors and inform post-transplant management.

Introduction

Kidney transplantation, particularly from a living donor, is the treatment of choice for most patients with end-stage renal disease (ESRD). Over the last five decades, there has been a steady increase in the median age of the living kidney donor [1,2], and in 2011, over one-quarter of all living kidney donors were ≥50 years old. Although this expansion of the donor pool to include older donors has helped to mitigate the shortage of organs while achieving similar short-term graft survival rates [3], it has been demonstrated that increasing living donor age is associated with lower recipient glomerular filtration rate (GFR) and reduced long-term graft survival, especially for younger recipients [3,4]. Gaining a better understanding of the factors that affect outcomes of older living kidneys can improve screening and selection of potential donors and allow us to tailor immunosuppression and optimize the medical management in the recipients.

A key feature of atherosclerosis is vascular calcifications, which tend to increase with age. Vascular calcification has been shown to be a marker of atherosclerotic plaque burden and a contributor to arterial stiffness [5]. The presence of abdominal aortic calcification (AAC) has been associated with adverse cardiovascular events, chronic kidney disease, and end-stage renal disease [6]. However, the impact of donor AAC on living kidney transplantation has not yet been explored. The aim of this study was to determine the

prevalence of AAC in older (≥50 years old) living kidney donors and to assess the effect of donor AAC on recipient allograft function and histology.

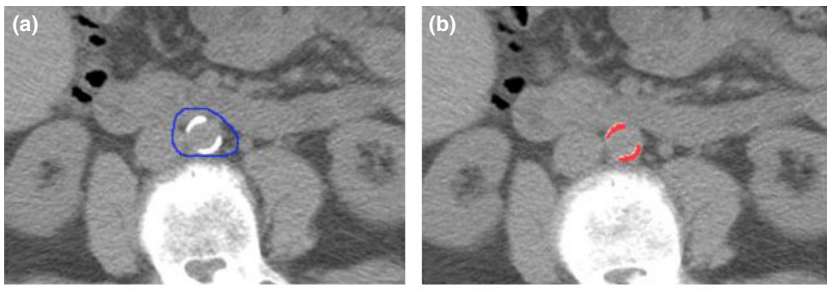
Materials and methods

This is a single-center retrospective study approved by the Institutional Review Board; informed consent was waived. An electronic database of donors and recipients was used to identify 292 consecutive living donor–recipient pairs from 2003 to 2013 with donor age ≥50 years ("older living donors"). The time frame was chosen to allow maximum completeness of data from our electronic medical record, which was utilized from 2003. Clinical and laboratory data including renal function and protocol biopsy data detailed below were obtained as part of standard clinical care for the donors and recipients. These data were retrospectively queried in our study.

Donors

Each donor underwent a renal donor protocol CT as part of the standard-of-care predonation workup. The CT examination was performed on a multidetector helical scanner at 120 kVp (peak kilovoltage), and auto mA. Each CT examination consisted of axial unenhanced images at 5-mm slice thickness from the liver dome to the ischium, followed by 1.25- or 2.5-mm slice thickness images from the liver dome to iliac crest during angiographic phase after administration of 150 cc of intravenous iodinated contrast material and then 1.25- or 2.5-mm slice thickness images from the liver dome to the ischium at 90 s delay. In our study, we measured donor AAC on the unenhanced CT images (obtained as part of the standard-of-care renal donor CT examination) using postprocessing software, calcium analysis tool (Aquarius Work Station, Terarecon, San Mateo, CA, USA) (Fig. 1). On each axial unenhanced image from the level of celiac axis to aortic bifurcation where calcification was seen, one author placed a region of interest (ROI) encompassing the abdominal aorta. The postprocessing software automatically calculated calcification volume score as the number of interconnected voxels with calcification (defined as CT density of 130 Hounsfield unit (HU) or higher) multiplied by the volume of one voxel. The threshold of 130 HU was selected because it is a commonly used threshold for CT assessment of coronary arterial calcification and is the recommended threshold by the software vendor. The total AAC volume score for each patient was then obtained by summing the scores of all individual calcifications and reflected the total volume (in mm^3) of the calcifications present in the abdominal aorta. This calcification volume scoring technique has been applied to the quantification of coronary artery and abdominal aortic calcification previously [7]. The renal lengths as measured in the longest dimension for each kidney in the donors were also recorded.

