GLOMERULAR LESIONS IN DIABETIC PATIENTS

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Summary

Diabetic nephropathy represents a major microangiopathic complication of diabetes mellitus. Its features are represented by: proteinuria, arterial hypertension and renal function decrease. But proteinuria in diabetic patients may represent non-diabetic renal disease, superimposed or not on diabetic renal lesions. The present study describes the glomerular lesions in diabetic patients with proteinuria. The study was performed on a group of 40 patients with diabetes mellitus and proteinuria. Retinoscopy, monitoring of blood pressure, proteinuria, hematuria, creatinine clearance, serum creatinine were performed in all patients. Renal biopsies were done with Tru-Cut system, using hematoxylin-eosin and periodic acid Schiff (PAS) staining. All the values were presented as mean ± standard deviation. The statistically analysis was done using Student’s t-test, p < 0.05 was considered statistically significant. The group of patients consisted of 25 males and 15 females, with the mean age of 44.37 ± 7.72 years. Among them, 11 patients had type 1 diabetes mellitus and 29 patients had type 2 diabetes mellitus. Histological exam showed: pure diabetic nephropathy in 24 patients (60%), and primary glomerulonephritis in 16 patients (40%). Diabetic retinopathy was found in 28 patients (70%). The values of proteinuria, creatinine clearance, serum creatinine, blood pressure did not show significant differences between the patients with pure diabetic nephropathy and primary glomerulonephritis (p > 0.05). The value of hematuria with dysmorphic cells was significant higher in patients with primary glomerulonephritis (p < 0.001). Proteinuria in diabetic patient may represent diabetic nephropathy, or primary glomerulonephritis, requiring further investigations, including renal biopsy.

Key words: diabetic nephropathy, primary glomerulonephritis, proteinuria

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Introduction

Diabetic nephropathy (DN) is the major microangiopathic complication of diabetes mellitus (DM), representing the main cause of end-stage renal disease (Gross et al, 2005). It is considered as a progressive glomerular disease, predominantly inflammatory, which evolves in diabetic milieu. The main features of DN are represented by proteinuria, arterial hypertension and progressive decrease of the renal function (Hasslacher, 2001). The appearance of proteinuria in diabetic patients may be the consequence of diabetic nephropathy, or non-diabetic renal diseases, super-imposed or not on diabetic glomerular lesions (Jalalah 2008).

In order to initiate the adequate therapy, it is very important to establish the etiology of proteinuria in these patients. Renal biopsies and histological exams are not routinely performed in diabetic patients. These procedures are performed only in special situations: the absence of diabetic retinopathy, short duration of diabetes (< 10 years), sudden onset of proteinuria, rapid deterioration of renal function, and presence of hematuria and/or red cell casts (Soni et al, 2006; Ghanni et al, 2009). The morphoclinical studies showed that precocious appearance of proteinuria in type 1 DM is probably due to non-diabetic nephropathies. In contrast, appearance of proteinuria after a period of DM evolution...
over 20 years is due to DN in almost cases (Hasslacher, 2001; Ghanni et al, 2009). The gold standard for the differential diagnosis of proteinuria in diabetic patients is renal biopsy and histological exams.

**Material and methods**

The study was performed on a group of 40 patients with diabetes mellitus and proteinuria.

Proteinuria, urinary sediment (using Addis-Hamburger method), urinary cultures, creatinine clearance, serum creatinine, imaging renal tests, retinoscopy, monitoring of blood pressure, and renal biopsy were done in all cases.

Proteinuria was determined in conditions of good metabolic control, absence of urinary tract infections, acute febrile illness, uncontrolled hypertension, and heart failure, using Biuret test.

The clearance of endogenous creatinine (Cl) was calculated using the formula:

\[
Cl = \frac{U \times V}{P},
\]

\((U = \text{urinary creatinine}, \ P = \text{plasmatic creatinine}, \ V = \text{urinary volume})\).

The creatinine values were obtained using Jaffe method.

Imaging renal tests consisted of renal ultrasonography, combined with Duplex Doppler of renal arteries and veins, with ALOKA ProSound 4000 device.

