Renal pathology patterns in type II diabetes mellitus: relationship with retinopathy

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Abstract

Background. The glomerular and retinal vessels are both affected in patients with type I and type II diabetes mellitus. However, the prevalence of the nodular form of diabetic glomerular sclerosis (Kimmelstiel–Wilson lesion) and other forms of glomerular pathology including diffuse mesangial sclerosis and their clinical correlates in type II diabetes are less well known. In addition, although recent studies have suggested that non-diabetic glomerular disease was a common cause of proteinuria in type II diabetes, the prevalence of other diseases is unknown. The literature on this subject is clouded by clinical bias regarding patients with diabetes who undergo renal biopsy.

Methods. Glomerular and retinal pathology and clinical correlates were studied in 36 patients enrolled in a prospective clinical trial of patients with type II diabetes mellitus, proteinuria, renal insufficiency, and hypertension.

Results. Seventeen biopsies had diabetic glomerular sclerosis with Kimmelstiel–Wilson nodules; 15 biopsies had glomerular changes characteristic of the diabetic state including enlarged glomeruli and an increase in mesangial matrix without Kimmelstiel–Wilson nodules (mesangial sclerosis lesion); and two had other primary glomerular diseases (IgA and membranous nephropathy). Patients with Kimmelstiel–Wilson nodules had elevated serum creatinines compared to patients with mesangial sclerosis lesions, but there were no other significant differences. Patients with Kimmelstiel–Wilson nodules had more severe overall retinopathy than those with mesangial sclerosis lesions (P = 0.0043): six of seven with proliferative retinopathy had Kimmelstiel–Wilson nodules, and seven of the eight patients without retinopathy had mesangial sclerosis lesions.

Conclusions. The two discrete patterns of glomerular pathology and the correlation between diabetic retinopathy and the Kimmelstiel–Wilson lesion but not the mesangial sclerosis lesion suggest that the Kimmelstiel–Wilson and mesangial sclerosis lesions of diabetic glomerulosclerosis are caused by different pathogenetic mechanisms. In this study, diabetic glomerulosclerosis was responsible for the clinical renal abnormalities in 94% of patients with type II diabetes mellitus.

Key words: diabetes mellitus; glomerulopathy; Kimmelstiel–Wilson; retinopathy; type II; renal failure

Introduction

In 1936, Kimmelstiel and Wilson [1] described specific glomerular lesions that were associated with advanced diabetes mellitus. On the basis of the age of the patients reported by these authors, it is reasonable to assume that their description applied to patients with type II diabetes mellitus. Over the ensuing decades, a good deal has been learned about the similarities and differences in the biochemical, metabolic, histopathological...
and clinical features of type I and II diabetes mellitus. It has been assumed that the renal lesions encountered in both types of diabetes mellitus were similar or identical. The glomerular lesions, including nodular glomerulosclerosis, diffuse mesangial sclerosis, arteriolar hyalinosis, microaneurysms, and exudative lesions are well described in both type I and type II diabetes mellitus [2–4]. In addition, ultrastructural features such as the characteristic thickening of the glomerular basement membrane and increase in mesangial matrix have been noted in both types.

Detailed studies in animal models, including spontaneously diabetic rats [5] and rats rendered diabetic by the use of the islet of Langerhans beta cell toxin streptozotocin [6–8] have allowed a better understanding of haemodynamic and biochemical events that may account for the morphologic changes seen in the diabetic state. In the streptozotocin model [6–8], the diabetic milieu is associated with significant enlargement of the glomerular capillary tuft, a morphological correlate of the increased renal blood flow and glomerular filtration rate that occurs in these animals. In addition, over time, diabetic animals develop many of the pathological features of diabetic glomerulosclerosis seen in human beings, including capillary microaneurysms, thickening of the glomerular basement membrane, an increase in mesangial matrix, and focal segmental glomerular scarring. However, classic nodular glomerulosclerosis, as originally described by Kimmelstiel and Wilson, is not consistently seen in any of the experimental models and appears to be specific to the human condition.

A variety of lesions not specific to the diabetic state has been observed in patients with nephropathy and type II diabetes mellitus (reviewed in [9]). In most of these studies renal biopsies were performed in diabetic patients because the clinical course or renal presentation was atypical, and there are few studies that have prospectively examined the prevalence of non-diabetic glomerular disease in patients with type II diabetes mellitus (reviewed in [10]). Still, some believe that patients with type II diabetes mellitus, who develop renal dysfunction and proteinuria, have a higher proportion of non-diabetic kidney disease compared to the younger patient with type I diabetes mellitus. This susceptibility to non-diabetic glomerular disease has been attributed to the older age, the increased level of hypertension, and the more complicated medical problems experienced by patients with type II diabetes mellitus [11–17].

