

# Thin Basement Membrane Nephropathy and Renal Transplantation

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The clinical implications of thin basement membrane nephropathy (TBMN) in renal transplantation must be considered from the perspectives of both the allograft recipient and the donor. Most individuals with TBMN have a benign course, but some develop end-stage renal failure (ESRF) and undergo transplantation. ESRF in patients with TBMN often results from the presence of additional glomerular or interstitial lesions and some of these, such as immunoglobulin (Ig)A disease, may recur in the renal allograft and affect outcome. In addition, individuals with TBMN always must be distinguished from those with glomerular membrane thinning due to Alport syndrome. This is not only to enable appropriate genetic counseling but also to anticipate the possible complication of posttransplant anti-glomerular basement membrane disease. From the perspective of the live renal donor, donation from individuals with TBMN (or carriers of X-linked Alport syndrome with thinned membranes) remains controversial because the risks remain unknown. Any effects of the thinned membranes themselves on allograft function are unclear. Further advances in our understanding of the clinical, pathologic, and molecular features of TBMN should result in improved assessment of potential live donors and help stratify those at risk for renal impairment.

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Decision making in renal transplantation involves an assessment of the risks to the recipient and to the potential live donor. For recipients, this is the likelihood of premature allograft failure with any individual cadaveric or live donor renal transplant, and for potential live donors it is the possibility of progressive renal disease.

Thin basement membrane nephropathy (TBMN) represents a challenge to this decision-making process. Despite significant advances in our understanding of its molecular and genetic basis, the risks for TBMN in potential recipients and live donors still largely are unknown.

## Renal Transplant Recipients and TBMN

### Patients With TBMN

#### Presenting for Renal Transplantation

Most patients with TBMN have an excellent prognosis,<sup>1-3</sup> and progression to end-stage renal failure (ESRF) and transplan-

tation is rare.<sup>3-6</sup> TBMN with impaired renal function may represent an aggressive variant, or occur because there are coincidental renal lesions (eg, immunoglobulin [Ig]A nephropathy or focal segmental glomerulosclerosis<sup>7,8</sup>), or because it actually is misdiagnosed Alport syndrome.<sup>9</sup> Recent genetic and molecular studies indicate TBMN and Alport syndrome are part of a heterogeneous group of inherited disorders of type IV collagen that have variable and overlapping clinical manifestations. The severity of the renal disease in TBMN may depend in part on the underlying genetic mutations or other modifying genetic or environmental factors that still are understood poorly.<sup>9,10</sup>

TBMN is common. It often is found incidentally when renal biopsy specimens are examined by electron microscopy, but many individuals remain undiagnosed, usually because they have not been tested. Dische et al<sup>11</sup> examined renal allograft biopsy specimens from 76 apparently normal donors and deduced the prevalence of TBMN to be 5.2% or 9.2% (depending on the definition of thinning) in the general population. Others have suggested that the prevalence is at least 1%<sup>6,9</sup> based on the frequency of persistent hematuria in the wider community<sup>2,12,13</sup> and the likelihood of TBMN in series of renal biopsy specimens from individuals with isolated hematuria.<sup>4,14</sup>

Renal impairment is not uncommon in some series of pa-

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tients with TBMN. One study reported 7% of patients with biopsy examination–proven disease had renal dysfunction with a serum creatinine level greater than 0.11 mmol/L.<sup>6</sup> Although most individuals with TBMN do not show progressive renal impairment, the duration of most longitudinal studies has been too short to reflect prognosis accurately. Significant proteinuria, hypertension, and, indeed, renal impairment all are risk factors for disease progression in TBMN. In progressive cases, as well as the thinned membranes, other biopsy specimen abnormalities that usually will determine the renal prognosis often are encountered. A discussion of these issues as well as the diseases that TBMN must be differentiated from is found in other articles in this issue and are covered here only briefly.<sup>15-19</sup>

The genetic basis of TBMN now is understood partly. At least 40% of individuals with TBMN have mutations in the *COL4A3* or *COL4A4* genes,<sup>20-23</sup> which code for the  $\alpha 3$  and  $\alpha 4$  chains of type IV collagen. These genes also are affected in autosomal-recessive Alport syndrome. However, in TBMN, in contrast to both X-linked and autosomal-recessive Alport syndrome, the  $\alpha 3(\text{IV})$ ,  $\alpha 4(\text{IV})$ , and  $\alpha 5(\text{IV})$  chains all are expressed in the glomerular basement membrane (GBM).