Renal biopsies were done with Tru-Cut system, using hematoxylin-eosin and periodic acid Schiff (PAS) staining.

All the values were presented as mean ± standard deviation. The statistically analysis was done using Student’s t-test, \(p < 0.05\) was considered statistically significant.

**Results**

The group of studied patients was formed by 25 males (62.5%) and 15 females (37.5%), with the mean age of 44.37 ± 7.72 years. The mean length of DM evolution was 13.71 ± 8.22 years. Among them, 11 patients had type 1 DM (27.5%) and 29 patients had type 2 DM (72.5%).

The values of monitored parameters are presented in table I.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Diabetic nephropathy</th>
<th>Primary glomerulonephritis</th>
<th>(p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>24</td>
<td>16</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>42.66 ± 12.88</td>
<td>45.18 ± 6.25</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Mean length of DM evolution (years)</td>
<td>15.28 ± 7.14</td>
<td>5.62 ± 1.25</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Diabetic retinopathy (number of patients)</td>
<td>24</td>
<td>4</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Proteinuria (g/24 hours)</td>
<td>2.42 ± 1.18</td>
<td>2.02 ± 0.96</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Hematuria (red cells/min)</td>
<td>968 ± 121</td>
<td>16720 ± 12521 (dysmorphic red cells) (fig. 1)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td>1.61 ± 1.09</td>
<td>2.11 ± 1.18</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Creatinine clearance (ml/min)</td>
<td>66.25 ± 24.92</td>
<td>48.12 ± 31.05</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Blood pressure (mmHg)</td>
<td>143.76 ± 25.91/</td>
<td>141.95 ± 18.99/</td>
<td>&gt; 0.05</td>
</tr>
</tbody>
</table>
Renal imaging tests showed normal aspects of the kidneys and renal vessels. The results of histological exams are presented in table II and figures 2, 3, 4, 5.

**Table II** Results of histological exams

<table>
<thead>
<tr>
<th>Diagnosis and Condition</th>
<th>Details</th>
</tr>
</thead>
</table>
| Pure diabetic nephropathy (24 patients) | • diffuse diabetic glomerular lesions (14 patients)  
• nodular diabetic glomerular lesions associated with diffuse glomerular lesions (10 patients) |
| Primary glomerulonephritis (12 patients) | • membranous glomerulopathy (4 patients)  
• IgA nephropathy (4 patients)  
• crescentic glomerulonephritis (4 patients) |
| Primary glomerulonephritis superimposed on diabetic glomerular lesions (4 patients) | • membranous glomerulopathy (1 patient)  
• IgA nephropathy (1 patient)  
• crescentic glomerulonephritis (2 patients) |

**Fig. 1** Dismorphic red cell

**Fig. 2** Diabetic nephropathy
Fig. 3 Crescentic glomerulonephritis superimposed on diabetic nephropathy

Fig. 4 Membranous glomerulopathy

Fig. 5 IgA nephropathy
Discussion

Proteinuria is the most common marker of renal diseases, but this sign can’t diagnose the nature of kidney lesion (Hricik et al, 2003).

DN represents the major microangiopathic complication of DM. This complication appears both in type 1 and type 2 DM. About 20-40% of diabetic patients develop diabetic renal disease (Kikkawa et al, 2003). DN is characterized by persistent proteinuria, arterial hypertension and a progressive decline of the renal function (Gross et al, 2005; Hasslacher, 2001). Beside DN, the patients with DM are liable to develop renal artery stenosis, ischemic nephropathy (macroangiopathic renal complications), chronic pyelonephritis (infectious diabetic complication). Non-diabetic renal diseases, either alone or superimposed on renal diabetic lesions may also appear in diabetic patients. Proteinuria is found in all of these diseases (Levey et al, 2003; Pham et al, 2007).

Proteinuria in long-term type 1 diabetic patients (> 15 years of DM duration) signifies DN, especially if diabetic retinopathy is present. In type 2 DM, the uncertainty of DN diagnosis exists, because of the real onset of diabetes is unknown and diabetic retinopathy is absent in 28% of these patients (Christensen et al, 2001).