We report the results of a prospective clinical and pathological study of patients with type II diabetes mellitus and defined levels of protein excretion, hypertension, and renal function, aimed to determine the character of the glomerular lesions which may be found in this patient population.

Subjects and methods

Patients and study design

Forty-seven patients with type II diabetes mellitus, hypertension, and proteinuria were enrolled in a randomized, double-blind, prospective, multicentre pilot study of the effects of the angiotensin II receptor antagonist, irbesartan, on renal function and urine protein excretion. Males and females over 30 years old were eligible if they had type II diabetes mellitus, a 24-h urine protein excretion ≥ 500 mg/24 h, a serum creatinine ≤ 3.0 mg/dl and either were currently receiving treatment for hypertension or had a diastolic blood pressure of 90–110 mmHg or a systolic blood pressure of 140–185 mmHg. Type II diabetes mellitus was defined by the absence of a history of ketoacidosis and the presence of one of the following conditions: hyperglycaemia requiring treatment with insulin and fasting C-peptide level of > 0.1 pmol/ml that at least doubles 90 min post-mixed meal (e.g. Sustacal), or fasting plasma glucose ≥ 140 mg/dl on two occasions. All patients satisfying these criteria during a single examination were eligible for the study. Patients were excluded if they were less than 20 years old at the onset of their diabetes mellitus, had uncontrolled diabetes mellitus (HbA1c > 10.5%), had lens opacities that precluded visualization of the retina, or had a medical condition that precluded optimal participation in the study (women with childbearing potential, cardiovascular disease, congestive heart failure, arrhythmias, and cerebrovascular disease).

Physical examination and laboratory studies were performed prior to randomization. Severity of retinopathy was determined using retinal fundus photographs of seven standard fields. The maximum grade was assigned accordingly. The grading levels were defined by a modified classification of the Early Treatment of Diabetic Retinopathy Study (Modified Airlie House Classification) [18]: no retinopathy, level 10; non-proliferative (microaneurysms), levels 21–53; and proliferative-levels 60–85. The patients were randomized to two treatment groups and were treated with either irbesartan or amlopidine for 14 weeks. A percutaneous renal biopsy was performed between treatment weeks 12 and 14.

Pathology studies

Renal biopsy was performed on 36 of 47 patients entered into the study. Eleven patients did not consent to be biopsied. The pathology material comprised glass slides stained for haematoxylin and eosin, Masson’s trichrome, periodic acid–Schiff, and methenamine silver periodic acid–Schiff (Jones’ stain), positive immunopathology documented on photomicrographs, and electron micrographs. This material was reviewed in the Central Pathology Laboratory by MMS and EJL. In each case the total number of glomeruli, the number of glomeruli with global sclerosis, the presence of Kimmelstiel–Wilson nodules, capsular droplets, fibrin caps, diagnostic patterns of glomerular immunoglobulin (granular, mesangial, or linear deposits), and fibrin (segmental or global) staining in the glomeruli, and the presence and location of electron-dense deposits were noted. The degree of mesangial expansion and arteriolar hyalinosis were semiquantitated from zero (absent) to 3+ (maximal expansion). The maximum and minimum glomerular diameters were measured from a PAS stain section using a calibrated eyepiece micrometer, and the geometric mean was to be the diameter of each individual glomerulus. The mean glomerular diameter of all the non-hyalinized glomeruli in the section was expressed as the result for each case. Glomerular basal lamina thickness was recorded as normal or thickened based upon the measured value from each laboratory. This result is not quantitated because the measurement was not standardized. Two biopsies had insufficient...
tissue for diagnosis, and the 34 remaining biopsies with adequate tissue were analysed. Tissue for light, fluorescence, and electron microscopy were available in 26 biopsies; four biopsies had light and electron microscopy; four biopsies had light and fluorescence microscopy; and two biopsies had only light microscopy.