Medical records of the donors were reviewed, and the presence or absence of hypertension, diabetes, heart disease,



Artery		Lesion	Vol
Other	D-AO	1	235.28
Other	D-AO	2	282.72
Other total		2	518.00
Total:		2	518.00

Figure 1 Representative AAC measurement using postprocessing software and calcium analysis tool (Aquarius Work Station, Terarecon, San Mateo, CA, USA). A region of interest (ROI) was manually placed on an axial unenhanced image encompassing the aorta where calcification was seen. The postprocessing software automatically highlighted the aortic calcification (color red) and calculated calcification volume score as the number of interconnected voxels with calcification (defined as CT density of 130 Hounsfield unit (HU) or higher) multiplied by the volume of one voxel. The table on the bottom right shows the individual and sum of the volume score in mm^3 (right hand column) of the two calcifications shown on the axial CT image. The column labeled "Vol" refers to the AAC volume score.

and proteinuria was recorded. Donor body mass index (BMI) was also recorded.

Recipients

The recipients' 12-, 24-, and 36-month serum creatinine, estimated GFR (eGFR), and spot urine protein: creatinine ratio (UPCR) were recorded. The eGFR was calculated using the Modification of Diet in Renal Disease (MDRD) Study equation: eGFR (ml/min/1.73 m^2) = 175 × (Scr) $^{-1.154}$ × (Age) $^{-0.203}$ × (0.742 if female) × (1.212 if African American).

Since 2009, a 6-month protocol biopsy has been conducted for renal allograft recipients at our institution. One hundred and eighty (180) of the 292 recipients of grafts from donor ≥ 50 years old in this study cohort had 6-month protocol biopsy. All protocol biopsies were interpreted by experienced clinical renal pathologists at our institution. The biopsy results in the electronic medical records were retrospectively reviewed by one author with attention to the presence of the following indices of chronic injury that have previously been associated with poor graft function and outcome: interstitial fibrosis, tubular atrophy, vascular fibrous intimal thickening, and arteriolar hyaline thickening. The quantitative scoring (0–3) for the above four parameters according to the Banff 97 working classification of the renal allograft pathology [8], scored by the renal pathologists and included in the clinical pathology reports, was recorded by one author of this study. The presence or absence of allograft rejection on the biopsy was also noted. As arteriolar hyaline thickening is also considered a characteristic lesion of calcineurin inhibitor nephrotoxicity, and >90% of renal transplant recipients at our institution are placed on the calcineurin inhibitor tacrolimus, the trough level of tacrolimus at the time of the 6-month biopsy was also recorded.

Statistical analysis

Two-tailed Student's *t*-test was used to compare the age, BMI, renal length, and eGFR between donors with AAC and donors without AAC. Two-tailed Student's *t*-test was also used to compare the following data between allografts from donors with AAC and those from donors without AAC: recipient eGFR at 12, 24, and 36 months, and recipient UPCR at 12, 24, and 36 months. Linear regression analysis was used to assess the relationship between donor AAC volume score and recipient eGFR at 12, 24, and 36 months. Fisher's exact tests were used to compare the percentage of allografts with interstitial fibrosis, tubular atrophy, vascular fibrous intimal thickening, and arteriolar hyaline thickening at 6-month protocol biopsy between grafts from donors with AAC and those from donors without AAC. Univariate and multivariate regression analysis was used to determine predictors of the above pathology findings at the 6-month protocol biopsy. Statistical significance was defined as *P*-values <0.05. Statistical analysis was performed using software (STATA, version 8.0, College Station, TX, USA).

Results

From 2003 to 2013, 292 consecutive living donor–recipient pairs with donor age ≥50 were identified at our institution. The mean age of the donors in this group was 56 years, range 50–78 years. Seven (7) of 292 donors had documented hypertension. No donors had diabetes or heart disease. All donors met the criteria of having <150 mg urine protein in a 24-h collection. AAC was present in 40.7% (119 of 292) of donors. The AAC volume scores ranged from 5 mm^3 to 12969 mm^3. The mean and median volume scores for the donors with AAC were 674 mm^3 and 201 mm^3, respectively. Majority had mild amount of AAC; 70% of donors with AAC had volume score <400. Table 1 compares the demographics, body mass index, renal length as determined at CT, and eGFR between donors with AAC and those without AAC. Donors with AAC were older (mean age 58.6 versus 54.7 years old, $P < 0.0001$) and more likely to be male (77.6% vs. 37.3%, $P = 0.004$). There was not a linear correlation between AAC volume score and donor age. There were no significant differences in the renal lengths or eGFR between donors with AAC and those without.

