# The width of the basement membrane does not influence clinical presentation or outcome of thin glomerular basement membrane disease with persistent hematuria

Cheuk-Chun Szeto[1], Fernand Mac-Moune Lai[2], Bonnie Ching-Ha Kwan[1], Chi-Bon Leung[1], Paul Cheung-Lung Choi[2], Wing-Fai Pang[1], Kai-Ming Chow[1], Ka-Bik Lai[1], Gang Wang[1] and Philip Kam-Tao Li[1]

*[1]Department of Medicine & Therapeutics, Prince of Wales Hospital, The Chinese University of Hong Kong, Shatin, Hong Kong, China and [2]Department of Anatomical and Cellular Pathology, Prince of Wales Hospital, The Chinese University of Hong Kong, Shatin, Hong Kong, China*

**Thin basement membrane disease (TBMD) typically presents with persistent microscopic hematuria, and is usually defined as a glomerular basement membrane (GBM) thickness <250 nm. Previous studies showed that neither the degree of thinning nor the extent of the abnormality correlate with the patient's clinical presentation or prognosis. To further define this, we enrolled a study group of 41 patients with isolated microscopic hematuria and a normal renal biopsy, except those with a GBM thickness of 250–320 nm, and compared them with 33 patients with traditional TBMD. We found no difference in baseline demographic or clinical parameter between the groups. After follow-up averaging 110 months, there was no significant difference in the risk of detectable or overt proteinuria, hypertension, or impaired renal function between the groups. By the end of the study, only five patients from the study group and four from the TBMD group had no outcome event. By Cox regression analysis, independent predictors of overt proteinuria were male gender, age at biopsy, baseline renal function, proteinuria, and hypertension. Age at biopsy was the only independent predictor for hypertension, and baseline proteinuria was the only independent predictor for impaired renal function. GBM thickness did not predict any outcome event. Hence, lifelong follow-up is advised, as the clinical features and prognosis of these patients with persistent microscopic hematuria and marginally thin GBM are similar to traditional TBMD.**

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**Correspondence:** *Cheuk-Chun Szeto, Department of Medicine & Therapeutics, Prince of Wales Hospital, The Chinese University of Hong Kong, Shatin, NT, Hong Kong, China. E-mail: ccszeto@cuhk.edu.hk*

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Thin basement membrane disease (TBMD), also called benign recurrent hematuria, is characterized by persistent microscopic hematuria and diffuse thinning of the glomerular basement membrane (GBM) under electron microscopy.[1,2] Both direct and indirect approaches suggest that TBMD occurs in >1% of the population, which makes it one of the most common conditions affecting the kidney after infections, hypertension, and stones.[2–5]

Traditionally, TBMD is believed to be benign, with little risk of hypertension or progression to chronic kidney disease.[6] However, more recent studies showed that the condition may not be universally benign, especially in adults.[2,7–9] A median of 50% adults with TBMD had some degree of proteinuria, 16% had proteinuria >500 mg/day, and 17% had hypertension, and up to 29% had renal impairment.[2] In addition, van Paassen *et al.*[7] found that ~15% of TBMD has substantial proteinuria, which is associated in the majority of cases with the lesions of focal segmental glomerulosclerosis, particularly those in late middle age. Furthermore, Nieuwhof *et al.*[9] reported that renal function may decline in a considerable proportion of patients with TBMD during prolonged follow-up, and blood pressure may increase in many affected individuals, suggesting that the long-term prognosis may be less favorable than previously believed. More recently, Voskarides *et al.*[10] identified specific mutations associated with the development of proteinuria, renal failure, and segmental glomerulosclerosis in patients with morphological TBMD.

The diagnosis of TBMD is morphological and somewhat arbitrary. Although GBM thickness is greater in normal males than females, whereas GBM is thinner in children than adults,[11] most authors agree that an average GBM thickness of <250 mm by the orthogonal intercept method (around two standard deviations below the mean of normal adult values) should be considered abnormal.[11,12] However,

previous studies showed that neither the degree of thinning nor the extent of the abnormality correlate with the patient's clinical presentation or prognosis. In fact, some patients present with persistent microscopic hematuria and have no renal pathology identified except a GBM thickness of 250–320 mm (that is, average value of normal female); their clinical behavior remains unknown.

## RESULTS

### Demographic and clinical features

The average duration from the time of presentation to renal biopsy was 42.5 ± 44.8 months. The baseline demographic and clinical data of the two groups are summarized and compared in Table 1. In short, there was no significant difference in any of the baseline parameters between groups.