Definition of histopathological lesions

The histological diagnosis of diabetic nephropathy was established principally by light microscopy. The Kimmelstiel–Wilson nodule was considered pathognomonic for diabetic glomerular disease in this patient population [3,4]. Kimmelstiel–Wilson nodules comprised segmental, nodular mesangial expansions by acellular, PAS positive material that was often lamellated on the silver stain. On occasion clusters of nuclei were seen around the central acellular area. The mesangial nodules were surrounded by patent glomerular capillaries. In the absence of Kimmelstiel–Wilson nodules, the diagnosis of diabetic renal disease was established by a combination of pathological features including diffuse mesangial expansion by PAS positive material, basement membrane thickening seen by light and electron microscopy, exudative glomerular lesions including fibrin caps and capsular droplets, arteriolar hyalinosis (especially when it involved both the afferent and efferent arterioles), and linear glomerular basement membrane deposits of IgG demonstrated by fluorescence microscopy. Cases with fluorescence or electron microscopic evidence of an immune complex glomerulonephritis were diagnosed separately even if they also had evidence of diabetic glomerulosclerosis.

Statistics

The continuous variables were compared by t test for unpaired data, and the discontinuous variables (sex, race, category of retinopathy, degree of mesangial expansion and arteriolar hyalinosis, and the presence or absence of GBM thickening) were tested for trend by the chi-squared test. A P value ≤0.05 was considered significant.

Results

Pathology results

The pathology results are summarized in Table 1. Seventeen biopsies had diabetic glomerulosclerosis with Kimmelstiel–Wilson nodules (KW). In addition, these biopsies demonstrated other features of diabetic renal disease including arteriolar hyalinosis, capsular droplets, fibrin caps, increased mesangial matrix, and glomerular basement membrane thickening. Fifteen biopsies had glomerular changes characteristic of the diabetic state, including large glomeruli, a variable increase in mesangial matrix, as well as other features associated with diabetes mellitus noted above. However, Kimmelstiel–Wilson nodules were not observed in this latter group (MS). The glomerular diameters in patients with the KW lesion were 206 ± 34 μM (mean ± SD), while those with MS were 198 ± 30 μM (Figures 1 and 2). In all cases of KW and MS the mean glomerular diameter was larger than age-matched non-diabetic controls (153 ± 26 μM) (P = 0.0054). Mesangial expansion and arteriolar hyalinosis were more severe in KW lesions than in MS, and global sclerosis was more frequent in biopsies with the KW lesion (P = 0.045). Glomerular basement membrane thickening tended to occur more frequently in patients with KW than MS, but this did not reach statistical significance.

Non-diabetic glomerular disease was observed in
Ophthalmology results

The results of the ophthalmological examination are summarized in Table 2. Diabetic retinopathy was observed in 23 of the 31 patients with biopsy-proven diabetic renal disease who had an ophthalmological study (75%). One patient with the KW lesion did not have an ophthalmological study. The distribution of patients among the retinopathy categories was different for those with the KW and the MS lesions ($P = 0.0043$). Seven of the eight patients without evidence of diabetic retinopathy had the renal pathological lesion of mesangial sclerosis without Kimmelstiel–Wilson nodules (MS). In contrast, only one patient with the KW form of diabetic glomerulosclerosis did not have retinopathy. Seven of 31 patients with ophthalmological examination had proliferative retinopathy (25%); and of these, six patients had the renal histopathological lesion associated with Kimmelstiel–Wilson nodules (KW). Approximately the same number of patients with KW and MS demonstrated non-proliferative diabetic retinopathy limited to the presence of microaneurysms. Overall, retinal disease, defined by the grading system, was significantly worse in those patients with Kimmelstiel–Wilson nodules in the glomeruli as discerned by a retinopathy level score for patients with Kimmelstiel–Wilson lesions of 48 ± 15 compared to those with mesangial sclerosis who had a mean level of 29 ± 19 ($P = 0.005$). The maximum retinopathy level score was not different in patients who had renal biopsies in this study when compared with all randomized patients.

Clinical pathological correlations

Clinical information is included in Table 3. There was no difference between patients with KW and MS lesions with respect to age, sex, race, known duration of proteinuria, body mass index, systolic blood pressure, diastolic blood pressure, or haemoglobin A1c. With respect to renal function, marked proteinuria was found in both groups. Those with KW lesions had a mean proteinuria of 4815 ± 2718 mg/day (mean ± SD) (range 1124–9625), compared with those with MS who had a mean proteinuria of 4544 ± 1332 mg/day (range 725–18353). The serum creatinine was higher in the KW group ($KW = 1.74 ± 0.54 \text{mg/dl vs MS} = 1.30 ± 0.39, P = 0.01$), and accordingly, the creatinine clearance (MS = 83 ± 34 ml/min, range = 229–165 vs KW = 42 ± 23, range 24–116 ml/min) was lower than in the MS group ($P = 0.004$). Comparison of all the randomized patients with those who underwent renal biopsy showed no significant differences in sex, age, race, time from onset of proteinuria to diagnosis, weight, body mass index, blood pressure