Of the 292 allograft recipients, 267 had up to 12-month eGFR, 239 had up to 24-month eGFR, and 195 had up to 36-month eGFR available for review. No significant correlations were seen between donor AAC volume score and recipient eGFR at 12, 24, and 36 months following trans-

Table 1. Donor demographics, body mass index, and renal length as determined at CT, and predonation eGFR between donors with AAC and those without AAC.

	Donors with AAC	Donors without AAC	*P*-value
N	119	173	
Gender (M/F)	52/67	47/126	**0.004**
Mean age	58.6 ± 6.0	54.7 ± 4.2	**<0.001**
Body mass index	25.7 ± 0.37	25.7 ± 0.33	>0.9
Renal lengths (cm)	Left: 10.5 ± 1.0 Right: 10.6 ± 0.9	Left: 10.8 ± 0.9 Right: 10.7 ± 1.1	>0.5
Predonation eGFR	86.6 ± 1.6	84.8 ± 1.2	0.15
Mean calcium volume score	674 ± 1613.6	0	

AAC, abdominal aortic calcification. Bold numbers indicate significant p-values.

plantation ($R = -0.02$ to -0.07, P-values = 0.4–0.7). Table 2 compares the eGFR and UPCR in the recipients when stratified by donors with AAC versus those without AAC. There were no significant differences in eGFR between grafts from donors with AAC and those from donors without AAC (all P values >0.2). Similarly, no significant differences in UPCR were noted between grafts from donors with AAC and those from donors without AAC (Table 2). Within the first 36 months following transplantation, there were 8 cases of death-censored graft failure. Five of the 8 cases were grafts from donors with AAC. The causes for graft failure were as follows: acute rejection ($n = 2$), chronic rejection ($n = 2$), graft thrombosis ($n = 2$), chronic ischemic injury ($n = 1$), and BKV-associated nephropathy ($n = 1$).

Of the 292 recipients in this cohort, 180 underwent a 6-month post-transplant protocol biopsy. Table 3 summarizes the findings of interstitial fibrosis, tubular atrophy, vascular fibrous intimal thickening, arteriolar hyaline thickening, and rejection in the grafts. There was a significantly higher percentage of allografts with vascular intimal thickening and arteriolar hyaline thickening from donors with AAC versus those without (vascular fibrous intimal thickening: 38.8% vs. 7.1% and arteriolar hyaline thickening: 35.8% vs. 7.1%; $P < 0.001$ for both) (Fig. 2). Univariate analysis showed that donor AAC and donor age were both significantly associated with the presence of vascular intimal thickening and arteriolar hyaline thickening in the grafts at 6-month protocol biopsies (Table 4). Multivariate regression analysis, after accounting for donor age, showed that the presence of donor AAC independently predicts the presence of vascular fibrous intimal thickening (OR: 7.2; CI: 2.9–17.9; $P < 0.001$) and arteriolar hyaline thickening (OR: 5.7; CI: 2.3–14.1; $P < 0.001$) in allografts at 6 month (Table 5).

Of the 180 recipients with 6-month protocol biopsy, 113 had up to 36-month eGFR available for review. The 36-month eGFR was lower in allografts with arteriolar hyaline thickening at 6-month protocol biopsy compared to those without (41.2 ± 14.1 vs. 47.8 ± 12.8, $P = 0.05$). The 36-month eGFR was not different between allografts when stratified by the presence of interstitial fibrosis, tubular atrophy, or vascular fibrous intimal thickening at 6-month protocol biopsy (P values 0.4–0.5).

Table 2. Recipients' eGFR and UPCR when stratified by donors with AAC versus those without AAC.

