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The Structure of the Glomerular Capillary Basement Membrane in Diabetes Mellitus with and without Nephrotic Syndrome*

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Summary. The investigations of the kidneys of 80 diabetics, of whom 29 had a nephrotic syndrome, on silver-impregnated semithin sections showed that different morphological changes of the glomerular basement membrane are involved in the nephrotic syndrome. Nine from 29 of the diabetics with nephrotic syndrome in whom punctures were performed owing to renal symptoms showed perimembraneous changes of the basement membrane (in 100% nephrotic syndrome). Apart from the perimembraneous lesions there were homogeneous thickening of the basement membrane (in 48% nephrotic syndrome), splitting of the basement membrane in the sense of a membranoproliferative glomerulonephritis (in 50% nephrotic syndrome) and cases with lightmicroscopically uneventful basement membrane which developed a nephrotic syndrome in 10%.

Owing to the diversity of the histological picture it is assumed that different pathogenetic mechanisms are involved in the nephrotic syndrome in diabetes mellitus.

Key words: Diabetes Mellitus — Glomerular Basement Membrane — Nephrotic Syndrome Perimembraneous Changes — Membranoproliferative Glomerulonephritis.

It has long been known [3, 4, 6, 7, 9, 10] that a nephrotic syndrome can develop during the course of diabetes mellitus. Thus far it has not been elucidated whether a homogeneous morphological substrate on the basement membrane of the glomerular capillaries is responsible for the nephrotic syndrome.

Material and Methods

Consequently we have systematically studied the basement membranes of the glomeruli in the kidneys of 80 diabetics showing signs of disturbed renal functions on PAS-stained paraffin sections and silver impregnated semithin sections (0.5–1 μ). Twenty-nine (13 men, 16 women) had a nephrotic syndrome (no data was furnished in 2 cases). Renal punctures had been performed in the remaining patients owing to indefinite renal symptoms but particularly to clarify the cause of hypertension in diabetes mellitus. The age of the patients ranged between 7 and 79 years. Forty-eight were men and 32 women. The duration of the nephrotic syndrome and of the diabetes mellitus were also investigated.

Results

1. In a total of 37 patients (46.3%) the basement membranes on the semithin section were light-microscopically uneventful. A nephrotic syndrome existed in 4 patients and no nephrotic syndrome was demonstrable in 33 patients (Table 1).

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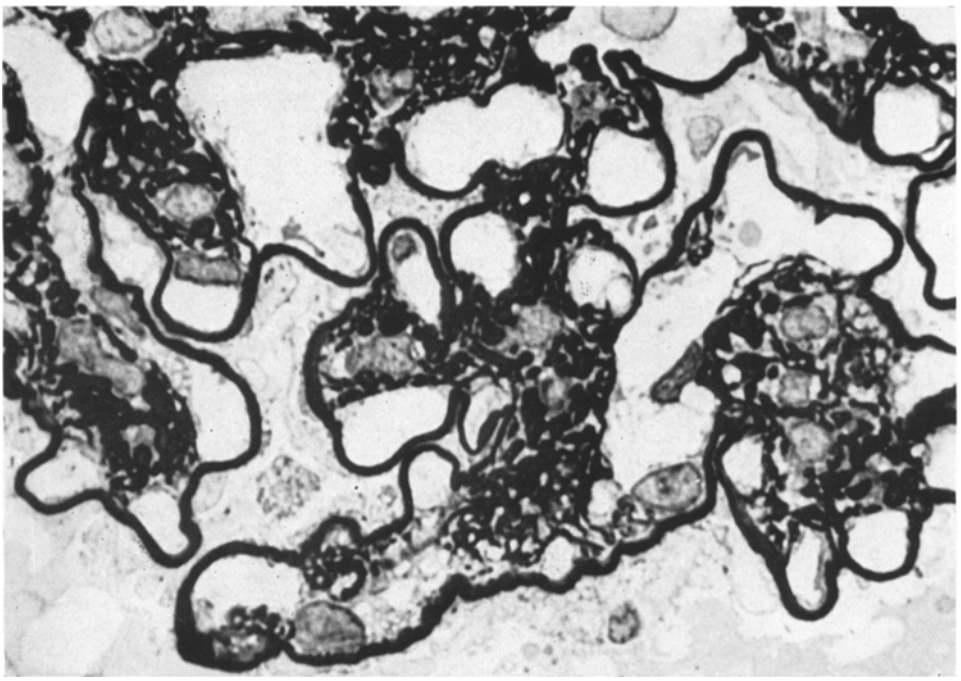

