Permselectivity in Thin Membrane Nephropathy

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Abstract

The glomerular permselectivity to polydisperse neutral dextrans was compared in 6 patients with thin membrane nephropathy (TMN) and 10 healthy controls. Despite having normal renal hemodynamics and minimal proteinuria, the patients with TMN had significantly increased fractional clearance of neutral molecules with Stokes radius > 42 Å. Conventional theories of glomerular barrier size selectivity cannot fully explain these data since they would predict that our patients would have had nephrotic range proteinuria. (*J. Clin. Invest.* 1994. 93:1881–1884.) Key words: kidney glomerulus • basement membrane • proteinuria • capillary permeability

Introduction

Thin membrane nephropathy (TMN)[1] is a common and relatively benign condition that usually presents with microscopic hematuria (1, 2). Proteinuria may or may not be present but the nephrotic syndrome is extremely unusual (3). It is uncommon for the condition to progress to renal failure. TMN is diagnosed by electron microscopy of renal biopsy specimens: the glomerular basement membrane (GBM) is uniformly thinned. It may be contrasted with Alport's syndrome, also considered a primary disorder of GBM, which has a worse prognosis, frequently progressing to end-stage renal failure. In Alport's, GBM thinning occurs but is patchy. In addition there may be characteristic thickening and splitting of the GBM with a basket-weave appearance (4).

The pathogenesis of TMN is not understood. It would appear that the subepithelial portion of the GBM is reduced, which alters the distribution of type IV collagen in the GBM (5). Apart from this, no specific defects have been found. The functional properties of the glomerular capillary barrier have not been described in TMN. We therefore studied renal hemodynamics and glomerular permselectivity in a group of patients with this condition.

Methods

Patients. Six patients with biopsy-proven TMN (mean GBM thickness, 198.5 [range, 148–227] nm) were recruited. They were considered to have TMN if electron microscopy showed uniform thinning of the GBM. GBM thickness was taken to be the harmonic mean of orthogonal intercepts using the method described by Jensen et al. (6). The normal value in our laboratory is 301.4 (range, 238–358) nm. Slit pore frequency was measured from electron micrographs ($\sim \times 10{,}000$) and expressed as slits/mm GBM (7). In none of the patients were the ultrastructural changes of Alport's syndrome seen and none had associated auditory problems (assessed with formal audiometry). A positive family history of hematuria was not considered to be an exclusion and was present in two patients.

All patients provided informed consent and the study was approved by the ethical subcommittee of the Cardiff Division of Medicine and conforms to the declaration of Helsinki.

Controls. 10 normal volunteers with normal renal function, no known illness, normal blood pressure, and normal urine on stick testing had hemodynamic studies and permselectivity measured as described below.

Permselectivity and hemodynamics. Each individual had their fasting renal hemodynamics and glomerular permselectivity studied once. Subjects were water loaded with 20 ml/kg before the test and then received 5% glucose intravenously at 150 ml/h during the investigation together with tap water ad libitum. Glomerular filtration rate (GFR) and effective renal plasma flow (ERPF) were calculated by measuring the renal clearance of a continuous combined infusion of ^{51}Cr-EDTA and ^{125}I-hippuran, respectively, after a loading bolus (total dose, 4 MBq). For the first 15 min, 130 mg/kg dextran 70 (peak, 48 Å) in 0.9% saline (Baxter Healthcare, Thetford, UK) was infused after the subject had received 20 ml dextran 1 (8) as a bolus to prevent allergic reactions. After 1 h for equilibration, two 0.5-h urine collections followed by two 1-h collections were made with appropriately bracketed blood samples. GFR and ERPF were expressed as the mean urinary clearance of isotope over 3 h. Fractional clearance of dextrans (θ_D) was calculated using the formula: $\theta_D = [(U/P)_D]/[(U/P)_{EDTA}]$, where $(U/P)_D$ and $(U/P)_{EDTA}$ refer to the ratio of urine to mean plasma concentrations of dextran and ^{51}Cr-EDTA, respectively, during the first 0.5-h collection made during the study. Dextran 70 was chosen in preference to dextran 40 in order to provide a greater urinary concentration of higher radius dextrans. Although dextran 70 will produce a marginally greater rise in colloid osmotic pressure than dextran 40 (and hence reduce net filtration pressure), this is the same for both groups and does not therefore affect comparisons between groups.

