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The Role of Kidney Biopsy to Determine Donation from Prospective Kidney Donors with Asymptomatic Urinary Abnormalities

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ABSTRACT

Background. There are no definite guidelines about donation among prospective donors with asymptomatic urinary abnormalities. We evaluated the pathology of prospective kidney donors with asymptomatic urinary abnormalities and assessed the clinical outcomes of their organs.

Methods. We reviewed the medical records of 15 prospective kidney donors who underwent kidney biopsy. We evaluated the role of kidney biopsy in terms of graft function, protocol biopsy, and follow-up biopsy. We further assessed the clinical outcomes of donors and recipients.

Results. Thin basement membrane nephropathy (TBMN) is the most common cause of the persistent microscopic hematuria (n = 7; 50%), followed by nonspecific findings (n = 4; 29%), IgA nephropathy (n = 2; 14%), and focal segmental glomerulosclerosis (n = 1; 7%). Of the 14 candidate donors with persistent microscopic hematuria, 9 were accepted as kidney donors: 5 with TBMN, 3 with mild mesangiopathy, and 1 with nonspecific interstitial changes. The function of the 9 grafts was relatively stable (mean serum creatinine level 2.38 mg/dL) over a mean follow-up of 57 months. Graft failure that developed in 2 grafts was not associated with biopsy findings: acute rejection and patient death with a functioning graft. Interestingly, basement membrane thickness in 2 allografts from donors with TBMN appeared normal by electron microscopy follow-up biopsy; the allografts did not show hematuria. Moreover, the clinical outcomes of donors were favorable (mean serum creatinine 0.94 ± 0.32 mg/dL) during the mean follow-up period of 34.7 ± 42.5 months. We did not observe new-onset hypertension or proteinuria in donors.

Conclusions. Kidney biopsy in prospective kidney donors with urinary abnormalities is a safe and effective diagnostic procedure to stratify candidates. Therefore, kidney biopsy should be actively performed to improve the prognosis of both donors and recipients.

In kidney transplantation, adequate evaluation of prospective donors is an important process to exclude individuals with underlying renal disease, which could have detrimental consequences. Urinalysis, one of the basic tests to evaluate potential donors, occasionally reveals urinary abnormalities, including microscopic hematuria and/or proteinuria. However, it is not known how frequently asymptomatic microscopic hematuria or borderline proteinuria (<300 mg/d) reflects underlying kidney disease in otherwise healthy prospective donors. Isolated microscopic hematuria is present in 5%–6% of the general population, and its prevalence increases with age.[1,2] Persistent microscopic hematuria occurs in 3% of the general population and is closely linked to pathologic findings.[3,4]

Although overt proteinuria (>300 mg/d) is a contraindication to kidney transplantation,[5] whether prospective donors with persistent microscopic hematuria or borderline proteinuria should be excluded from donation is debatable. Indeed, there are no specific guidelines regarding kidney donation by prospective kidney donors with asymptomatic urinary abnormalities. Therefore, we evaluated the role of

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kidney biopsy among prospective donors with asymptomatic urinary abnormalities to determine suitability for donation.

METHODS

We reviewed the medical records of 15 prospective kidney donors who underwent a kidney biopsy from January 1996 to December 2010. The results of the kidney biopsy indicated the presence of asymptomatic persistent microscopic hematuria (n = 14; 93.3%) or borderline proteinuria (n = 1; 6.7%). Persistent microscopic hematuria was defined as >2 (in men) and >5 (in women) red blood cells per high-power field on ≥3 urinalyses obtained over a 1-month period. Overt proteinuria was defined as >300 mg/d, borderline proteinuria as <150–300 mg/d. Furthermore, urologic causes of hematuria were excluded by ultrasonography, intravenous pyelogram (IVP), or cystoscopy. We investigated the role of renal biopsy in terms of graft function, protocol biopsy, and follow-up biopsy. In addition, we assessed clinical outcomes of both donors and recipients. Protocol biopsies, were performed at 2 weeks and follow-up biopsies at 3 or 5 months after kidney transplantation.

