Short-Term Prognosis of Living-Donor Kidney Transplantation From Hypertensive Donors With High-Normal Albuminuria

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Background. High-normal albuminuria (HNA) is an independent predictor of cardiovascular risk in the general population. Although hypertensive donor (HTD) candidates with HNA were considered acceptable donors by the Amsterdam Forum 2004, the transplant prognosis of HTDs with HNA has not been determined. Therefore, we investigated the transplant prognosis of HTDs with HNA.

Methods. We retrospectively analyzed 52 adult living-donor kidney transplants performed at Kagawa University Hospital. HNA was defined as albuminuria of 15 to 30 mg/g Cr. Changes in kidney function of donors and recipients were assessed up to 2 years after transplantation.

Results. Overall, 38 donors were normotensive and 14 were hypertensive. Nine of 14 HTDs exhibited HNA before donation. More HTDs with HNA had arteriosclerotic vasculopathy or glomerulosclerosis than did normotensive donors (NTDs). Hypertension and the degree of albuminuria did not affect the donors' posttransplantation kidney function. The risk of discompensatory changes in kidney function after donation was significantly higher in HTDs with HNA than in NTDs (odds ratio, 10.5; 95% confidence interval, 1.51–72.9; P=0.02). In multivariate analysis, the coexistence of hypertension and HNA was not significantly associated with discompensatory changes after donation (adjusted odds ratio, 6.04; 95% confidence interval, 0.19–192; P=0.31). Recipients of HTDs with HNA had similar allograft survival rates but lower allograft function compared with recipients of NTDs.

Conclusions. Although further studies are needed to confirm our results, the short-term prognosis of living-donor kidney transplantation was similar between HTDs with HNA and NTDs.

Keywords: High-normal albuminuria, Hypertension, Living-donor kidney transplantation, Marginal donor, Preimplantation kidney biopsy.

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Kidney transplantation is the preferred therapy for patients with end-stage renal disease (ESRD) for several reasons, including significant improvements in quality of life, better patient survival, lower cardiovascular risk, and decreased medical expenditure compared with dialysis (*1–3*). However, donor shortage is a serious problem worldwide because of the limited availability of deceased-donor kidneys (*4*). In Japan, for example, many patients must wait for more than 10 years for deceased-donor kidney transplantation (*5*). Therefore, living-donor kidney transplantation is now frequently performed worldwide, and it is now debated whether kidneys from marginal donors are suitable for kidney transplantation. Marginal donors are defined as donor candidates

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with borderline donor criteria defined by the Amsterdam Forum 2004 (*6*). In particular, hypertension was considered to be a contraindication for kidney donation (*6*). However, the Amsterdam Forum 2004 developed consensus guidelines for hypertensive donors (HTDs), which stated that "some patients with easily controlled hypertension who meet other defined criteria (e.g., age >50 years, estimated glomerular filtration rate [eGFR] >80 mL/min, and urinary albumin excretion [UAE] <30 mg/day) may represent a low-risk group for the development of kidney disease after donation and may be acceptable as kidney donors" (*6*). However, no studies have determined whether the prognosis of hypertensive marginal donors is truly safe. Because of the increasing demand for donors, it is necessary to verify transplant prognosis of HTDs with UAE <30 mg per day.

Lower albuminuria levels (e.g., 10–30 or 15–30 mg/g Cr) are generally defined as high-normal albuminuria (HNA) (*7, 8*). It was recently that albuminuria is a risk factor for cardiovascular events in the general population with adequate kidney function, even among individuals with albuminuria <30 mg/g Cr (*7–10*). Another study revealed that the risk of cardiovascular events was no higher in donors than in the general population (*11*). However, it remains unknown whether the degree of albuminuria before donation affects compensatory changes in kidney function or cardiovascular disease risk after donation.

Although renal morphology in diabetic patients with HNA has been reported (*12, 13*), it has not been assessed in nondiabetic patients with HNA. Preimplantation kidney biopsy offers a valuable opportunity to evaluate kidney morphology in well-screened apparently healthy living donors at the time of donation and provides useful parameters to predict allograft outcomes (*14, 15*). Morphologic assessment of donors with HNA may provide new insight into the early morphologic changes associated with hypertensive nephrosclerosis.