Fig. 1. 72/2/1370. Homogeneous thickening of the glomerular basement membrane, accumulation of basement membrane-like material in the mesangium. Silver impregnation after Movat. Semithin section. ×1600 (42 year old woman, 20 years diabetes, hypertension)

Table 1. Alterations of the basement membrane in diabetics and incidence of the nephrotic syndrome (NS)

	n	NS (%)
Uneventful basement membrane	37	10.8
Homogeneously thickened basement membrane	28	48.0
Perimembraneous changes	9	100.0
Splitting of the basement membrane	6	50.0

2. The basement membranes were homogeneously thickened in 13 patients with nephrotic syndrome and in 13 patients without nephrotic syndrome (total 28 patients = 35% of the cases) (Table 1, Fig. 1).

3. In 9 patients with nephrotic syndrome, i.e. in 11.2% of the cases, we found alterations of the basement membrane such as we have otherwise only observed in perimembraneous glomerulonephritis. Patients without nephrotic syndrome were not found in this group. Six were cases of diffuse glomerulosclerosis, in 2 there was a mixed form and one was a case of nodular glomerulosclerosis (Table 1, Fig. 2).

4. In 6 patients (7.5%) the basement membrane was split as in membranoproliferative glomerulonephritis; 3 of these patients had a nephrotic syndrome (Table 1, Fig. 3).

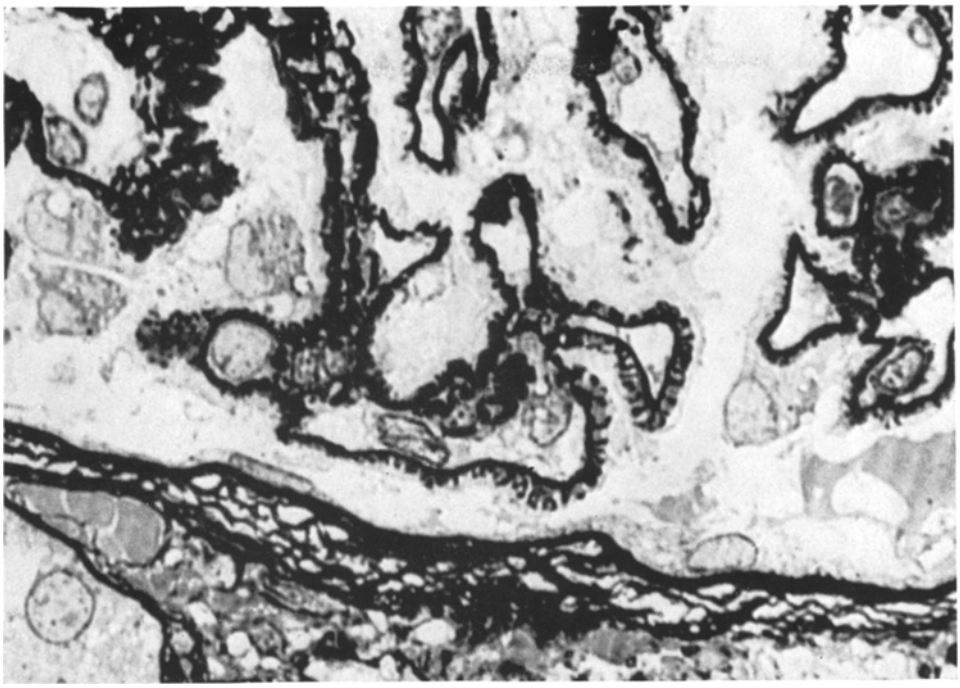

Fig. 2. 71/5/938. Perimembraneous changes. Silver impregnation after Movat. Semithin section. ×1600 (38 year old man, 12 years diabetes, 3 years nephrotic syndrome, blood pressure 130/85, insulin therapy)