Recipient	*n*	Donors w. AAC	Donors w/o AAC	*P*-value
eGFR 12 m	267	48.3 ± 12.8	47.4 ± 11.0	0.54
eGFR 24 m	239	48.2 ± 11.9	47.8 ± 11.8	0.27
eGFR 36 m	195	48.0 ± 13.1	47.3 ± 12.2	0.3
UPCR 12 m	112	0.19 ± 0.43	0.20 ± 0.44	0.57
UPCR 24 m	80	0.24 ± 0.59	0.18 ± 0.38	0.2
UPCR 36 m	62	0.22 ± 0.38	0.22 ± 0.68	0.42

eGFR, estimated glomerular filtration rate; UPCR, urine protein creatinine ratio; and AAC, abdominal aortic calcification.

Table 3. Summary of 6-month protocol biopsy findings of interstitial fibrosis, tubular atrophy, vascular fibrous intimal thickening, arteriolar hyaline thickening, and rejection in the grafts.

	Score			
Pathology parameters	0 (*N*)	1 (*N*)	2 (*N*)	3 (*N*)
Interstitial fibrosis	97	72	10	1
Tubular atrophy	91	79	8	2
Vascular fibrous intimal thickening	146	24	7	3
Arteriolar hyaline thickening	148	26	5	1
		Present (*N*)		
Rejection		31		
Type I		16		
Type II		12		
Type III		3		

Discussion

AAC is a common finding on imaging studies, especially with advancing age, and it is associated with cardiovascular and renal diseases [9–11]. Due to the increasing number of older kidney donors, incidental AAC is noted with increasing frequency in otherwise healthy donors during their predonation imaging workup. Indeed, in our series, AAC was present in over 40% of donors ≥50 years old and was more common in men. The prevalence of AAC noted in our study is similar to the AAC prevalence of 31% reported in a study of 103 donors with a mean age of 46 years [12]. Little is known about the significance of AAC discovered in these healthy renal donors. The presence or severity of AAC was not associated with donor glomerular filtration rate (GFR) or systolic blood pressure in the previous study [12]. In our study, we also did not note any differences in eGFR between donors with AAC and those without. In our study, only seven of 292 donors had documented hypertension. Additionally, the renal length, a surrogate marker of renal volume and which is decreased in renal vascular disease [13], was not significantly different between donors with AAC and those without. Therefore, the presence of AAC in donors appears to be largely clinically silent prior to donation. Future studies of living donors are needed to determine whether the presence of AAC impacts the rate of decline of renal function postdonation and the risk of kidney disease in the donor.

In our study, we found that 17.8% and 18.9% of allograft from donors ≥50 years had vascular fibrous intimal and arteriolar hyaline thickening, respectively. We

Table 4. Univariate analysis of the association between clinical variables and pathology findings at protocol biopsy.

	Interstitial fibrosis			Tubular atrophy			Vascular fibrous intimal thickening			Arteriolar hyaline thickening		
Variables	OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*
Donor AAC	1.2	0.6–2.1	0.65	1.3	0.7–2.5	0.38	8.3	3.5–19.9	<0.001	7.3	3.1–17.6	<0.001
Donor age	1.1	1.0–1.2	0.006	1.1	1.0–1.2	0.001	1.1	1.0–1.2	0.01	1.1	1.0–1.2	0.001
Donor gender	1.4	0.7–2.6	0.35	1.3	0.7–2.6	0.36	1.6	0.8–3.6	0.21	1.8	0.8–4.1	0.13
Recipient age	1.0	0.9–1.1	0.22	1.0	0.9–1.0	0.52	1.0	0.9–1.1	0.83	1.0	0.9–1.1	0.07
Recipient gender	0.7	0.4–1.3	0.30	1.0	0.5–1.7	0.90	0.7	0.3–1.5	0.39	0.7	0.3–1.6	0.40
Tacrolimus level	1.0	0.9–1.1	0.33	1.0	0.9–1.1	0.41	1.0	0.9–1.1	0.79	0.9	0.8–1.1	0.18
Recipient hypertension	0.7	0.3–1.4	0.24	1.0	0.4–2.0	0.90	1.5	0.6–3.7	0.39	1.0	0.4–2.8	0.95
Recipient diabetes	0.9	0.4–1.5	0.41	1.2	0.4–1.7	0.67	1.5	0.6–3.3	0.36	1.6	0.7–3.7	0.24
Recipient new-onset diabetes after transplant	0.9	0.3–2.7	0.83	1.0	0.3–3.0	0.97	1.1	0.1–3.3	0.65	0.9	0.1–2.7	0.30
Vascular rejection (type II and III)	1.2	0.4–3.6	0.73	1.0	0.3–3.0	0.97	1.8	0.5–6.2	0.34	1.1	0.1–3.6	0.72

AAC, abdominal aortic calcification.