Therefore, the present study was conducted to test the hypothesis that HTDs with HNA have a similar prognosis to normotensive donors (NTDs). To test this hypothesis, we investigated the effects of HNA and hypertension on transplant prognosis of the donors after living-donor kidney transplantation.

RESULTS

Pretransplantation Characteristics

The pretransplantation characteristics of the donors are shown in Table 1. Of 38 NTDs, 16 had normoalbuminuria (NA+NTDs), 14 had HNA (HNA+NTDs), and 8 had low-grade microalbuminuria (MA+NTDs) at the time of donation. Of 14 HTDs, 5 had NA (NA+HTDs) and nine had HNA (HNA+HTDs) at the time of donation. The characteristics of donors, except for UAE at the time of donation, were similar between NA+NTDs, HNA+NTDs, and MA+NTDs. HNA+HTDs were older than NA+NTDs at the time of donation. Systolic blood pressure was higher in HTDs than in NTDs. None of the donors had inadequate kidney function (eGFR <70 mL/min/1.73 m^2) or abnormal urinalysis before donation. Although pretransplantation eGFR was not significantly different between the groups, it tended to be lower in HNA+HTDs than in NA+HTDs. The number of prescribed antihypertensive drugs was similar in NA+HTDs and HNA+HTDs. Donor classification and the degree of albuminuria before donation are summarized in Figure S1 (see **SDC,** http://links.lww.com/TP/A875).

The pretransplantation characteristics and transplant conditions of the recipients of kidneys from NA+NTDs, HNA+NTDs, MA+NTDs, NA+HTDs, and HNA+HTDs were similar. These data are presented in Table S1 (see **SDC,** http://links.lww.com/TP/A875).

Effects of Albuminuria and Hypertension on Pretransplantation Kidney Morphology

The morphologic analysis of preimplantation kidney biopsies is shown in Figure 1. All biopsy samples were adequate for morphologic analysis. The glomerulosclerosis index in HNA+HTDs (23 [13]%) was significantly higher

TABLE 1. Characteristics of the donors before transplantation

	NA+NTDs	HNA+NTDs	MA+NTDs	NA+HTDs	HNA+HTDs	*P*
Donors, n	16	14	8	5	9	
UAE (mg/g Cr)	9.5 (3.6)	20.1 (4.1)[a]	37.0 (5.2)[a]	10.7 (3.3)	24.4 (7.0)[a,b]	<0.001
Age (years)	58 (8)	53 (12)	61 (9)	59 (10)	67 (7)[a]	0.02
Male, n (%)	5 (31)	4 (29)	5 (63)	1 (25)	4 (45)	0.59
SBP (mm Hg)	118 (11)	120 (11)	120 (12)	138 (8)[a]	144 (11)[a]	<0.001
Dyslipidemia, n (%)	5 (31)	8 (57)	6 (75)	3 (60)	1 (11)	0.06
BMI (kg/m^2)	23 (3)	22 (3)	22 (1)	25 (3)	24 (2)	0.08
Urinary protein (%)	0	0	0	0	0	—
Occult blood in urine (%)	0	0	0	0	0	—
Pretransplantation eGFR (mL/min)	83 (13)	85 (17)	90 (16)	100 (25)	80 (17)	0.22
Anti-hypertensive drugs, n (%)	—	—	—	0.7 (0.3)	1.1 (0.3)	0.36
Use of ARBs, n (%)	—	—	—	1 (25)	5 (56)	0.30
Use of CCBs, n (%)	—	—	—	3 (60)	4 (44)	1.00

[a] $P<0.05$ vs. NA+NTDs.
[b] $P<0.05$ HNA+HTDs vs. NA+HTDs.
Values are mean (SD) or n (%).
ARBs, angiotensin II receptor blockers; CCBs, calcium channel blockers; HNA+HTD, HTDs with HNA; HNA+NTD, NTDs with HNA; MA+NTD, NTDs with MA; SBP, systolic blood pressure.