Some patients with a diagnosis of TBMN and progressive renal failure actually may have Alport syndrome. Renal failure is unusual in TBMN, and a family history of males with ESRF suggests X-linked Alport syndrome, especially if there are extrarenal manifestations such as high-tone sensorineural hearing loss, anterior lenticonus, or retinopathy. The renal biopsy specimen in Alport syndrome typically shows GBM thickening and lamellation, but these changes are absent or patchy early in the disease, and often are patchy in females. Immunohistochemistry of the renal biopsy specimen distinguishes Alport syndrome from TBMN. The glomerular and tubular membranes of males with X-linked disease fail to express the  $\alpha 3(\text{IV})$ ,  $\alpha 4(\text{IV})$ , and  $\alpha 5(\text{IV})$  collagen chains and Bowman's capsule and the distal tubular membranes lack the  $\alpha 5(\text{IV})$  and  $\alpha 6(\text{IV})$  chains.<sup>24,25</sup> Likewise, there is no staining in the skin for  $\alpha 5(\text{IV})$  and  $\alpha 6(\text{IV})$ .<sup>25</sup> Female carriers show mosaicism with partial staining. Normal staining for all these chains supports the diagnosis of TBMN.

Patients with TBMN and progressive renal failure<sup>1,26,27</sup> eventually present for renal transplantation. Glomerulosclerosis often is associated with advancing renal impairment but it is unclear whether this glomerular injury is secondary to the basement membrane abnormality or is part of the primary defect.<sup>7,8,17</sup>

Other coexistent glomerular lesions also lead to renal impairment in TBMN.<sup>7,14,17,26-30</sup> These occur in about 5% of patients with TBMN,<sup>7,14,26</sup> and are likely to determine their clinical course and the outcome of a renal allograft if these patients proceed to transplantation. These diseases include IgA disease, membranous nephritis, mesangiocapillary glomerulonephritis, systemic lupus erythematosus, and diabetes.<sup>17</sup> However, TBMN must be differentiated from the GBM thinning that often occurs secondary to actual glomerular disease and repair. This thinning often is focal whereas GBM thinning in TBMN usually affects more than 50% of glomeruli and at least 50% of individual capillary loops.<sup>6,15</sup>

## TBMN and ESRF: Implications for Receiving a Transplant

In general, individuals with TBMN who undergo renal transplantation have a prognosis that is comparable with that of the rest of the transplant population. Allograft outcome and the risk for recurrence of the original disease depend predominantly on the nature of any lesions in the native kidneys rather than on the presence of TBMN itself. For example, IgA nephropathy and focal segmental glomerulosclerosis recur in transplanted kidneys. Individuals with TBMN and a coincidental or associated glomerular lesion may have this disease recur in their transplant. The underlying genetic defects in TBMN are absent from the transplant and do not influence the outcome of a graft.

## Alport Syndrome and Transplantation

An important reason for accurately diagnosing and clearly differentiating between TBMN and Alport syndrome in patients undergoing transplantation is the complication of anti-GBM disease sometimes seen after renal transplantation in Alport patients. This occurs in approximately 2% to 5% of transplanted subjects with Alport syndrome and does not preclude transplantation in most patients, except in situations where it has occurred previously. This is because the risk for recurrence in subsequent transplants is very high.<sup>24,31</sup> Although anti-GBM antibodies are pathogenic, the antibody response is T-cell dependent, and the T cells themselves may have a direct role in glomerular injury. Patients with Alport syndrome who progress to ESRF should be considered for renal transplantation if they are medically suitable. The medical assessment of a patient with glomerular hematuria and renal impairment, should ideally include a renal biopsy that is carefully examined by both electron microscopy and immunohistochemistry (ideally including special stains for type IV collagen if available) in order to distinguish between TBMN and Alport Syndrome. In contrast to the Goodpasture autoantibodies that target mainly the  $\alpha 3(\text{IV})$  collagen chain,<sup>32-34</sup> alloantibodies induced by the missing collagen chains in Alport syndrome are directed against exposed determinants on the noncollagenous domains of the  $\alpha 3$ ,  $\alpha 4$ , and  $\alpha 5(\text{IV})$  chains. In X-linked Alport syndrome, these chains are absent in utero and throughout life, and presumably self-tolerance fails to occur. These antigens are seen in an immunologic sense for the first time in the renal transplant resulting in an alloantibody response.