Table 5. Multivariate analysis of independent predictors of vascular fibrous intimal thickening and arteriolar hyaline thickening at 6-month protocol biopsies.

	Vascular fibrous intimal thickening			Arteriolar hyaline thickening		
Variables	OR	95% CI	*P*	OR	95% CI	*P*
Donor AAC	7.2	2.9–17.9	<0.001	5.7	2.3–14.1	<0.001
Donor age	1.0	1.0–1.1	0.30	1.1	1.0–1.2	0.07

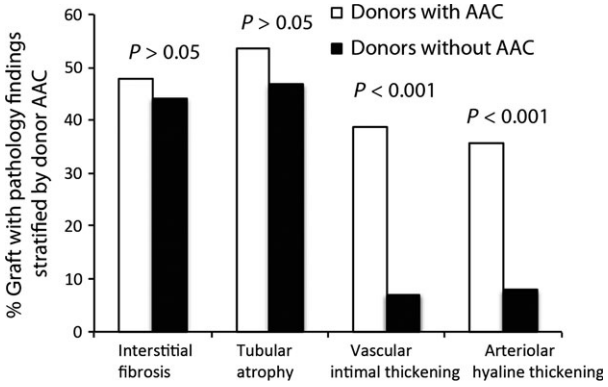


Figure 2 Percentage of grafts with pathology findings when stratified by the presence or absence of donor abdominal aortic calcification. There was a significantly higher percentage of allografts with vascular intimal thickening and arteriolar hyaline thickening from donors with AAC versus those without.

hypothesize that the findings of vascular fibrous intimal thickening and arteriolar hyaline thickening in the allografts at 6 months largely reflect pre-existing vascular disease in the donors. Indeed, previous studies have shown a high prevalence of vascular disease in living kidney donors, as manifested by vascular fibrous intimal thickening and arteriolar hyaline thickening seen in over a third of the pre-implantation biopsies [14,15]. Additionally, increasing donor age was shown to be strongly correlated with the presence and severity of vascular disease [14,16]. Vascular disease in the donor biopsy specimen was also correlated with chronic intimal thickening and arteriolar hyalinosis score of the allograft at 3-month protocol biopsy [17].

To our knowledge, the effects of donor AAC on recipient graft function and histology have not been previously reported. We found, at 6-month protocol biopsy, a fivefold higher incidence of vascular fibrous intimal thickening and arteriolar hyaline thickening in allografts from donors with AAC compared to those without. The presence of donor AAC was an independent predictor for the presence of the above two histologic findings at 6-month protocol biopsy. No significant difference was seen in the incidence of interstitial fibrosis or tubular atrophy in donors with and without AAC. As AAC is a known marker of atherosclerosis and vascular diseases, it is logical that allografts from donors with AAC are more likely to demonstrate pre-existing vascular injury at histology. On the other hand, interstitial fibrosis and tubular atrophy often represent the final stages of multiple different types of injuries to the kidney and may be less specific for vascular disease. These observations support our hypothesis that the observed vascular abnormality at 6-month protocol biopsy reflects donor pre-existing vascular disease, of which AAC may be a surrogate marker.

As noted previously, arteriolar hyaline thickening is a well-known feature of chronic tacrolimus (a calcineurin inhibitor) nephrotoxicity [18]. In our study, there was no significant association between the tacrolimus trough level at the time of the 6-month biopsy and the presence of graft

arteriolar hyaline thickening. While a contributing effect of tacrolimus toxicity cannot be excluded, we believe that the several fold higher incidence of allograft arteriolar hyaline thickening from donors with AAC at an early time point post-transplant in large part reflects pre-existing vascular injury in the donors.

In our study, the presence and severity of donor AAC did not correlate with recipient eGFR or UPCR up to 36 months following transplantation. This finding is not unexpected in the context of previous studies showing that grafts from older donors have preserved kidney function in the short term and the impact on graft outcome may take longer to manifest [4]. Therefore, longer follow-up is needed to truly evaluate the impact of donor AAC on graft function.

