Distinguishing Features in Comparing Diabetic Nephropathy with or without Concurrent Non-Diabetic Renal Disease

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Abstract

BACKGROUND: Despite diabetic nephropathy (DN) being the leading cause of end stage renal disease, the incidence and characteristics of non-diabetic renal disease (NDRD) in patients with DN remains unknown. The present study examined the prevalence of NDRD in diabetic patients with kidney involvement and identified differential features between DN with or without coexisting NDRD by comparing clinical manifestations and histopathologic findings.

METHODS: We retrospectively reviewed 49 patients that were diagnosed with diabetic nephropathy by renal biopsy. Both the clinical and pathological features were reviewed and recorded. We then compared these patients between with or without coexisting NDRD.

RESULTS: In our study, 23 patients (47%) were male and their mean age at the time of biopsy was 53.9 ± 13.2 years. Thirty-seven patients (76%) had typical histological features of DN and 12 patients (24%) had coexisting glomerulopathy. Focal segmental glomerulosclerosis (FSGS) was the most common concurrent NDRD. Both groups had a similar diabetes duration, renal function, and nephrotic range proteinuria. The kidney size of DN was significantly larger than that of with concurrent NDRD. Diabetic retinopathy was more common in the DN group (69% vs. 30%, P < 0.05). Histological examination revealed the Kimmelstiel-Wilson nodule was more frequently observed in DN (56.8% vs. 8.3%, P < 0.01).

CONCLUSION: The prevalence of NDRD in diabetic patients is not uncommon. Compared to those with concurrent NDRD, patients with DN had a higher prevalence of diabetic retinopathy and their kidney size was significantly larger. Further, Kimmestiel-Wilson nodule was more commonly observed in the renal tissue of patients with DN. (Acta Nephrologica 2011; 25: 119-124)

KEY WORDS: diabetic nephropathy, Kimmelstiel-Wilson nodule, glomerulonephritis

Introduction

Diabetic nephropathy (DN) is the leading cause of end stage renal disease (ESRD) (1). The prevalence of DN is increasing due to an actual increase in the prevalence of diabetes, increasing age of the diabetes population, and a better survival rates for patients with diabetes, thus allowing more time for diabetic nephropathy to develop (2, 3). Both early identification and prevention from DN to progress to ESRD are important issues of diabetes care.

However, patients with diabetes are still susceptible to non-diabetic renal disease (NDRD). It has been indicated diabetic patients with severe proteinuria should be suspected of also having NDRD, especially when the diabetes duration is short or without co-
existing retinopathy (4-6). Early recognition and proper diagnosis of the NDRD is important because appropriate treatment can be initiated to prevent deterioration of renal function and improve the outcome. The prevalence of NDRD in diabetes greatly varies (6-9). Several clinical predictors, such as short diabetes duration, presence of microscopic hematuria, absence of diabetic retinopathy and severe proteinuria have been specified (5, 9). Nevertheless, study results are not universal, probably due to selection bias and lack of complete clinical course.

Although previous studies have demonstrated clinical features that can be identified to discriminate glomerulopathy in diabetes, details of the pathological features have rarely been described. Whether the co-existing NDRD can influence histological features of DN is largely unknown. The present study examined the prevalence of NDRD in diabetic patients with pathologically diagnosed renal involvement. In addition to demographic data, the result of laboratory tests, incidence of retinopathy, kidney size and histological features were all compared between DN with or without concurrent NDRD.

Methods

Patients

Out of a chart review of 2364 renal biopsies from 1986 to 2008 in our hospital, we found 57 type 2 diabetic patients underwent renal biopsy with the diagnosis of diabetic nephropathy. After eight cases were excluded due to incomplete chart record, 49 patients were available for further analysis. Type 2 diabetes mellitus was diagnosed by the definition of World Health Organization (10). Indications for renal biopsy in type 2 diabetes patients included proteinuria or renal impairment in the absence of retinopathy, heavy proteinuria, unexplained hematuria of glomerular origin, and rapid renal function deterioration of an uncertain cause. Based on the results of renal biopsies, patients were divided into two groups according to the presence of NDRD or not. Their demographic data including age, gender, body mass index, duration of diabetes, usage of angiotensin converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB), diabetic retinopathy, renal size measured by renal sonographic examination were reviewed and recorded. Laboratory data including serum blood urea nitrogen (BUN), creatinine, estimated glomerular filtration rate (eGFR), albumin, uric acid, total cholesterol were collected. The results of serology study such as the levels of immunoglobulin A (IgA), IgG, IgE, IgM, complement 3 (C3), C4 were reviewed. Daily urinary protein loss was collected during their hospitalization for kidney biopsy. The duration of diabetes was defined as the period between the age onset of diabetes and the time of kidney biopsy. Renal size was determined by renal ultrasonography prior to kidney biopsy. Diabetic retinopathy was diagnosed on fundoscopy examination by ophthalmologists with pupils adequately dilated. Renal function presented by eGFR was calculated by the MDRD formula \[\text{eGFR} = 180 \times \frac{\text{creatinine}}{\text{age}^{-0.203} \times \text{weight}^{-0.583} \times \text{BMI}^{-0.12} \times \text{race}}\] (female) (11). Microscopic hematuria was defined as more than 5 red blood cells (RBC) in microscopy examination under a high power field.