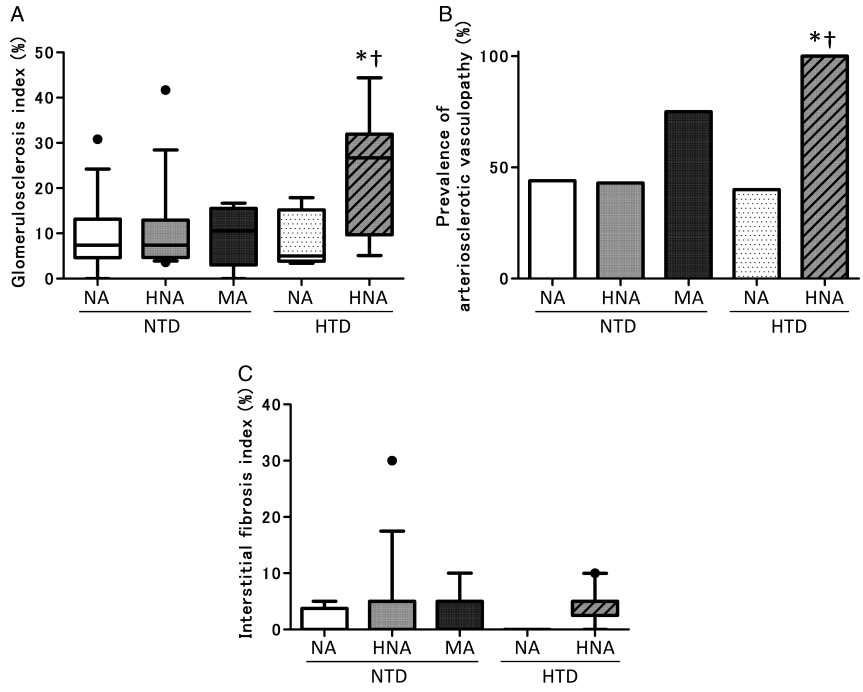

FIGURE 1. Pathologic analysis of pretransplantation biopsies. A, glomerulosclerosis index. B, prevalence of arteriosclerotic vasculopathy. C, Interstitial fibrosis index. AS, arteriosclerosis; *P<0.05 vs. NA+NTDs; †P<0.05 vs. NA+HTDs.

than that in NA+NTDs (10 [8]%; P=0.03) or NA+HTDs (9 [6]%; P=0.04). The prevalence of arteriosclerotic vasculopathy was significantly higher in HNA+HTDs (100%) than in NA+NTDs (44%; P=0.008) or NA+HTDs (40%; P=0.03). The interstitial fibrosis index in HNA+HTDs was similar to that in the other donor groups. Although arteriosclerotic vasculopathy tended to be higher in MA+NTDs than in NA+NTDs, this was not statistically significant (odds ratio [OR], 3.86; 95% confidence interval [CI], 0.59–25.3; P=0.21). The glomerulosclerosis index and interstitial fibrosis