Interestingly, among recipients with 6-month protocol biopsy, the 36-month eGFR was lower in allografts with arteriolar hyaline thickening than those without. While the arteriolar hyaline thickening at 6-month protocol biopsy likely reflects pre-existing donor vascular disease as described above, it is possible that prolonged tacrolimus exposure leads to worsened arteriolar hyaline thickening and lower 36-month eGFR. Long-term follow-up studies with ideally serial biopsies will be needed to assess the significance of the vascular findings shown at 6-month biopsy on long-term graft function and outcome. However, if our initial findings are confirmed, it would suggest that recipients of an older living donor kidney with arteriolar hyaline thickening on an early protocol biopsy may benefit from a calcineurin inhibitor free regimen. In our study, no significant difference in 36-month eGFR was seen between allografts with vascular intimal thickening and those without. In contrast, a previous study showed that allografts with pre-existing arteriosclerotic intimal thickening on pre-implantation biopsies had lower function at 1 and 3 years after transplantation [19]. The reason for the discrepancy is unclear, but could be related to different methods for measuring intimal thickening or different patient characteristics such as recipient blood pressure which has been shown to influence the impact of pre-existing vasculopathy on graft function [20] or differences in immunosuppression. Future studies are needed to examine the interplay between donor kidney vascular disease, recipient vascular disease, and the immunosuppressive regimen in order to evaluate the relative impact of each on long-term allograft function.

Our study has several limitations. First, it is a retrospective study with associated limitations including selection bias. Many recipients did not have complete and long-term laboratory data for review as they were lost to follow up over the years. Additionally, only allografts after year 2009 had undergone the 6-month protocol graft biopsy. Nonetheless, the findings from our initial retrospective study provide rationale for future prospective studies with a larger patient cohort to fully understand the impact of donor vascular disease, such as that manifested by AAC, on long-term graft function. Second, in our analysis, we made histology findings binary (present versus absent) because majority of allografts with abnormal histology had mild (score of 1) findings. Future studies with a large number of cases with mild, moderate, and severe histology are needed to both confirm our initial finding and to assess the correlation between AAC volume score and the score of the histologic abnormality described above. Third, at our institution, time zero (pre-implantation) protocol biopsy is not routinely performed, which can more definitively assess any abnormal graft histology related to pre-existing donor disease. However, we believe that the 6-month period from transplantation is short enough that the abnormal histology at biopsy cannot be entirely accounted for by recipients' underlying vascular disease such as hypertension or subsequent immunosuppressive drug toxicity. Indeed, recipient pre-existing hypertension, diabetes, and new-onset diabetes after transplantation were not significantly associated with the presence of abnormal histology at 6-month protocol biopsy. Fourth, we did not assess all of the factors that may potentially affect graft function or histology in this study. For example, a previous study has shown that factors such as decreased donor size, age disparity, and immunologic reaction between donors and recipients were all associated with an increased risk of suboptimal graft function at one year post-transplantation [21].

Notwithstanding these limitations, our study showed that donor AAC was common, seen in over 40% of donors ≥50 years old. The presence and severity of donor AAC did not correlate with recipient graft function as evaluated by eGFR up to 36 months following transplantation. However, donor AAC was an independent predictor for the presence of vascular fibrous intimal thickening and arteriolar hyaline thickening in the allografts at 6-month protocol biopsy and may potentially serve as an imaging marker of pre-existing vascular disease in the donor kidneys. Longer follow-up is necessary to determine the impact of donor AAC on long-term graft function and to determine whether the presence of donor AAC can be used to improve screening of potential donors and to optimize medical management of the recipients.

Authorship

EW: participated in the research design, writing of the manuscript, performance of the research and writing of data analysis and has no conflicts of interest to report. DW: participated in the research design, writing of the manuscript, performance of the research, data analysis and has no conflicts of interest to report. SC, BY, MP, and AW: par-

ticipated in the writing of the manuscript and data analysis and have no conflicts of interest to report. ZW: participated in the research design, writing of the manuscript, performance of the research, and writing of data analysis and has no conflicts of interest to report.

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