**Table 1 | Comparison of clinical presentation between groups**

| Group | Study group | TBMD group |
|---|---|---|
| Total no. of patients | 41 | 33 |
| Sex (M:F) | 10:31 | 3:30 |
| Age (years) | 36.7 ± 10.3 (15–55) | 37.1 ± 7.9 |
| Body weight (kg) | 60.0 ± 11.8 (38–80) | 58.6 ± 8.0 |
| *Blood pressure (mm Hg)* | | |
| Systolic | 132.7 ± 17.1 | 129.8 ± 17.1 |
| Diastolic | 77.9 ± 14.5 | 75.6 ± 10.8 |
| *Clinical features (no. of cases (%))* | | |
| Microscopic hematuria | 41 (100%) | 33 (100%) |
| Macroscopic hematuria | 1 (2.4%) | 2 (6.1%) |
| Detectable proteinuria | 24 (58.5%) | 22 (66.7%) |
| Hypertension | 15 (36.6%) | 6 (18.2%) |
| Proteinuria ⩾1 g/day[a] | 6 (14.6%) | 8 (24.2%) |
| Impaired renal function[a] | 2 (4.9%) | 0 |
| *Family history (no. of cases (%))* | | |
| Hematuria | 2 (4.9%) | 2 (6.1%) |
| Renal failure | 0 | 2 (6.1%) |
| Hearing problem | 1 (2.4%) | 0 |
| *Glucose intolerance (no. of cases (%))* | | |
| Diabetes[b] | 1 (2.4%) | 2 (6.1%) |
| Impaired fasting glucose | 4 (9.8%) | 2 (6.1%) |
| *Biochemical parameters* | | |
| Serum creatinine (μmol/l) | 76.1 ± 29.0 | 71.4 ± 13.5 |
| Estimated GFR (ml/min per 1.73 $m^2$) | 92.5 ± 25.7 | 89.6 ± 17.3 |
| Proteinuria (g/day) | 0.49 ± 0.74 | 0.64 ± 0.70 |
| *GBM thickness (nm; mean ± s.d. (range))* | | |
| Mean thickness[c] | 275.8 ± 18.3 (251–325) | 224.9 ± 21.9 (172–249) |
| ISD[d] | 63.4 ± 11.8 (38–92) | 59.7 ± 15.2 (33–87) |

Abbreviations: GFR, glomerular filtration rate; GN, glomerulonephritis; ISD, intraindividual standard deviation of basement membrane thickness; s.d., standard deviation; TBMD, thin basement membrane disease.
[a]Some patients were labeled as having proteinuria over 1 g/day or impaired renal function by the referring physician, but they actually did not have such a problem when being assessed by us or around the time of kidney biopsy.
[b]All required diet control only.
[c]$P < 0.0001$ between the groups.
[d]$P = 0.26$ between the groups.

None of the patients had hearing impairment clinically. However, 13 patients from the study group and 9 from the TBMD group were randomly selected and referred for pure-tone audiometry. Five from the study group and one from the TBMD group were found to have sensorineural hearing loss (Fisher's exact test; $P = 0.3$).

### Immunofluorescence

Immunofluorescence for α-3 and α-5 chains of type IV collagen was performed in 27 patients of the study group and 26 of the TBMD group. One patient of the TBMD group showed absence of α-5 chains of type IV collagen; one patient from the study group (who also had sensorineural hearing loss) and four from the TBMD group showed fragmented staining, suggestive of heterozygous for mutations of Alport's syndrome.

### Clinical outcome

The average duration of follow-up was 109.8 ± 74.2 months. At the end of the study period, 33 patients of the study group had detectable proteinuria, 17 had overt proteinuria, 17 had hypertension, and 4 had impaired renal function. For the TBMD group, 29 patients had detectable proteinuria, 15 had overt proteinuria, 10 had hypertension, and 1 had impaired renal function. The Kaplan–Meier plots of event-free survival of the two groups are shown in Figure 1. In short, there was no significant difference in the risk of any outcome measure between the groups. By the end of the study period, only five patients from the study group and four from the TBMD group had no outcome event (that is, remained free of any detectable proteinuria, hypertension, or impaired renal function). Of the six patients who had absent or fragmented GBM staining for α-5 chains of type IV collagen, five developed detectable proteinuria, one had hypertension, one had overt proteinuria, and none had impaired renal function at the end of the study period. The result remained similar when patients with absent or fragmented GBM immunofluorescence staining were excluded from the analysis (details not shown).

### Effect of basement membrane thickness

We compared the GBM thickness between patients who did and did not develop detectable proteinuria, overt proteinuria, hypertension, or impaired renal function (Figure 2). In short, no significant difference was found. There was also no significant difference in the intraindividual variation of GBM thickness between patients who did and did not develop clinical events (details not shown).

The result of Cox regression analysis on the predictors of development of outcome events is summarized in Table 2. From the Cox models, independent predictors for the development of overt proteinuria were male sex, age at biopsy, baseline renal function, proteinuria, and hypertension. On the other hand, age at biopsy was the only independent predictor for the development of hypertension, whereas baseline proteinuria was the only independent