Generally, proteinuria is due to DN, when are present: diabetic retinopathy, history of glomerular hyperfiltration and microalbuminuria, no evidence of other renal/extrarenal disorders. Proteinuria is caused by other nephropathies, when are present: hematuria, suddenly appearance of proteinuria, especially heavy (nephrotic syndrome), without any history of glomerular hyperfiltration or microalbuminuria, abnormalities of renal imaging tests (dilated urinary tract, asymmetrical kidney volume), evidence of other diseases with secondary renal involvement (amyloidosis, viral hepatitis, systemic vasculitis, systemic lupus erythematosus) (Hasslacher, 2001).

Differential diagnosis of proteinuria in diabetics is usually based on the medical history, physical examination, laboratory evaluation, and imaging renal tests. The absence of diabetic retinopathy is a useful finding for the differential diagnosis, but it is not the best criterion (Hricik et al, 2003). Only the renal biopsy and the histological exams (in light microscopy, immunofluorescence, even in electronic microscopy) establish the etiology of proteinuria in diabetic patients (Gross et al, 2005; Ghanni et al, 2009).

In the present study, all the patients presented proteinuria and/or rapid decline of renal function at the time of renal biopsy. Histological exams revealed: pure diabetic nephropathy (24 patients), primary glomerulonephritis (12 patients), primary glomerulonephritis superimposed on diabetic glomerular lesions (4 patients).

The mean length of DM evolution was longer in patients with diabetic nephropathy (p < 0,001). Hematuria with dysmorphic red cells was present in patients with primary glomerulonephritis (p < 0,001). Diabetic retinopathy was identified only in patients with diabetic glomerular lesions (p < 0,001).

In patients with pure diabetic nephropathy were described: diffuse diabetic glomerular lesions (14 patients) and nodular diabetic glomerular lesions associated with diffuse glomerular lesions (10 patients). Primary glomerulonephritis, representing 40% of diabetic studied patients with proteinuria, were classified as: crescentic glomerulonephritis (6 patients), membranous glomerulopathy (5 patients), IgA nephropathy (5 patients). The frequency of non-diabetic renal disease is reported at widely variable range 33-45,8% of the total renal biopsies of the diabetic patients (Castellano et al, 2002; Huang et al, 2007; Bergner et al, 2006; Wong et al, 2002).

In diabetics, may appear: membranous glomerulopathy, crescentic glomerulo-
nephritis, minimal change disease, IgA nephropathy, focal segmental glomerulonephritis, membrano-proliferative glomerulonephritis. The pathogenesis of non-diabetic renal disease in diabetic patients is not well known. Pre-existing glomerular alterations might initiate an immune reaction in glomerular structures. Gans et al. suggested that the coexistence of IgA nephropathy in diabetic patients may share a common pathogenesis (Soni et al, 2006, Gans et al, 1992).

In diabetic patients with proteinuria, only renal biopsy and histological exams may establish the correct diagnosis of renal disease. The indications of renal biopsy in proteinuric diabetic patients are represented by: presence of glomerular hematuria and/or red cell casts, absence of diabetic retinopathy (especially in type 1 DM), suddenly appearance of proteinuria, with no history of microalbuminuria or glomerular hyperfiltration, renal involvement with a short duration of diabetes (< 5 years), rapid loss of renal function (days or weeks). It is very important to have a correct diagnosis, because non-diabetic nephropathies (especially primary glomerulonephritis) have specific treatment, different from the DN therapy (Hasslacher, 2001, Ghanni et al, 2009). Even in diabetics, renal biopsy is a safe procedure. In the studied group of patients, renal biopsies were not followed by any incidents.

**Conclusion**

Appearance of proteinuria in diabetic patients is not equivalent with DN, requiring further investigation, including renal biopsy and histological exams. Primary glomerulonephritis may appear in diabetic proteinuric patients either alone, or superimposed on diabetic glomerular lesions.

**References**


