THE DIABETIC PATIENT WITH RENAL INSUFFICIENCY

Ph. VANHILLE

SUMMARY - Diabetic mellitus is often complicated by nephropathy with progression to renal failure. Most patients with clinical diabetes who present with renal insufficiency have diabetic glomerulosclerosis, although some (particularly in Type 2 diabetes) present with other glomerular diseases. The purpose of this study was to provide practical recommendations for the management of patients with diabetes and renal failure and evaluate the prevalence of non-diabetic glomerulopathies in Type 2 diabetic patients. Various forms of glomerulonephritis have been associated with diabetes, occasionally leading to alternative management of these patients in attempts to reverse or contain renal failure.

Key-words: diabetes mellitus, renal insufficiency, non-diabetic glomerulopathies.

RÉSUMÉ - Le diabétique insuffisant rénal.
Le diabète se complique fréquemment d’une néphropathie dont la progression vers l’insuffisance rénale est inexorable. Dans la plupart des cas, l’insuffisance rénale des diabétiques est liée à une glomérorosclérose. Néanmoins, d’autres néphropathies gloméruaires peuvent être observées, notamment au cours du diabète de type 2. Les buts de cet article sont 1) de proposer des recommandations pratiques sur la prise en charge du patient diabétique et insuffisant rénal 2) d’évaluer la prévalence des gloméroropathies non diabétiques au cours du diabète de type 2. De nombreuses variétés de glomérorénopathies peuvent être associées au diabète; le diagnostic précis de l’atteinte rénale gloméruaire est susceptible de modifier la conduite thérapeutique et le pronostic.

Mots-clés : diabète, insuffisance rénale, gloméroropathies non diabétiques.
Type 2 diabetes has become the single most frequent cause of end-stage renal disease (ESRD) in the United States. From 1988 to 1997, the incidence of US patients with diabetes and ESRD increased from 50 to 132 per million population/year. In Western Europe, there has been a dramatic and continuous increase in diabetic patients admitted for renal replacement therapy during the last decade [1]. In France, the prevalence of diabetic patients undergoing dialysis was 6.4% in 1989 and increased to 14.2% in 1995 [2]. The incidence is much greater in regions close to the Belgian and German borders where it peaks to 50-55 patients per million population/year [3]. This rising tide of ESRD in patients with diabetes (mostly Type 2) is due to the fact that diabetes (particularly Type 2) is increasing in prevalence and that survival in diabetic patients has improved as a result of therapy for hypertension and coronary heart disease [4].

OVERT DIABETIC NEPHROPATHY

It has been assumed that the risk of overt diabetic nephropathy, defined as a syndrome of persistent albuminuria (i.e. UAE > 300 mg/d or proteinuria > 500 mg/d), early elevation of blood pressure, and a relentless decline in the glomerular filtration rate (GFR), was lower in Type 2 than Type 1 diabetic patients [5]. More recently, however, Hasslacher et al. showed a similar cumulative risk of development of proteinuria at any given duration of diabetes in patients with Type 1 and 2 diabetes. Moreover, the risk of renal failure (serum creatinine > 1.4 mg/dl) after 5 years of proteinuria was similar in both Type 1 (59%) and Type 2 (63%) diabetes [6]. Roughly 30% to 40% of diabetic patients, whether Type 1 or 2, will develop a progressive renal disease during their lifetime, leading to ESRD over a period of 8 to 10 years (Fig. 1).

In patients with renal failure, the diagnosis of diabetic nephropathy is strongly supported by the following clinical data: a long history of diabetes (≥ 10 years); increasing proteinuria following microalbuminuria, without hematuria or pyuria; a rate of deterioration of GFR of 5 to 10 ml/min/year; concurrent hypertension, evidence of extrarenal microvascular disease, such as retinopathy and neuropathy; and a family history of Type 2 diabetes.

The above clinical findings are closely associated with structural lesions of the kidneys typical of diabetic nephropathy: mesangial expansion, diffuse or nodular thickening of glomerular basement membrane, patchy hyaline deposits in afferent and efferent arterioles, and tubular degeneration with interstitial fibrosis; microaneurysms, exudative lesions, and a linear localisation of IgG along the GBM in immunofluorescence are often observed [7]. When the above criteria are met for a diabetic patient with renal failure, renal biopsy is not performed as it would not be helpful for clinical management.