Urine and plasma concentrations of albumin and IgG were measured at the same time points and their fractional clearance was calculated in the same way.

Arterial blood pressure was measured with a standard mercury sphygmomanometer. Patients performed a 24-h urine collection for estimation of protein excretion on the day before their renal hemodynamics were studied.

Laboratory methods. ^{51}Cr-EDTA and ^{125}I-hippuran were counted in a gamma counter. GFR and ERPF were calculated in the normal way (9).

After precipitation of protein with trichloroacetic acid (10) (to give a final concentration of 10%) dextrans were separated in blood and

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1. *Abbreviations used in this paper:* ΔP, transcapillary hydraulic pressure gradient; ERPF, effective renal plasma flow; GBM, glomerular basement membrane; GFR, glomerular filtration rate; K_f, ultrafiltration coefficient; r*[1%], 1% of glomerular filtrate passes through pores with radius greater than this value (log-normal model); r_o, mean pore size (isoporous with shunt membrane model); TMN, thin membrane nephropathy; u, mean pore size (log-normal membrane model); ω, proportion of glomerular filtrate passing through non selective "shunt" pathway.

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urine on an HR 10/30 column containing Superose 6 using an FPLC system (Pharmacia Ltd., Milton Keynes, UK). Phosphate-buffered saline (pH 7.3) was used as eluent. The column was calibrated with 11 standard dextran fractions (Polymer Laboratories Ltd., Church Stretton, UK) whose peak molecular weight was known and from which the Stokes radius (SR) could therefore be calculated (11). For repeated column calibrations the correlation coefficient (R^2) for the fit between elution volume and stokes radius was 0.961 ± 0.01 (95% CI, 0.94–0.983). The column was able to clearly separate the larger radius dextrans: during repeated calibrations the difference in elution volume between 55 and 60 Å was 0.486 ± 0.013 ml, and between 60 and 65 Å was 0.447 ± 0.012 ml.

The concentration of dextran was measured continuously with an on-line refractive index meter (12, 13) (Varian Associates Ltd., Walton-upon-Thames, UK) and the total dextran concentration of each 0.2 ml of eluate was integrated using the FPLC microprocessor. Potential errors due to possible differences in recovery of dextran between runs from the column were eliminated by the addition of an internal standard of high molecular weight dextran to each sample. Since the refractometer measures dextran concentrations in arbitrary units of refractance, the dextran concentrations in the specimen were related to the height of the standard peak. For n = 109, Coefficient of Variation (CV) of the internal standard was 14.8%. There was no difference in the sensitivity for dextran concentrations across the range of dextran radii studied. To further minimize any day-to-day variation in column characteristics, individual subjects' specimens were always run sequentially (although in random order) on the same day. In the range of 30–60 of Å, there was no difference in the recovery of dextran between dextran in deproteinized serum and dextran in eluant; there is no evidence that dextran coprecipitates with protein.

Plasma albumin and IgG were measured by nephelometry. Urinary albumin was measured by an immuno-chemiluminescent assay (14) and urinary IgG by ELISA (15).

Statistical analysis. Because of the low numbers, data were considered to be nonparametric. Results are generally expressed as the median with range. Statistical comparisons were made using the Mann-Whitney U test.

Results

The six patients comprised four women and two men with a mean age of 31.4 (24–41) yr. The 10 healthy controls were 9 males and 1 female, with a mean age of 35.3 (27–50) yr. Four of the patients had no detectable proteinuria and the remaining two had 0.4 and 1.1 g/24 h, respectively. The patients were normotensive and on no medication.