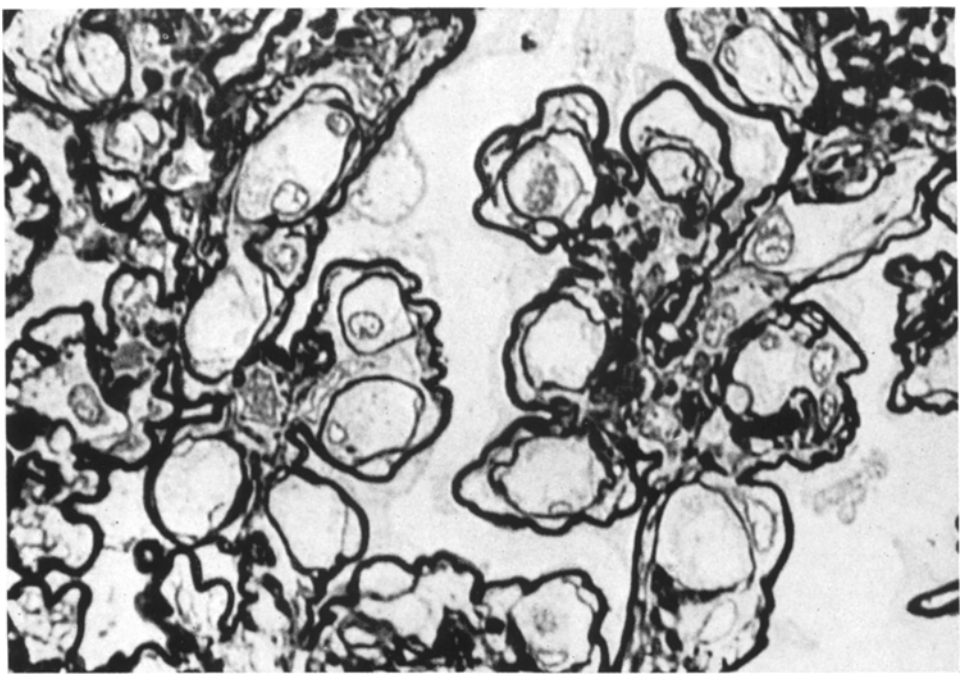

Fig. 3. 72/4/848. Section from a glomerulus with so-called splitting of the basement membrane. Under the "primary" basement membrane a "second" finer evidently newly formed basement membrane with partly intermediate cells. Silver impregnation after Movat. Semithin section. ×1600 (69 year old man, blood pressure 210/100, haematuria, 6.8‰ Esbach)

Table 2. Clinical data in 80 diabetics with and without nephrotic syndrome showing changes of the basement membrane of the glomerular capillaries

	Uneventful bm		Homogeneously thickened bm		Peri-membra-neous changes with NS	Splitting of the bm	
	with NS	without NS	with NS[a]	without NS		with NS	without NS
n	4	33	13	13	9	3	3
Age (years)	34–61 (51)	25–72 (48)	22–68 (45)	28–69 (47)	12–79 (52)	49–61 (56)	7–63 (40)
Sex	3m, 1f	18m, 15f	5m, 8f	11m, 2f	4m, 5f	1m, 5f	3f
Mean duration of nephrotic syndrome (years)	1	—	5	—	1.5	4.6 (mo)	—
Mean duration of diabetes (years)	5.4	10	12.5	18	4.5	5.3	11.5
Mean RR	157/95	155/100	160/90	170/100	140/80	206/96	130/80

[a] No data concerning nephrotic syndrome in 2 cases. bm = basement membrane, NS = nephrotic syndrome, ( ) = means, *n* = no. of cases, m = male, f = female, RR = blood pressure.

Table 3. Changes of the basement membrane in diabetes mellitus and diabetes therapy

	Insulin $n = 22$	Oral $n = 12$
Unenventful basement membrane	6/22	8/12
Homogeneously thickened basement membrane	12/22	1/12
Splitting of basement membrane	1/22	3/12
Perimembraneous changes	3/22	0/12

Of the further findings of our investigations the following are worthy of special notice (Table 2). Diabetics with glomerular lesions of the perimembraneous glomerulonephritis type are on average older (52 years) than diabetics with normal or homogeneously thickened basement membrane (45 and 48 years respectively). At the point of time of the biopsies the diabetes in patients with perimembraneous glomerulonephritis was of shorter duration (4.5 years) as compared with patients with homogeneously thickened basement membrane and nephrotic syndrome (12.5 years). The nephrotic syndrome manifests itself considerably earlier in patients who during the course of their diabetes mellitus present perimembraneous lesions than in patients with homogeneous thickening of the basement membrane. The syndrome was observed in patients with perimembraneous changes on average already 3 years after diagnosis of the diabetes mellitus and in patients with homogeneous thickening of the basement membrane on average 7.5 years after diagnosis of the diabetes mellitus. It is not possible to draw such unequivocal conclusions in this respect in the other group with nephrotic syndrome owing to the small number of cases. Nevertheless it is worthy of notice that in cases with splitting of