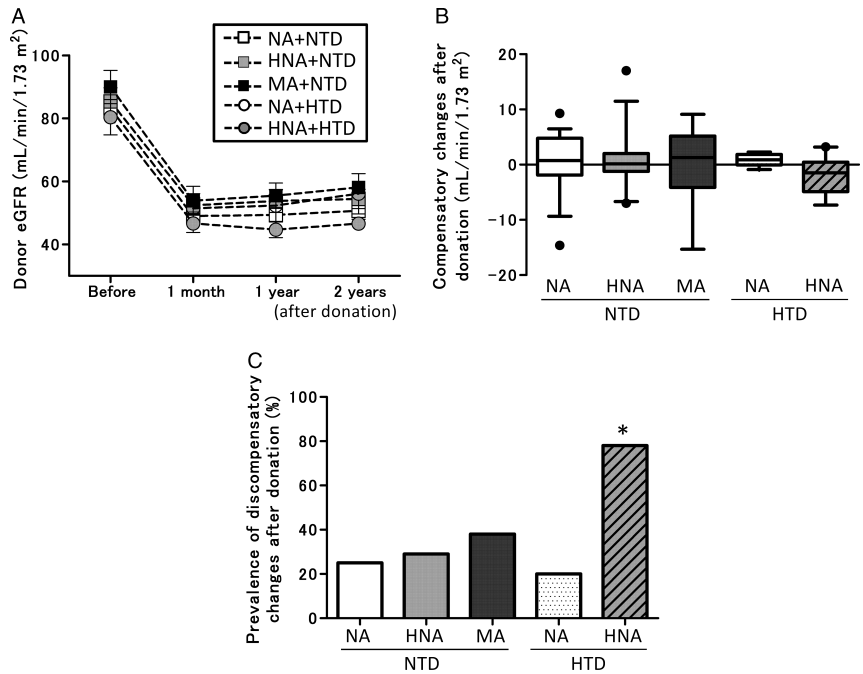

FIGURE 2. Donor kidney function after donation. A, serial eGFR profiles. B, compensatory changes in kidney function after donation. C, prevalence of discompensatory changes in kidney function after donation. *P<0.05 vs. NA+NTDs.

TABLE 2. Risk factors for discompensatory changes in kidney function after donation

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*P*	Adjusted OR (95% CI)	*P*
Age >60 years	6.44 (1.82–22.8)	<0.01[a]	4.87 (1.13–20.1)	<0.03[a]
Male	1.46 (0.45–4.66)	0.56	1.48 (0.34–6.46)	0.60
Hypertension	3.27 (0.92–11.6)	0.10	0.60 (0.04–9.67)	0.72
UAE >15 mg/g Cr	2.64 (0.78–9.00)	0.15	1.59 (0.30–8.47)	0.59
Hypertension and UAE >15 mg/g Cr	9.04 (1.64–49.8)	<0.01[a]	6.04 (0.19–192)	0.31
BMI >25 kg/m^2	1.12 (0.31–4.07)	1.00	0.70 (0.10–5.00)	0.70
Dyslipidemia	0.43 (0.13–1.42)	0.25	0.59 (0.13–2.68)	0.49
Pretransplantation eGFR <70 mL/min/1.73 m^2	1.80 (0.57–5.72)	0.38	0.76 (0.17–3.32)	0.72

[a] $P<0.05$.

index were not significantly different between the groups of NTDs.

Effects of Albuminuria and Hypertension on Donor Prognosis

There were no cardiovascular events in any donors after donation during the 2-year follow-up. Furthermore, none of the NTDs developed hypertension during the 2-year follow-up. At 2 years after transplantation, there were no significant differences between NA+HTDs and HNA+HTDs in either systolic blood pressure (133.8 [3.4] vs. 124.8 [2.8] mm Hg; *P*=0.09) or diastolic blood pressure (79.3 [2.9] vs. 72.3 [4.3]; *P*=0.31).

The kidney function of the donors after donation is shown in Figure 2. The serial changes in donor eGFR are shown in Figure 2A. There were no significant differences in posttransplantation eGFR between the groups of donors, but eGFR tended to be lower in HNA+HTDs than in NA+HTDs at 1 year after donation. The compensatory changes in kidney function after donation tended to be lower in HNA+HTDs than in the other donor groups, although the differences were not statistically significant (Fig. 2B). The risk of discompensatory changes in kidney function after donation was significantly higher in HNA+HTDs than in NA+NTDs (Fig. 2C; OR [95% CI], 10.5 [1.51–72.9]; *P*=0.02).

The risk factors, with ORs and adjusted ORs, for discompensatory changes in kidney function after donation are shown in Table 2. Nineteen (36.5%) patients had discompensatory changes after donation. Donor age above 60 years was significantly associated with discompensatory changes after donation in univariate and multivariate analysis. The coexistence of hypertension and UAE >15 mg/g Cr was associated with discompensatory changes after donation in univariate analysis but not in multivariate analysis (adjusted OR [95% CI], 6.04 [0.19–192]; *P*=0.31). Surprisingly, donor hypertension or UAE >15 mg/g Cr alone were not significantly associated with discompensatory changes after donation in univariate or multivariate analyses. The pathologic characteristics of preimplantation biopsies were not significantly associated with discompensatory changes after donation in univariate analysis (glomerulosclerosis index >10%, OR [95% CI], 2.64 [0.82–8.46]; *P*=0.15; arteriosclerotic vasculopathy, OR [95% CI], 1.43 [0.45–10.2]; *P*=0.58; interstitial fibrosis index >10%, OR [95% CI], 0.86 [0.07–10.2]; *P*=1.00).