RESULTS

Of 15 prospective donors, 9 were female. The mean age at renal biopsy was 48 ± 11 years. Nine prospective donors were genetically related to their prospective recipients. The donors' mean systolic blood pressure was 117.3 ± 11.4 mm Hg and mean diastolic blood pressure 76.8 ± 7.2 mm Hg. The glomerular filtration rate (eGFR) estimated using the Modification of Diet in Renal Disease formula was 95.3 ± 17.4 mL/min/1.73 m^2.

We observed thin basement membrane nephropathy (TBMN) to be the most common cause of asymptomatic persistent microscopic hematuria (n = 7; 50%), followed by mild mesangiopathy (n = 3; 22%), immunoglobulin A nephropathy (IgAN; n = 2; 14%), focal segmental glomerulosclerosis (FSGS) (n = 1; 7%), and nonspecific interstitial changes (n = 1; 7%). In addition, the prospective donor with borderline proteinuria revealed glomerulosclerosis (26%) and arteriosclerosis. Of the 14 candidate donors with persistent microscopic hematuria, 9 were accepted as kidney donors: 5 with TBMN, 3 with mild mesangiopathy, and 1 with nonspecific interstitial changes. However, 5 potential donors with persistent microscopic hematuria and 1 candidate donor with borderline proteinuria were excluded from donation owing to IgAN (n = 2; 33%), TBMN (n = 2; 33%), FSGS (n = 1; 17%), and arteriosclerosis (n = 1; 17%). Of the 7 prospective donors with TBMN, 6 were female and 2 were excluded from donation, one showing a significant discrepancy in eGFR between the 2 kidneys (right 38.4%, left 59.6%) as measured by ^{99m}Tc-DTPA renal scintigraphy, and immunofluorescence microscopy revealing a segmental increase in mesangial cells and matrices in the other, the mesangial immune depositions (IgA, IgM, C3, and C1q) possibly representing early lesions due to membranoproliferative nephropathy or IgAN.

We also studied the recipients of the 9 donated kidneys. The mean age of recipients was 47.5 ± 11.8 years at transplantation, 7 were male, and there were no previous renal transplantations. The mean number of HLA mismatches was 2.7. The function of the 9 allografts was relatively stable during the follow-up with the exception of 2 cases: 1 recipient experienced graft failure due to acute rejection, and 1 with a functioning graft died due to cardiac arrest. Over a mean follow-up of 56.9 months, we observed the mean eGFR at 1 year after transplantation and the current eGFR to be 57.1 ± 17.3 and 47.7 ± 30.8 mL/min/1.73 m^2, respectively.

There were 3 acute rejection episodes. In addition, although there were few differences in the pathologic findings between the protocol and the pretransplantation biopsies, we did observe some changes in the follow-up biopsy (Table 1). In particular, glomerulosclerosis was aggravated and mesangial lesions showed either regression or aggravation over time. Interestingly, basement membrane thickness in 2 allografts from donors with TBMN appeared normal by electron microscopy at the follow-up biopsy and did not show hematuria. Moreover, the clinical outcomes of donors were favorable (mean serum creatinine 0.94 ± 0.32 mg/dL) during the mean follow-up period of 34.7 ± 42.5 months. We did not observe new-onset hypertension or proteinuria in the donors.

DISCUSSION

Primary chronic glomerulonephritis is the third leading cause of end-stage renal disease (ESRD). It usually presents with asymptomatic urinary abnormalities: hematuria and/or proteinuria. Hematuria is observed among the general population with a variable prevalence (0.18%–16.1%).[6,7] It generally originates from the lower urinary tract. However, only a low percentage of hematuria cases are caused by glomerular disease (<10%).[7] Vivante et al reported hematuria to be associated with a low but significantly increased risk for ESRD, which accounted for ~4.3% of all treated patients in the Israeli Registry.[8] In addition, Kido et al showed that persistent hematuria before donation was sustained thereafter. Moreover, during a mean follow-up period of 2.3 years after donation, the overall prevalence of