the basement membrane the diabetes and the nephrotic syndrome are of very short duration, whereas the diabetes in cases without nephrotic syndrome is mostly of far longer duration. In 34 cases data were furnished concerning the therapy of the diabetes. Twenty-two patients were treated with insulin and 12 with oral hypoglycaemics. It is worthy of notice that the cases with homogeneous thickening of the basement membrane were treated more frequently with insulin than the patients whose renal corpuscles showed light-microscopical delicate basement membranes (Table 3).

Discussion

On reviewing the results of our investigations we find that:

1. All 80 diabetics whose kidneys were studied showed a diabetic glomerulosclerosis. This was of a diffuse character in 45 cases and of nodular character in 15 cases. In the remaining 20 patients there was a partly diffuse and partly nodular diabetic glomerulosclerosis.

2. Twenty-nine patients, i.e. 36.2%, whose kidneys had been mainly studied owing to renal symptoms, had developed a nephrotic syndrome during the course of the diabetes.

3. This nephrotic syndrome did not correspond to a homogeneous morphological substrate on the basement membrane of the glomerular capillaries. The nephrotic syndrome can occur in diabetes mellitus facultatively in the presence of delicate and homogeneously thickened or split basement membrane. It is observed obligatively only if during the course of the diabetes a glomerular affection occurs which cannot be differentiated from a perimembraneous glomerulonephritis.

The incidence of the nephrotic syndrome in diabetes mellitus which we mention is very high as compared with the results of other authors. For instance, Salomon (1963) found an incidence of 4%, Ditscherlein (1969) one of 3%, and Kimmelstiel and Porter (1948) an incidence of less than 10%. Studies on biopsy material of Gellman and associates (1959) revealed an incidence of 26% and Dachs and associates (1964) found an incidence of 24%. The main reason for the high incidence in our material is that punctures were performed in patients solely owing to renal symptoms in the course of diabetes mellitus.

However it still remains unclarified as to why the nephrotic syndrome occurs in diabetes mellitus. Based on our studies it is a proven fact that it always occurs when perimembraneous changes are present and in a high percentage when changes exist as in membranoproliferative glomerulonephritis.

Consequently the question arises as to whether these alterations of the basement membrane belong to diabetic glomerulosclerosis, so to speak as variants of this clinical picture, or whether patients with diabetes mellitus suffer particularly frequently from a perimembraneous or membranoproliferative glomerulonephritis. This question cannot be answered at the present time. It is however worthy of notice that the incidence of basement membrane changes of the perimembraneous glomerulonephritis type in diabetics with renal symptoms (11.2%) is practically the same as in non-diabetic glomerulonephritis (8.4%) [1].

However thus far such perimembraneous changes in diabetes mellitus have only been described in a few and as isolated cases [2, 3, 11]. A recent study of

Murphy and associates (1973) showed 6 diabetics among patients with membraneous glomerular affections in whom the diabetes—the same as in our cases—had existed already before the renal disease. Three of the patients were insulin-dependent. Two patients showed positive depositions of IgG and beta-1c-globulin in granular form in the glomeruli and four were immunohistologically negative. We observed findings similar to these, i.e. positive granular immunofluorescence, in genetically diabetic KK mice with perimembraneous changes. During the course of the diabetes these animals developed changes of the basement membrane such as we have described for human diabetics, i.e. in these mice one finds membraneous basement membrane changes [5, 12], homogeneous basement membrane thickening [5] and splitting of the basement membrane as in membranoproliferative glomerulonephritis [12]. Whereas broadening of the basement membrane in diabetics is a well-known phenomenon, as far as we know changes as in membranoproliferative glomerulonephritis have not as yet described in diabetic glomerulosclerosis.

Hence, various morphological changes are involved in the nephrotic syndrome of diabetes mellitus which in part are known as separate pathological states of the renal corpuscles. This variety of morphological lesions of the glomerular basement membrane in diabetes mellitus is possibly an expression of different pathogenetic mechanisms. On the other hand the findings described in genetically diabetic mice, the same as cases of diabetes mellitus with changes as in perimembraneous and as in membranoproliferative glomerulonephritis and nephrotic syndrome, suggest a common pathogenetic mechanism, eventually in the sense of an immune mechanism.

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