Effects of Albuminuria and Hypertension on Recipient Prognosis

The serial eGFR changes in the recipients are shown in Figure 3. The eGFR in recipients of HNA+HTDs (RHNA+HTDs) tended to be lower than that in recipients of NA+NTDs (RNA+NTDs) at 3 months and 1 year after transplantation and was significantly lower than that in RNA+NTDs at 2 years after transplantation. There were no significant changes in the recipients' eGFRs at 3 months or at 1 and 2 years after transplantation between the other groups of recipients. The allograft survival rate at 2 years after transplantation was 100%, except in RHNA+HTDs (89%), which was not significantly different.

DISCUSSION

In the field of living-donor kidney transplantation, it is imperative to provide a guarantee for the prognosis of living donors after donation. Our results revealed that HNA+HTDs had a higher risk of discompensatory changes in kidney function after donation compared with NA+NTDs or NA+HTDs. However, logistic regression analysis showed that the coexistence of donor hypertension and UAE

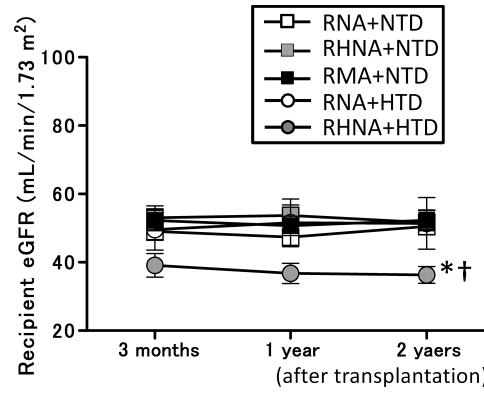

FIGURE 3. Serial eGFR profiles of the recipients. RNA+NTDs, recipients of NTDs with NA; RHNA+NTDs, recipients of NTDs with HNA; RMA+NTDs, recipients of NTDs with MA; RNA+HTDs, recipients of HTDs with NA; RHNA+HTDs, recipients of HTDs with HNA. *$P<0.05$ vs. RNA+NTDs; †$P<0.05$ vs. RNA+HTDs.

>15 mg/g Cr was not significantly associated with discompensatory changes in kidney function after donation.

The annual decrease in eGFR after donation tended to be greater in HNA+HTDs than in the other donor groups but was similar to that of older Japanese subjects with hypertension and lower eGFRs, which was reported to be about 0.8 mL/min/1.73 m^2 (*16*). Therefore, we considered that the short-term prognosis of living-donor kidney transplantation from HNA+HTDs was similar to that of the other donor groups, except for discompensatory changes in donor kidney function and lower allograft function. Although longer-term and larger-scale studies are necessary, we should not exclude hypertensive candidates with HNA as possible candidates for living-donor transplantation if there are no other suitable candidates or if the recipients are expected to wait for a long time for deceased-donor kidney transplantation. However, HNA+HTDs should be regularly followed up by a nephrologist to assess the degree of albuminuria, blood pressure, and kidney function after donation. Allograft function was lower in the RHNA+HTDs than in other recipient groups. Nevertheless, decreases in eGFRs or allograft survival rates were not observed in the RHNA+HTDs. These results imply that donation from the kidneys of HNA+HTDs is a potential strategy for treating patients with ESRD.

A greater increase in serum creatinine after donation was reported in HTDs than in NTDs (*17*). Reduced nitric oxide bioavailability, a characteristic of endothelial dysfunction, is common in hypertensive patients (*18*). Several studies have demonstrated that the endothelium and endothelium-derived nitric oxide play critical roles in compensatory renal growth by modulating the hemodynamic changes (*19, 20*). However, we found that the compensatory changes after donation were similar between NA+HTDs and NTDs. Because albuminuria is a marker for endothelial dysfunction, the presence of HNA at the time of donation may be associated with compensatory renal growth after donation.