Table 2. Ophthalmology results

<table>
<thead>
<tr>
<th>Retinopathy level</th>
<th>KW</th>
<th>MS</th>
<th>$P$ value</th>
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<tbody>
<tr>
<td>(n)</td>
<td>16</td>
<td>15</td>
<td>—</td>
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<tr>
<td>Retinopathy category</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>None (level 10)</td>
<td>1</td>
<td>7</td>
<td>—</td>
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<tr>
<td>Non-proliferative (level 21–53)</td>
<td>9</td>
<td>7</td>
<td>0.0043</td>
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<tr>
<td>Proliferative (level 60–85)</td>
<td>6</td>
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<td>—</td>
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</table>

$^1$Mean ± SD.

Table 3. Clinicopathological correlations

<table>
<thead>
<tr>
<th>(n)</th>
<th>KW</th>
<th>MS</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proteinuria (mg/day)</td>
<td>4815 ± 2718</td>
<td>4544 ± 1332</td>
<td>NS</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>1.74 ± 0.54</td>
<td>1.30 ± 0.39</td>
<td>0.0132</td>
</tr>
<tr>
<td>Creatinine clearance (ml/min)</td>
<td>50 ± 24</td>
<td>84 ± 37</td>
<td>0.0041</td>
</tr>
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<td>HBA1c</td>
<td>8.72 ± 1.26</td>
<td>8.43 ± 1.25</td>
<td>NS</td>
</tr>
<tr>
<td>Age (years)</td>
<td>57 ± 6</td>
<td>59 ± 11</td>
<td>NS</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>10/7</td>
<td>12/3</td>
<td>NS</td>
</tr>
<tr>
<td>Race (White/Black)</td>
<td>12/4</td>
<td>7/7</td>
<td>NS</td>
</tr>
<tr>
<td>Diagnosis to biopsy (years)</td>
<td>17 ± 9</td>
<td>14 ± 12</td>
<td>NS</td>
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<tr>
<td>Weight (kg)</td>
<td>87 ± 23</td>
<td>103 ± 19</td>
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<tr>
<td>Body mass index</td>
<td>31 ± 8</td>
<td>34 ± 7</td>
<td>NS</td>
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<tr>
<td>Systolic blood pressure (mm/Hg)</td>
<td>158 ± 10</td>
<td>159 ± 15</td>
<td>NS</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>89 ± 6</td>
<td>83 ± 11</td>
<td>NS</td>
</tr>
</tbody>
</table>

$^1$Mean ± SD; ^2NS, not significant.
(systolic and diastolic), serum creatinine, 24-h protein excretion, creatinine clearance, and haemoglobin-A\textsubscript{1c} (data not shown).

### Discussion

We describe two distinct patterns of glomerular pathology in patients with type II diabetes mellitus and nephropathy. In one instance the classic glomerular lesion of nodular glomerulosclerosis (Kimmelstiel–Wilson) is prominent (KW), while in the other, one observes mesangial sclerosis without nodular changes (MS). The latter pattern of glomerular pathology includes the diffuse form of diabetic glomerular sclerosis [2], and the existence of this lesion may explain why so many similar patients with type II diabetes mellitus are reported to have a non-diabetic form of glomerular disease. Our conclusion that the MS lesion is morphologically distinct and, by implication, has a different pathogenesis from the KW lesion is open to alternative interpretations of the data. For example, the MS lesion may be an earlier form of diabetic glomerulosclerosis that evolves over time into the KW lesion. We think this pathogenetic sequence is unlikely because the MS and KW patients are similar in terms of the known duration of clinical disease, the degree of diabetic control, and the magnitude of hyperglycaemia. In addition, both groups of patients have extensive pathological changes in their kidneys. While the patients in our series who had the KW lesion had more advanced pathology, those with the MS lesion also demonstrated prominent abnormalities. Hence, in the KW and MS groups, glomerular hypertrophy was equal. In addition, a large proportion of the glomeruli associated with both lesions were obsolescent (global sclerosis).