Table 1. Pathologic Findings of Protocol and Follow-up Biopsies

Donors		Recipients		
GS (%)	Mesangial Abnormality	GS (%)	Mesangial Abnormality	Time After Transplantation
0	+	0	+	2 wk
2	–	7	–	2 wk
7	+	25	–	2 wk
0	–	0	+	2 wk
0	+	0	–	2 wk
0	–	0	–	3 mo
7	–	0	–	5 mo
0	+	7	–	5 mo
0	–	4	+	31 mo
0	+	57	–	174 mo

Abbreviation: *GS, glomerular sclerosis.*

persistent hematuria increased to 15.3%, with 8.3% of donors developing persistent proteinuria. Therefore, it was concluded that potential donors with persistent glomerular hematuria should be excluded from kidney donation.[9] However, because renal biopsy was not performed in these studies, the differential diagnosis of persistent hematuria was not established. We think that the use of renal pathology to stratify potential donors improves the prognosis for donors with persistent hematuria.

Kim et al showed that the most common cause of persistent microscopic hematuria in Korea is IgAN (33.3%), followed by mesangial proliferative glomerulonephritis (MsPGN) (23.7%), minor glomerular lesions (15.4%), and TBMN (12.8%).[4] Similarly, in a study by Tiebosch of 80 patients with idiopathic hematuria, IgAN was found in 27 patients (33.5%) and TBMN in 18 (22.5%). A total of 24 patients (30%) had normal renal findings. Furthermore, 11 patients (14%) showed MsPGN (6%), interstitial nephritis (3.7%), or focal global glomerulosclerosis (3.7%).[10]

Thus, prospective kidney donors with persistent microscopic hematuria may be permitted to donate according to the underlying cause of hematuria as diagnosed by renal biopsy; candidates with minor glomerular lesions, mesangial, or interstitial changes could be able to donate, whereas potential donors suffering from IgAN, FSGS, and MsPGN should be excluded from kidney donation.

However, controversy exists regarding prospective donors with TBMN, a genetic disease of the glomerular basement membrane (GBM) involving the $\alpha3/\alpha4/\alpha5$ network of type IV collagen.[11] Indeed, the general consensus is that donors with both TBMN and risk factors for renal disease, such as proteinuria, renal insufficiency, or hypertension, should be excluded from kidney donation. The role of renal biopsy is crucial in cases of TBMN particularly. If there are underlying pathologic features, including IgAN or X-linked Alport syndrome, which cannot be determined clinically.[12] Because the majority of cases of IgAN are sporadic, a family history of hematuria is infrequent. Alport syndrome is an inherited progressive renal disease with extrarenal manifestations, which are associated with sensorineural deafness and ocular abnormalities. A significant proportion of Alport syndrome cases are X-linked; the remaining cases are autosomal recessive.[11] X-Linked Alport syndrome, which is much less common than TBMN, is frequently identified in family members by its typical clinical features (lamellated GBM without an $\alpha3/\alpha4/\alpha5$ network of type IV collagen), by gene linkage studies, or by demonstration of a mutation in the *COL4A5* gene. In addition, careful assessment of the potential donor's family history, extrarenal manifestations, and the pathologic features of Alport syndrome may assist to clarify existing renal disease among potential donors.[12]

Until now, potential donors who display proteinuria of >300 mg/d have been excluded from donation.[13] However, for candidates with borderline proteinuria (250–300 mg/d) and no known renal risk factors, donation may be considered if urinary albumin excretion is negative.[5] In addition, our study indicated that renal biopsy should be performed to stratify potential donors with borderline proteinuria.

Renal biopsy is considered to be essential for the diagnosis of glomerular disease and to guide treatment plans. Improvements in imaging and the refinement of needle biopsy have resulted in the ability to obtain larger quantities of renal tissue that are suitable for diagnosis in >98% of instances.[14] These technical advances have increased the safety of renal biopsy, reducting the rate of life-threatening complications that can result in death from 0.12% to 0.02%.[15] Therefore, although renal biopsy is an invasive method, we consider it to be a safe necessary procedure for differential diagnosis of prospective donors with asymptomatic urinary abnormalities.

In conclusion, kidney biopsy for prospective donors with urinary abnormalities is a safe and effective diagnostic procedure to stratify adequate donors.

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