Compensatory changes in kidney function predict the risk of impaired kidney function developing sometime after donation (*21*). Our results showed that the compensatory changes in kidney function were insufficient in older (>60 years old) donors, which is consistent with a previous report (*22*). However, there was no obvious deterioration in kidney function after donation in older donors. Older donors are considered to be at low risk of developing ESRD because of their relatively short remaining life, even if they have hypertension and HNA. By contrast, our results indicate that younger (<60 years old) donors had a lower risk of discompensatory changes after donation. However, we and the Amsterdam Forum 2004 proposed that younger (<50 years old) candidate HNA+HTDs are not acceptable living donors because younger donors with hypertension are at high risk of developing ESRD because they are exposed to a higher risk of hypertensive kidney injury for a longer time (*6*).

Early morphologic changes in the kidney are usually subclinical before the development of overt albuminuria (*23*). In this study, the HNA+HTDs had early hypertensive nephrosclerosis in their kidneys, although kidney function was adequate and albuminuria was not overt. These findings may apply to the general population. Early hypertensive nephrosclerosis characterized by a high glomerulosclerosis index and arteriosclerotic vasculopathy is likely to occur in the kidney of hypertensive patients with HNA and may be associated with glomerular hyperfiltration. On the contrary, higher interstitial fibrosis index was not observed, even in the kidneys of HNA+HTDs, which is consistent with previous reports (*24, 25*). Our previous study showed that arteriosclerotic vasculopathy in the donated kidneys predicted allograft function (*14*), but the present study revealed that the pathologic characteristics of the donated kidneys did not predict discompensatory changes in the donor's kidney function after donation.

We also found that the glomerulosclerosis index was similar between the groups of NTDs irrespective of the degree of albuminuria. However, at the first detection of albuminuria in hypertensive nephrosclerosis, the urinary albumin is considered to be derived from juxtamedullary glomeruli (*23, 26, 27*). Unfortunately, we did not obtain an adequate number of these glomeruli in needle biopsy samples to analyze them independently of the superficial glomeruli. Therefore, we cannot exclude the possibility of morphologic changes in the juxtamedullary glomeruli of MA+NTDs. Obesity is one of the physiologic causes of MA (*28, 29*). However, the body mass index (BMI) was similar between the groups of NTDs. Therefore, we can conclude that low-grade MA itself did not affect transplant prognosis among NTDs.

There are several limitations to this study. In particular, there was a small number of HNA+HTDs, the observation period was only 2 years, ambulatory blood pressure monitoring was not performed in donors, a definition of HNA has not been established, and 24-hr urine collection and repeated sampling were not performed to evaluate the degree of albuminuria. In particular, the small sample size of this study may increase the possibility of type II error. These problems need to be resolved in future perspective studies.

In summary, our results showed that the short-term prognosis of living-donor kidney transplantation was similar between HNA+HTDs and NTDs. Although we should be vigilant for lower allograft function, we believe that donation from HNA+HTDs is a potential strategy for expanding the living-donor criteria of living-donor kidney transplantation. Further long-term and larger-scale studies are needed to confirm our conclusions.

MATERIALS AND METHODS

Subjects

We retrospectively analyzed 52 consecutive adult living-donor kidney transplantations performed at Kagawa University Hospital between November 2006 and March 2011. The analysis included all donors and recipients of the 52 transplants. All living-kidney transplantations were conducted using relatives as donors in accordance with the guidelines of the Japan Society for Transplantation.

Donors were carefully evaluated in terms of their medical and psychologic histories. Donor suitability in terms of hypertension and albuminuria was evaluated according to the Amsterdam Forum 2004 (*6*). Briefly, patients with a blood pressure >140/90 mm Hg were not acceptable as donors, but candidate donors with easily controlled hypertension who met specific criteria (>50 years old and UAE <30 mg/g Cr) were accepted as donors. We determined the threshold of renal function for eligibility for kidney donation as an eGFR of 70 mL/min/1.73 m^2, as this threshold is used in most transplant centers in Japan (*30–32*). Among candidate NTDs, those with low-grade MA (30–100 mg/g Cr) were accepted, but those with overt albuminuria (>100 mg/g Cr) were not. The protocols and informed

consent forms were approved by the Ethics Committee of Kagawa University (No. H25-001).