Electron microscopy of the patients' biopsies gave a mean GBM thickness of 198.5 (range, 148–227) nm. Their slit pore frequency was 1,554 (1,496–1,779) slits/mm GBM; normal range is 1,453–1,822.

Individual patient data are shown in Table I. Median GFR for the patients was 93.4 (87.1–109.9) ml/min for body surface area (BSA) 1.73 m^2, while median ERPF was 473.7 (389.4–973.9) ml/min. Corresponding values for the controls were 86.7 (64.3–104.7) ml/min (GFR) and 409.1 (237.9–623.0) ml/min (ERPF). There was no significant difference between groups although the median values for GFR and ERPF were higher in the patients than the controls. Filtration fraction was not different between the groups: 0.215 (0.14–0.302) in controls and 0.19 (0.113–0.246) in TMN. There are no data available concerning the extraction ratio of ^{125}I-hippuran in TMN. Since in disease states with impaired GFR this may be reduced (16), caution is therefore needed in comparing data dependent on this measurement between groups.

Table I. Patient Data

Patient	GFR	ERPF	Serum protein	Proteinuria
	ml/min	*ml/min*	*g/l*	*g/24 h*
1	96.2	468.2	64	0
2	91.05	464.36	69	0
3	109.9	933.9	61	1.1
4	95.7	389.9	67	0.4
5	90.8	495.9	79	0
6	87.1	479.3	68	0

All patients showed an increased fractional clearance of polydisperse neutral dextrans compared with controls (Fig. 1). This was significant at the 5% level for dextran molecules > 42 Å. As molecular size increased, the difference between the fractional clearance of equivalent sized molecules was more marked, and at a Stokes radius of 55 Å, P had reached 0.001 (Mann-Whitney U, Z = −3.254). In the TMN patients the increased urinary excretion of larger dextrans allowed the fractional clearance to be calculated of molecules up to 65 Å whose excretion could not be detected in controls. The two patients with proteinuria have fractional clearances of dextran that fall either side of the TMN mean. Both have fractional clearances of dextran greater than the mean for normal subjects for all molecular sizes > 42 Å.

These sieving data were modeled mathematically using the log-normal model of glomerular permeability (17). Assuming the trans-capillary hydraulic pressure gradient (ΔP) to be 35 mmHg, controls had a median pore size (u) of 44.65 (32.3–52.1) Å with a standard deviation for the individual log-normal probability curve of 1.18 (1.12–1.32). This would predict that 1% of the filtrate passed through pores ≥ 75.6 (69–83.8) Å (r*[1%] = 75.6 Å). In TMN, for the same ΔP, u = 45.5 (20.3–68.4) Å, standard deviation of the distribution (s) = 1.23 (1.04–1.51), and r*[1%] = 87.2 (74.7–117.6) Å (P = 0.03 for r*[1%]; the differences in u and s are not significant). At this ΔP, the calculated ultrafiltration coefficient (K_f,) for TMN is 10.22 (8.38–18.76) ml/min per mmHg, and for controls, 14.45 (8.47–33.3) ml/min per mmHg (no significant difference).

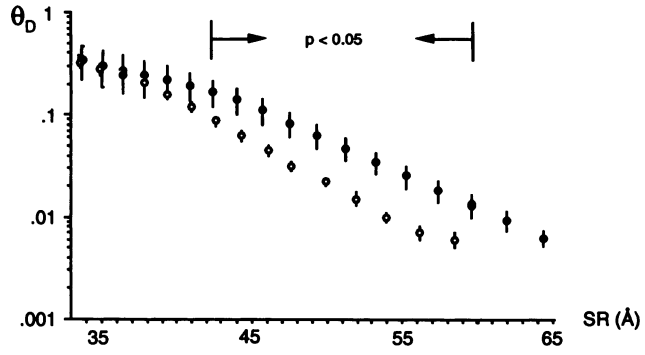

Figure 1. Fractional clearance of neutral dextrans (θ) of TMN (•) compared with normal control (○). *SR*, Stokes radius. Values represent the mean (±SEM) fractional clearance for each dextran size in the two groups of subjects.