THE DIABETIC PATIENT WITH RENAL FAILURE

Renal failure cannot be firmly attributed to a diabetic glomerulopathy if retinopathy is lacking, urinary abnormalities other than proteinuria are present, or the course of renal damage is unknown or does not fit with the natural history of diabetic nephropathy [8]. In such circumstances, a non-diabetic renal disease should be suspected, and a careful evaluation of the diabetic patient is needed to reach the appropriate diagnosis.

The following case report illustrates the differential diagnoses of a proteinuric diabetic patient with renal failure:

A 62-year-old man was admitted for evaluation of nephrotic syndrome and renal insufficiency. He had a 5-year history of diabetes mellitus and mild hypertension for 9 years. His sister had Type 2 diabetes and was on regular haemodialysis. Physical examination...
showed peripheral oedema, blood pressure of 140/80 mmHg, and no retinopathy in funduscopy. Laboratory findings were: creatinine 2.0 mg/dl, albumin 2.5 g/dl, haematocrit 37%, and normal AST, ALT and alkaline phosphatase. A monoclonal IgG kappa paraprotein was detected (1.7 g/dl). Urinalysis revealed occasional red blood cells (10,000/ml), nephrotic-range proteinuria (9 g/dl), and kappa light chains (Bence Jones proteinuria). Complement levels were normal, and cryoglobulin and antinuclear and antineutrophil cytoplasmic antibodies were not detected. In ultrasound, both kidneys were of normal size. Bone marrow biopsy was normal, with no atypical plasma cytosis. Percutaneous renal biopsy revealed membranous nephropathy with granular IgG deposits, concurrent diffuse glomerulosclerosis, and no evidence of light chain-related renal disease.

Several questions should be addressed when evaluating a diabetic patient with renal failure:
1) What is the severity and course of renal insufficiency?
2) Which tools are useful for diagnosis of non-diabetic nephropathy in a diabetic patient? Which patients should undergo renal biopsy?
3) Does precise definition of the pattern of renal involvement provide better guidelines for clinical management?

Assessment of renal function

The level of serum creatinine is the most widely used measurement of renal function in everyday practice. However, there are several limitations related to using serum creatinine as a marker of the glomerular filtration rate (GFR): First, as GFR falls, the rise in serum creatinine is partially offset by enhanced creatinine secretion, resulting in an overestimation of true GFR. Secondly, some drugs (cimetidine, trimethoprim) increase serum creatinine by decreasing creatinine secretion. Thirdly, extrarenal creatinine clearance is increased, particularly in patients with low GFR. Fourthly, the generation of creatinine is influenced by changes in muscle mass and dietary intake of protein [9]. Some of these problems can be avoided by measuring endogenous creatinine clearance using creatinine to block tubular secretion. Since this method requires timed urine collections, it cannot be used in cases of diabetic cystopathy. The Cockcroft-Gault formula has been shown to give a valid estimate of GFR in diabetic nephropathy, although there is still controversy on this point [10].

Cockcroft formula (ml/min): $K \times (140 - \text{age}) \times \text{weight (kg)/creatinine (\mu mol/l)}$

$K$: man: 1.23; woman: 1.04.

In the aggregate, these methods overestimate true GFR by 10-30%. Therefore, when an accurate estimation of GFR is required, $^{51}$Cr-EDTA plasma clearance is considered to be a more precise technique than estimated or measured creatinine clearance in diabetic nephropathy [11].

Investigations: imaging and laboratory investigations

In a second step, clinical examination of a diabetic patient with renal failure must focus on the following main points: making sure that the patient has no obstacle to urinary flow and no urinary and/or renal infection; searching for diffuse atheroma and ischaemic nephropathy, possibly superimposed on diabetic nephropathy; and identifying a non-diabetic renal or systemic disease causing renal impairment.

Therefore, radiological studies and laboratory investigations are used to manage the diabetic patient with renal failure.