Study Design and Transplant Classification

The 52 donors were classified as either NTDs (n=38) or HTDs (n=14) based on the absence/presence of hypertension, which was defined as clinic-measured blood pressure >140/90 mm Hg recorded at least twice or administration of oral antihypertensive agents at the time of donation, in accordance with the guidelines of the Japanese Society of Hypertension 2009. At the time of donation, blood pressure was well controlled by medications or lifestyle interventions in all HTDs. UAE in donors was examined using one measurement of the first morning void urine (*33*) and is presented as the albumin/creatinine ratio. Albuminuria was classified as NA (0–15 mg/g Cr), HNA (15–30 mg/g Cr), or low-grade MA (30–100 mg/g Cr) (*7*).

Based on these criteria, NTDs were divided into three subgroups according to the degree of albuminuria at the time of donation; 16 were classified as NA+NTDs, 14 as HNA+NTDs, and 8 as MA+NTDs. The HTDs were divided into two subgroups based on the degree of albuminuria; 5 were classified as NA+HTDs and 9 as HNA+HTDs. The 52 recipients were classified into five subgroups according to the origin of the donated kidneys; 16 received kidneys from NA+NTDs (RNA+NTDs), 14 received kidneys from HNA+NTDs (RHNA+NTDs), 8 received kidneys from MA+NTDs (RMA+NTDs), 5 received kidneys from NA+HTDs (RNA+HTDs), and 9 received kidneys from HNA+HTDs (RHNA+HTDs).

Kidney function in the donors and recipients was determined based on the eGFR, which was calculated using the Modification of Diet in Renal Disease study equation modified for Japanese individuals (*34*). Kidney function in donors was evaluated before donation, at 1 month, and at 1 and 2 years after donation. The compensatory change in the donor's kidney function after donation was calculated using the following formula: (eGFR at 1 year after donation)-(eGFR at 1 month after donation) (mL/min/1.73 m^2). Discompensatory changes in kidney function after donation were defined as a compensatory change after donation of <0 mL/min/1.73 m^2. Donor dyslipidemia was defined as low-density lipoprotein-cholesterol levels >140 mg/dL or triglyceride levels >150 mg/dL. Allograft function (recipient eGFR) was evaluated at 3 months and at 1 and 2 years after transplantation. The immunosuppressive regimens were principally based on four drugs (tacrolimus, mycophenolate mofetil, methylprednisolone, and basiliximab), which were used in combination (*35*).

Biopsy and Pathologic Analyses

In all donated kidneys, biopsies were performed before transplantation at the bench, after perfusion with cold Euro-Collins solution, using an 18G biopsy needle. The biopsy samples were fixed in formalin and embedded in paraffin. Sections (<4 μm thick) were stained with hematoxylin-eosin, Elastica Van Gieson, or Masson trichrome stains. Biopsies containing eight or more glomeruli were defined as adequate. The glomerulosclerosis index was defined as the percentage of sclerotic glomeruli of the total number of glomeruli counted (*14*). Arteriosclerotic vasculopathy was defined as the presence of fibrous intimal thickening in the interlobular artery (*14*). Interstitial fibrosis index was determined as the percentage of the Masson-stained area of the entire interstitial area (*36*).

Statistical Analysis

All analyses were performed using SPSS software version 20.0 for Windows (IBM Japan, Tokyo, Japan). Values are presented as mean (SD) or n (%). The Kolmogorov–Smirnov test was used to assess the normality of distributions. Clinical variables were compared between groups using the chi-square test for categorical variables and Student's *t* test or one-way analysis of variance for continuous variables. $P<0.05$ was considered to indicate statistical significance.

To identify the factors associated with discompensatory changes in kidney function after donation, we calculated the ORs, adjusted ORs, and 95% CIs for each covariate. The covariates included conventional risk factors (classified as yes or no) and dichotomized variables, including donor age (>60 vs. <60 years), UAE (>15 vs. <15 mg/g Cr), BMI (>25 vs. <25 kg/m^2), and pretransplantation donor eGFR (<70 vs. >70 mL/min/1.73 m^2). Multivariate analysis was performed using logistic regression in which donor factors (age, sex, hypertension, UAE, coexistence of hypertension and UAE, BMI, dyslipidemia, and pretransplantation eGFR) were included as covariates.

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