Fractional clearance of albumin was not significantly different from controls: 2.25×10^{-5} (1.7×10^{-7}–1.9×10^{-4}) vs. 1.06×10^{-6} (6.7×10^{-7}–2.7×10^{-6}). Fractional clearance of IgG was marginally lower than the normal range (3×10^{-6} vs. 13.95–108.65 $\times 10^{-6}$).

Discussion

This study is the first detailed investigation of glomerular barrier function in TMN. For neutral dextran molecules > 42 Å, the fractional clearance of the molecule is increased in TMN compared with normal controls, and as the curves diverge the level of significance rises. The two curves are similar in shape but that for TMN is displaced upwards. The striking abnormality is the increased fractional clearance of neutral dextran molecules despite the absence of significant proteinuria.

Changes of this magnitude are almost unique. Similar but quantitatively smaller changes in permselectivity are described in Pima Indians with noninsulin-dependent diabetes of recent onset who demonstrate an increased fractional clearance of all dextrans, significant for molecules > 48 Å (18). Their GBM thickness is not known. In normal humans, angiotensin II infusion provokes a similar but much smaller rise in dextran sieving and appears antiproteinuric (19); the explanation is unclear.

The glomerular barrier has been modeled mathematically in various ways using dextran sieving data, GFR, ERPF, assumed values for ΔP, and calculated values for K_f (which is derived from ΔP, GFR, RPF, and total protein).

Current mathematical models can only partly explain our data. The heteroporous ("isoporous with shunt") model (20) considers the normal barrier as having one large population of uniform pores that are size selective and relatively impermeable to proteins. Diseases in which proteinuria is present have a separate nonselective pathway across the barrier that allows passage of macromolecules into the urine. This hypothesis allows the barrier to be completely described by three functions: K_f, ω_o, and r_o, where K_f is the ultrafiltration coefficient, ω_o is a hypothetical construct roughly equal to ω (the proportion of the GFR passing through the shunt pathway), and r_o represents the radius of the size-selective pores.

A second model describes the barrier as a structure containing pores whose size varies in a log-normal distribution (17). This is described by two variables: u, the mean of the distribution; s, the standard deviation of the distribution and a contingent variable, r*[1%]. 1% of the glomerular filtrate passes through pores of diameter greater than or equal to this value. In diseases where proteinuria is present, r*[1%] will rise as the pore distribution shifts in favor of larger pores.

These models have been derived from sieving experiments performed using inulin as the GFR marker. In our studies we have used ^{51}Cr-EDTA, and the values of GFR are at the lower end of the normal range (21). It has recently been suggested that "normal" values have fallen possibly as a result of changing diet (22). Since both groups of subjects received ^{51}Cr-EDTA, any differences in fractional clearance between the groups cannot, however, be attributed to the GFR marker.

Both of these models allow some deductions to be made from our data since both predict how a dextran sieving curve will change if ΔP or K_f alter.

In principle, a fall in K_f or rise in ΔP will shift the sieving curve down and to the left and vice versa. This is particularly true for smaller molecules. It seems likely therefore that at least a partial explanation of our patients' altered sieving could be due to a rise in K_f. Certainly this would be a rational explanation since they are known to have abnormally thin GBM. However, the calculated K_f was actually nonsignificantly reduced and the deviations in θ_D become larger as molecular size increases. It would appear that a rise in K_f is not the full explanation therefore. A fall in ΔP is possible but we have no evidence to support this suggestion.