Plain film of the abdomen (KUB: “kidneys, ureter, bladder”), tomograms through renal regions, and ultrasonography are systematically performed. These techniques are relatively inexpensive and provide a rapid means of assessing renal contour and size, calciﬁcations, and urinary tract obstruction. In diabetic patients, it is usually claimed that large kidneys may persist until the onset of ESRD. However, nephromegaly is less common in elderly Type 2 diabetic patients because nephrosclerosis is commonly superimposed on diabetic glomerulosclerosis in this category of patients [12]. Moreover, small contracted kidneys with a smooth outline or asymmetry in renal size are suggestive of ischaemic renal disease and require additional investigations such as colour-Doppler imaging or MR angiography to exclude renal artery stenosis, which is very common in Type 2 diabetic patients [13]. Finally, shrunken irregular kidneys with cortical scars, suggestive of chronic pyelonephritis, are usually the result of relapsing urinary infection, which is frequent in the diabetic patient with autonomous vesical neuropathy. It should be emphasised that diabetic patients with pre-existing renal insufficiency are particularly susceptible to acute renal failure after administration of radiocontrast media. Alternative imaging methods without administration of iodinated agents should be preferred whenever possible.

Urinalysis depends on proteinuria and microscopy to identify formed elements. Once detected, proteinuria is quantitated on 24-hour urine collection. Alternatively, the protein/creatinine ratio provides an accurate quantitative measurement on a single early morning urine specimen and correlates closely with daily protein excretion. Haematuria and leucocyturia can be assessed by urine microscopy. Red blood cell casts and dysmorphic erythrocytes are virtually diagnostic of proliferative glomerulonephritis. Infection is the most common cause of pyuria. However, in addition to neutrophils, eosinophils and lymphocytes can also be seen in urine. Eosinophils can be identified by a Hansel’s stain of the sediment, and their presence is
compatible with, but not specific for, drug-induced acute interstitial nephritis.

In a series of 320 diabetic patients, Lopes de Faira et al. reported an incidence of 13.4% of glomerular hematuria, which was significantly associated with male sex, high serum creatinine and 24-h proteinuria greater than 150 mg [14]. O’Neil et al. studied 30 patients with clinical and laboratory features of diabetic nephropathy and found significant haematuria in 30% of their patients and red cell casts in 13% [15]. These findings suggest that haematuria may be an occasional manifestation of diabetic nephropathy. The presence of microaneurysmal dilation of glomerular capillaries is a possible, but yet unproven, explanation for some cases of glomerular haematuria in diabetic patients, and the prognostic significance of this condition is unknown. Although glomerular haematuria can be found in patients with otherwise typical diabetic nephropathy, a nephritic sediment (defined as the presence of haematuria and proteinuria) suggests the diagnosis of a non-diabetic glomerulonephritis (focal or diffuse) when haematuria is associated with more marked proteinuria and renal impairment.

Non-diabetic glomerular diseases in Type 2 diabetes

Previous investigators attempted to determine how often non-diabetic glomerular disease occurs in Type 2 diabetes mellitus. The prevalence of non-diabetic glomerulopathies ranged from 12% to 64% in retrospective studies, whereas in five recent prospective studies 6% to 39% of patients were found to have a non-diabetic renal disease isolated or possibly superimposed on a diabetic nephropathy (in [16-19]; Table I).

In 1992, Parving et al. conducted a prospective study in Type 2 patients under 66 years of age to determine the prevalence and causes of persistent albuminuria (> 0.3 g/d). Eight (23%) of these patients with non-diabetic glomerular lesions already had albuminuria at the time of diagnosis of diabetes as well as absence of retinopathy and low prevalence of neuropathy (in [16]). Among a Chinese population of 51 Type 2 diabetic patients with proteinuria over 1 g/d, Mak et al. found a 34% incidence of non-diabetic renal disease, with a high proportion (59%) of IgA nephropathy [18]. Schwartz et al. [19] studied glomerular and retinal pathology in 36 patients enrolled in a prospective clinical trial of patients with Type 2 diabetes mellitus, proteinuria (> 500 mg/d), renal insufficiency (creatinine ≤ 3.0 mg/dl), and hypertension. In this series, only 2 of 36 patients were found to have a non-diabetic glomerulopathy.