Many patients with Alport syndrome who undergo renal transplantation develop detectable circulating anti-GBM antibodies. The frequency of detection depends on the method and sensitivity of the assay used.<sup>35,36</sup> Nevertheless, the incidence of anti-GBM disease posttransplantation is low.<sup>24,31,36-40</sup> This lack of correlation between circulating antibodies and the development of anti-GBM disease posttransplantation is explained by the nature of the underlying genetic mutation, differences in the antibodies' specificity and affinity, the type of immunosuppression used, and the genetically controlled variability of the immune response. For example, males with Alport syndrome who have sensorineural

deafness appear to be at higher risk for developing anti-GBM disease, whereas those with late-onset disease, and females have a lower risk.<sup>24</sup> However, overall, patients with Alport syndrome who undergo transplantation have similar graft survivals compared with patients with other diagnoses,<sup>24,31,41</sup> and most allografts in Alport patients fail because of chronic allograft nephropathy and acute rejection.

When anti-GBM disease occurs posttransplantation in Alport syndrome, it usually occurs within the first year.<sup>31</sup> The onset of anti-GBM disease is associated with a high rate of graft loss, a possibly poorer response to the conventional treatment for anti-GBM disease such as plasma exchange and cyclophosphamide, and an increased recurrence rate in subsequent grafts.

## Renal Transplant Donors With TBMN

A controversial clinical issue for which there is limited long-term data is the acceptance of individuals with TBMN or women who are heterozygous for the COL4A5 genetic defect as live renal transplant donors. Although it is not possible to summarize clear evidence-based recommendations, an increasing number of diagnostic tools such as immunohistochemical analysis for type IV collagen defects and rapid molecular analysis should enable confirmation of the diagnosis and possibly stratification in the future. There is general agreement that patients with TBMN who have risk factors for progressive disease, such as proteinuria, hypertension, or overt renal insufficiency, should not be donors. Careful assessment of the potential donor's family history, presence of hematuria in family members, and extrarenal manifestations of Alport syndrome may help clarify existing diseases in potential donors. Those with isolated glomerular hematuria must be assessed thoroughly for atypical features and when these are present, should usually undergo a renal biopsy examination. This will detect undiagnosed Alport syndrome and also any other significant disease such as IgA glomerulonephritis before donation. Renal donation from mothers of males with Alport syndrome has been reported with good short-term outcome for both the donor and recipient.<sup>42,43</sup> However, again, potential donors with proteinuria, hypertension, renal impairment, or evidence of extrarenal pathology should not be permitted to proceed.

Although individuals with typical TBMN and carriers of Alport syndrome have donated kidneys,<sup>44</sup> the actual long-term risks remain unknown. Many transplant physicians view individuals with TBMN as potential marginal donors whose kidneys can be used only if there are no other poor prognostic factors. Others exclude live donors with TBMN entirely from the donor pool. However, each case must be assessed in the context of the potential donor's wishes, the recipient's wishes and medical needs, and a full explanation of the possible outcomes.

## Conclusion

In summary, TBMN is a very common condition that generally, but not always, is associated with a good prognosis. When renal failure occurs, renal transplantation usually can proceed without significant risk for unique complications in the recipient. However, the exclusion of Alport syndrome is important. Donor kidneys with TBMN can be transplanted successfully and at this stage are not known to have an altered outcome. When a live donor with possible TBMN is being considered, careful assessment as well as counseling is required to exclude those individuals at risk for progression.

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