Histological Assessment of Kidney Biopsy

We briefly described the findings of glomerulus, tubule, interstitium, and some miscellaneous characters of diabetic nephropathy, such as Kimmelstiel-Wilson (K-W) nodule, capsular drop, and hyaline cap. The sclerotic ratio was defined as the number of sclerotic glomeruli divided by the number of observed glomeruli. The degree of glomerular cellular proliferation, glomerular mesangial matrix increase, tubular vacuolization, tubular atrophy, interstitial fibrosis, and interstitial inflammation were semiquantitated from zero (absent), 1+ (mild, focal or occasional), 2+ (moderate) to 3+ (severe or marked). The degree of glomerular size exaggeration, tubular necrosis, and arteriolar wall thickening were semiquantitated from zero (absent), 1+ (focal or occasional) to 2+ (moderate to marked). The K-W nodule, which is characterized by segmental, nodular mesangial expansions with palisading mesangial nuclei around the nodule and compression of glomerular capillaries, was specifically identified in each patient (12). Another lesion, the capsular drop and hyaline cap, which is defined as exudative glomerular lesions along the parietal surface of Bowman’s capsule and in the glomerular capillary subendothelial space, was also examined (13).

Statistics

Statistical analysis was performed using SPSS version 17.1 for Windows. A Chi-Square test or Fisher’s exact test was used to assess the comparison between or among the categorical data. For continuous variables, independent t-test and Mann-Whitney test were utilized to compare group difference depending on the distribution of studied variables. A P value < 0.05 was considered statistically significant.

Results

According to the result of histopathological examination, isolated DN was found in 37 (76%) patients and the rest (24%) had combined NDRD. In patients with concurrent NDRD, five had the diagnosis of
focal segmental glomerulosclerosis, four of membranous glomerulonephritis, and three of membranoproliferative glomerulonephritis (Table 1).

Table 2 presents the demographic and laboratory data of our study population. Their age and duration of diabetes were similar between the two groups. The proportion of patients under the treatment with either ACEi or ARB for diabetic kidney disease was also similar between two groups. The prevalence of diabetic retinopathy was two-fold higher in patients with isolated DN. Since the prevalence of retinopathy was much lower in patients with concurrent NDRD, the relationship between DN and diabetic retinopathy was further analyzed. We found identification of retinopathy was a good predictor of DN (sensitivity 68%, specificity 88%), while absence of retinopathy was a poor predictor of NDRD (sensitivity 70%, specificity 41%). The renal size, which was determined by sonography performed prior to kidney biopsy, was significantly smaller in patients with concurrent NDRD either in the left or right kidney. Laboratory tests showed patients enrolled in our study had comparable renal function. There was no significant difference in BUN and creatinine levels. The calculated eGFR of both groups belonged to chronic kidney stage 4. Both groups had hypoalbuminemia with hypercholesterolemia. The hemoglobin A1C was lower in patients with concurrent NDRD, but this difference did not reach statistical significance. Although statistically non-significant, the incidence of hematuria was lower in patients with NDRD. The amount of urine daily protein loss did not differ between the two groups. The results of the serology study were as follows: IgA (DN: 288.9 ± 83.4 mg/dL,
DN with NDRD: 298.5 ± 83.4 mg/dL, IgG (902.8 ± 327.0 mg/dL vs. 819.3 ± 272.3 mg/dL), IgE (288.4 ± 119.8 mg/dL vs. 211.8 ± 178.0 mg/dL), IgM (159.3 ± 129.8 mg/dL vs. 103.6 ± 42.7 mg/dL), C3 (115.9 ± 36.5 mg/dL vs. 119.8 ± 24.1 mg/dL), and C4 (33.6 ± 19.2 mg/dL vs. 31.1 ± 9.1 mg/dL). All these results were within normal limits, and there was a significant difference between the two groups.