The diagnostic specificity of the MS lesion may also be challenged statistically. The absence of KW lesions (a focal segmental form of glomerular pathology) from the MS biopsies may result from the sample being too small to include an involved glomerulus. However, the KW and the MS biopsies contained an equal number of glomeruli (KW = 18.5 ± 14 (mean ± SD) vs MS = 18.1 ± 13). With this number of glomeruli it can be demonstrated from the binomial equation that there is only a 10% chance of missing a lesion that is present in 10% of the glomeruli [19]. Thus, there is a finite possibility of not sampling a KW lesion in a biopsy of this size, but this possibility is shared equally by patients with MS and KW lesions.

In the absence of KW nodules it is legitimate to ask why the pathology was not interpreted as some form of primary glomerular disease superimposed upon the diabetic kidney. This question is most acute in the six MS patients in this series who had only mild mesangial expansion (Table 1). Four of the six patients had negative linear staining of the GBM by fluorescence microscopy and/or basal lamina of apparently normal thickness by electron microscopy, but urinary protein excretion was <1.0 g/day in three, and one of three patients with \( \geq 3.0 \) g/day proteinuria had thick basal lamina and linear staining of the GBM for IgG, changes that are characteristic of diabetic glomerular disease. Because immune complex disease was excluded by fluorescence and/or electron microscopy in all but two patients in the entire series, the differential diagnosis is practically limited to minimal-change disease and focal segmental glomerulosclerosis, but only one of five patients had diffuse foot process effacement by electron microscopy. The well documented presence of type II diabetes mellitus, marked glomerular hypertrophy and the presence of other features of diabetic glomerulopathy in patients with the MS lesion support the interpretation that they are diabetics with proteinuria rather than idiopathic nephrotic syndrome, and when the patients are examined critically, they do not fit the clinical or morphological criteria for minimal-change disease, primary focal segmental glomerulosclerosis, or any other primary form of glomerular disease. The alternative interpretations of our data are valid, and they may in fact exclude some of the MS cases. However, the central question raised by this study remains unanswered. Why do so many typical type II diabetic patients, undistinguished clinically from KW patients, fail to develop the pathognomonic renal morphological finding of this disease, the Kimmelstiel–Wilson nodule?

We also found that the classic renal–retinal syndrome of proliferative retinopathy is associated with the KW form of glomerulopathy. Patients with the MS lesion more frequently have no evidence of diabetic retinopathy or only have retinal microaneurysms. The often described lack of correlation between retinal and renal disease described in patients with type II diabetes mellitus [9,14,20,21] appears to derive from this latter renal histopathological category. Clinically, there was little difference between the KW and MS groups with respect to age, hypertension, BMI and diabetes control as reflected by haemoglobin A\textsubscript{1c} levels. Marked proteinuria was associated with both lesions. Although those with KW had lost a larger proportion of their renal function, there was a significant overlap, which demonstrates that in the absence of a kidney biopsy, it would be difficult to predict the renal lesion.

Our renal histology findings accord with those of Gambara et al. [16] and Olsen and Mogensen [9], who showed that similar proportions of their patients with type II diabetes had non-nodular glomerular sclerosis. While many of the features of diabetic glomerulopathy, including large glomeruli, were noted in patients with non-nodular lesions in the former study [16], the recognition of this pattern as a discrete lesion in type II diabetic nephropathy was not reported. With respect to the lack of correlation between retinal and glomerular pathology seen in patients with the MS lesion, Olsen and Mogensen [9] have also reported that patients with non-nodular diabetic glomerulosclerosis frequently have no evidence of proliferative retinopathy. Hence, the two distinct glomerular lesions appear to be reflected in the retinal findings in these patients.

Also noteworthy in the findings of this prospective
study was the fact that glomerular lesions other than those associated with diabetes were found in only two patients. We therefore are unable to confirm those reports which found a larger proportion of patients with type II diabetes mellitus to have non-diabetic glomerular disease. We conclude that nephropathy in the patient with type II diabetes mellitus is associated with two distinctive patterns of glomerular pathology. It is therefore implied that the complex pathogenetic mechanisms presumed to be associated with the development of glomerulopathy in the diabetic state differ in patients with these two forms of diabetic glomerulosclerosis in some way. The correlation of retinal and glomerular pathologies further suggests a distinctive pathophysiological processes in KW as compared to MS. That both lesions are associated with marked glomerular enlargement suggests that similar renal growth and haemodynamic alterations characteristic of the diabetic milieu may be operating in both cases. In this prospective evaluation, we were unable to confirm the report of other authors that non-diabetic glomerular pathology occurs frequently in this patient population.

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References


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