Deen et al. (20) have reported that in nephrotic patients the increased urinary excretion of macromolecules is due to the presence of a nonselective shunt pathway across the GBM (20). These changes are reflected in the dextran sieving curves of normals compared with nephrotics, where the increased clearance of larger neutral dextrans is a measure of the increased shunt fraction. Fig. 2 compares the sieving curves for patients with TMN to patients we have previously described with heavy proteinuria due to membranous nephropathy (23). As can be seen, θ_D for molecules with SR 55 Å is actually higher for patients with TMN than those with severe proteinuria, yet these TMN patients have only minimal proteinuria. When our data are analyzed using the log-normal model, there is a minimal reduction in mean pore size but a considerable increase in r*[1%]. To date, the increase in r*[1%] would have been predicted to occur in association with moderate or heavy proteinuria (24), which was not present in our patients. Thus current modeling seems unable to explain our data fully.

It is conceivable that reptation of dextran molecules (25), which are modeled as spheres but are actually ellipsoid (26), could increase their fractional clearance in TMN. The absolute thickness of the GBM compared with the molecular length is so large in both TMN and normals, however, that this explanation seems unlikely.

In the present study, the absence of proteinuria in the presence of abnormal barrier function suggests that although the GBM may contribute to overall permselectivity, the integrity of the glomerular epithelial cells and the maintenance of charge prevents defects being clinically manifest. This is supported by the previously unreported observation that slit pore frequency is normal in TMN and this contrasts sharply with published data in membranous nephropathy (27) and our own experience of eight subjects with this condition whose median slit pore frequency is 431 slits/mm ($P < 0.01$ vs. TMN).

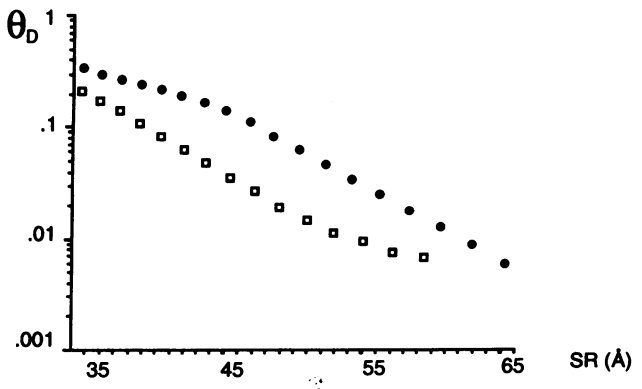

Figure 2. Fractional clearance of neutral dextrans (θ) of TMN (●) compared with patients with nephrotic syndrome and membranous glomerulonephritis (□).

Permselectivity appears to be due to the size-selective and charge-selective properties of the glomerular capillary barrier. Although Venkatachalam et al. and Graham and Karnovsky (28, 29) have shown that large molecules can pass through the GBM, the present study together with previous work (30) suggests that the GBM still contributes significantly to the size-selective barrier. Recent studies have also shown that cellular function is important in maintaining both size selectivity (31) and charge selectivity (32, 33). In addition, there is increasing evidence that epithelial podocytes and the filtration slits are important in this regard (34), confirming Rodewald and Karnovsky's conclusions from ultrastructural studies in 1974 (35). The relative contribution to hydraulic permeability of different portions of the barrier have recently been assessed by Drumond and Deen (34); they have rightly emphasized the role of the filtration slits. They have also shown, however, that some 60% of the hydraulic permeability is contributed by the GBM; hence, it would be premature to completely abandon the concept that the GBM contributes to the permselective properties of the barrier.

In conclusion, these data demonstrate that glomerular size selectivity is abnormal in TMN. Slit pore frequency is normal. The significant increase in the fractional clearance of dextran molecules in the absence of substantial proteinuria make it unlikely that overall glomerular barrier function can be explained by current mathematical models that are derived solely from size selectivity data. Other factors including charge and cell function must be considered when evaluating the filtration barrier.

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