Discussion

For most patients with diabetes, documentation of renal involvement is usually made on the basis of clinical features. Glomerulopathy in diabetes may include typical DN, and occasionally coexisting glomerulonephritis or less commonly non-diabetic glomerulopathy alone. A kidney biopsy is the only tool to make a correct diagnosis. Previous studies have compared these entities and tried to find reliable predictors (5-7). Our study included DN patients with or without NDRD. In these diabetics with heavy proteinuria, we found about one quarter of patients with DN had concurrent NDRD. Patients with concurrent NDRD had less retinopathy. Their kidney size was smaller than those with isolated DN. We also noted the hallmark of DN, such as a K-W nodule, developed more frequently in patients with isolated DN.

Even though a diagnostic model has been proposed for accurate diagnosis of DN (9), the exact mechanism responsible for the development of NDRD in diabetes remains unknown. On average, our patients had a history of diabetes of more than 10 years, and both groups showed heavy proteinuria and significant renal impairment. Their eGFR was below 30 mL/min, which is classified as chronic kidney disease stage 4. Although their clinical manifestations varied, both groups showed heavy proteinuria and significant renal impairment. Their eGFR was below 30 mL/min, which is classified as chronic kidney disease stage 4. Although their clinical manifestations varied, both groups showed heavy proteinuria and significant renal impairment. Their eGFR was below 30 mL/min, which is classified as chronic kidney disease stage 4. Although their clinical manifestations varied, both groups showed heavy proteinuria and significant renal impairment. Their eGFR was below 30 mL/min, which is classified as chronic kidney disease stage 4. Although their clinical manifestations varied, both groups showed heavy proteinuria and significant renal impairment. Their eGFR was below 30 mL/min, which is classified as chronic kidney disease stage 4. Although their clinical manifestations varied, both groups showed heavy proteinuria and significant renal impairment. Their eGFR was below 30 mL/min, which is classified as chronic kidney disease stage 4. Although their clinical manifestations varied, both groups showed heavy proteinuria and significant renal impairment. Their eGFR was below 30 mL/min, which is classified as chronic kidney disease stage 4. Although their clinical manifestations varied, both groups showed heavy proteinuria and significant renal impairment. Their eGFR was below 30 mL/min, which is classified as chronic kidney disease stage 4. Although their clinical manifestations varied, both groups showed heavy proteinuria and significant renal impairment. Their eGFR was below 30 mL/min, which is classified as chronic kidney disease stage 4. Although their clinical manifestations varied, both groups showed heavy proteinuria and significant renal impairment.

Table 3. Histopathological features of isolated DN and DN with concurrent NDRD (means ± SD)

<table>
<thead>
<tr>
<th>Feature</th>
<th>DN</th>
<th>DN with NDRD</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sclerotic ratioa</td>
<td>0.32 ± 0.32</td>
<td>0.3 ± 0.23</td>
<td>0.86</td>
</tr>
<tr>
<td>Glomerular cellular proliferationb</td>
<td>1.3 ± 0.8</td>
<td>1.3 ± 0.7</td>
<td>0.93</td>
</tr>
<tr>
<td>Glomerular mesangial matrix increaseb</td>
<td>2.1 ± 0.6</td>
<td>2.0 ± 0.6</td>
<td>0.67</td>
</tr>
<tr>
<td>Glomerular size exaggeration (lobular architecture)b</td>
<td>1.6 ± 0.8</td>
<td>1.7 ± 0.8</td>
<td>0.67</td>
</tr>
<tr>
<td>Tubular vacuolizationb</td>
<td>1.6 ± 0.6</td>
<td>1.3 ± 0.8</td>
<td>0.24</td>
</tr>
<tr>
<td>Tubular necrosisb</td>
<td>1.5 ± 0.6</td>
<td>1.8 ± 0.4</td>
<td>0.51</td>
</tr>
<tr>
<td>Tubular atrophyb</td>
<td>2.1 ± 0.9</td>
<td>1.9 ± 1.2</td>
<td>0.84</td>
</tr>
<tr>
<td>Interstitial fibrosisb</td>
<td>1.5 ± 0.9</td>
<td>1.3 ± 0.9</td>
<td>0.37</td>
</tr>
<tr>
<td>Interstitial inflammationb</td>
<td>1.3 ± 0.9</td>
<td>1.0 ± 0.7</td>
<td>0.38</td>
</tr>
<tr>
<td>Arteriolar wall thickeningc</td>
<td>1.3 ± 0.9</td>
<td>0.7 ± 0.9</td>
<td>0.05</td>
</tr>
<tr>
<td>Presence of K-W nodule</td>
<td>56.8%</td>
<td>8.3%</td>
<td>0.006*</td>
</tr>
<tr>
<td>Presence of capsular drop</td>
<td>16.2%</td>
<td>0%</td>
<td>0.136</td>
</tr>
<tr>
<td>Presence of hyaline cap</td>
<td>54.1%</td>
<td>25%</td>
<td>0.104</td>
</tr>
<tr>
<td>Presence of foamy cell</td>
<td>13.8%</td>
<td>10%</td>
<td>0.75</td>
</tr>
</tbody>
</table>

a. Sclerotic ratio = number of sclerotic glomeruli/number of observed glomeruli.
b. Histological Grading as 0-not present, 1-mild, focal or occasional present, 2-moderate present, 3-severe, marked present.
c. Histological Grading as 0-not present, 1-slightly or occasionally present, 2-present.
some retinopathy after 20 years (15). About 60% of our patients had concurrent retinopathy, which is comparable to another study (9). Diabetic retinopathy has long been considered an indicator of diabetic nephropathy (16). It is thus reasonable to accept the absence of retinopathy as a good predictor of NDRD (4-6). In patients with concurrent NDRD, we found the incidence of retinopathy was less than half of that in patients with isolated DN. A similar finding was described in a previous study (17). The reason patients with concurrent NDRD had less retinopathy is unclear. Because the diabetes duration was similar, factors other than the natural course of the disease are speculated.

The kidney size in the early stage of DN was reported to be larger than normal due to glomerular hypertrophy, which is responsible for the pathophysiology of early DN (18). In contrast to chronic glomerulonephritis, kidney size is usually maintained in DN, even progressing to terminal failure. The kidney size in DN with concurrent NDRD has never been studied previously. We found kidney size in patients with concurrent NDRD was smaller than isolated DN. Because their renal function was comparable, we speculate with the coexisting NDRD, it may limit or diminish the progressive pathological alteration in DN, thus the kidney size was reduced. A previous study also demonstrated, compared with isolated NDRD, DN had greater kidney volume (9). One recent study showed a large kidney was associated with poor outcome in diabetic patients with advanced CKD stage (19). Although no definite pathological diagnosis was provided, this finding indicated a grave prognosis in advanced diabetic glomerulopathy.

The histopathologic features of diabetic glomerulopathy have been studied and documented over decades. Nodular glomerulosclerosis (alternatively named Kimmelstiel-Wilson nodule), was first described by Paul Kimmelstiel and Clifford Wilson (20). The nodular is considered a distinct entity highly specific for diabetic glomerulopathy, and identified as a specific class of DN (21). This pathological hallmark was convinced to be a transition from an early to a progressive and advanced lesion of the disease (22). We found there a striking difference in its distribution between two groups. The K-W nodule was observed in more than half of patients with DN accompanied by other pathological alterations. Previous studies indicated the presence of the K-W nodule was associated with longer diabetes duration and poor renal outcome. Since the duration of diabetes was similar and renal function was comparable between the two groups, the reason explaining the marked difference between DN with or without coexisting NDRD is unclear in our study. The concurrent glomerulopathy may change or modulate the progressive course of kidney pathology in diabetes. Patients with K-W nodule were found to correlate with retinopathy (22, 23). It has been suggested both K-W nodule and diabetic retinopathy may have similar pathogenic mechanism (24). Although our study did not provide direct evidence, both retinopathy and K-W nodule were more prevalent in DN. The capsular drops and hyaline caps are also important pathological features of DN, which are frequently examined (21). These lesions were less frequently observed in patients with concurrent NDRD in our study cohort. Our study also demonstrated a marginal difference in vascular change, such as arterial wall thickening between two groups. Although a vascular lesion may also reflect a pathological change in systemic vasculature, pathological changes of either efferent or afferent arterioles in renal tissue is one of the pathological lesions observed in DN (21).

The renal outcome in patients with concurrent NDRD has been reported to be comparable, regardless of whether there is concurrent NDRD (25). With the pathological diagnosis, patients can thus be treated timely and appropriately. However, various factors can influence the renal prognosis. Time interval from disease onset to kidney biopsy may limit the treatment duration. The control rate of risk factors for disease progression and treatment response of NDRD are all determining factors of renal outcome. Because not all our patients have a complete follow-up record, our study did not provide a long-term prognosis.

In conclusion, concurrent NDRD in patients with DN is not uncommon. Comparing with or without concurrent NDRD, these patients had similar clinical features with heavy proteinuria and reduced renal function. Diabetic retinopathy was less in patients with concurrent NDRD. For patients with isolated DN, their kidney size was larger, and a K-W nodule was more frequently observed. These patients also tended to have more severe vascular lesions.

References

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