How do we determine which diabetic patient needs or would benefit from a renal biopsy for possible detection of non-diabetic nephropathy? As stated by the Workshop on the Use of Renal Biopsy in Research

### Table I. Glomerulopathies in Type 2 diabetes.

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>No. of patients</th>
<th>Diabetic Glomerulopathy</th>
<th>Non-Diabetic Glomerulopathy</th>
<th>Diabetic and non-Diabetic Glomerulopathy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Nodular (%)</td>
<td>Diffuse (%)</td>
<td>Total (%)</td>
</tr>
<tr>
<td>Amoah (1988)</td>
<td>60</td>
<td>–</td>
<td>–</td>
<td>72</td>
</tr>
<tr>
<td>Richards (1992)</td>
<td>46</td>
<td>–</td>
<td>–</td>
<td>50</td>
</tr>
<tr>
<td>Kleinknecht (1992)</td>
<td>35</td>
<td>34</td>
<td>26</td>
<td>60</td>
</tr>
<tr>
<td>Parving (1992)</td>
<td>35</td>
<td>23</td>
<td>54</td>
<td>77</td>
</tr>
<tr>
<td>Gambara (1993)</td>
<td>52</td>
<td>–</td>
<td>–</td>
<td>37</td>
</tr>
<tr>
<td>John (1994)</td>
<td>80</td>
<td>–</td>
<td>–</td>
<td>19</td>
</tr>
<tr>
<td>Suzuki (1994)</td>
<td>128</td>
<td>20</td>
<td>65</td>
<td>85</td>
</tr>
<tr>
<td>Lipkin (1994)</td>
<td>82</td>
<td>–</td>
<td>–</td>
<td>61</td>
</tr>
<tr>
<td>Pinel (1995)*</td>
<td>30</td>
<td>13</td>
<td>70</td>
<td>83</td>
</tr>
<tr>
<td>Olsen (1995)</td>
<td>33</td>
<td>61</td>
<td>27</td>
<td>88</td>
</tr>
<tr>
<td>Mak (1997)</td>
<td>51</td>
<td>–</td>
<td>–</td>
<td>67</td>
</tr>
<tr>
<td>Schwartz (1998)</td>
<td>34</td>
<td>50</td>
<td>44</td>
<td>94</td>
</tr>
</tbody>
</table>

* microalbuminuric patients included
on Diabetic Nephropathy, “a clinically indicated renal biopsy is one performed in the anticipation that the information provided will have direct clinical usefulness in a given patient, either for a decision regarding institution or avoidance of a specific therapeutic intervention, for diagnosis or prognosis” [20]. Among patients with diabetes mellitus, the major clinical clues suggesting a non-diabetic glomerular disease and the need to consider renal biopsy are the following:

- acute onset of renal disease, which would include the onset of nephrotic-range proteinuria or the development of acute renal failure of unknown origin;
- a rate of decline of GFR or a worsening of proteinuria outside established norms for patients with diabetic nephropathy;
- when clinical or laboratory findings indicate the likelihood of another primary or secondary renal disease, such as significant glomerular haematuria, red cell casts, or systemic symptoms suggestive of vasculitis;
- onset of renal failure less than 10 years, and of proteinuria less than 5 years, from documented onset of diabetes;
- absence of retinopathy in Type 1 diabetes, whereas in Type 2 a lack of retinopathy is a poor predictor of non-diabetic kidney disease.

According to the studies of Parving et al. and Lipkin et al., the diagnostic specificity of retinopathy is 100%, while the diagnostic sensitivity (predictive value of a negative test) is only 40% (in [16, 17]).

Based on the series mentioned in Table I, it appears that the non-diabetic glomerulopathies most commonly found include membranous (19%), IgA and Schönlein-Henoch glomerulonephritis (19%), post-infectious (16%), rapidly progressive glomerulonephritis (9%) and minimal change nephropathy (14%). In many circumstances, the precise definition of the pattern of glomerular involvement could be helpful in predicting disease outcome and providing better guidelines for management. However, this assumption remains controversial. Indeed, a recent study showed that the rate of renal disease progression in proteinuric Type 2 diabetic patients was rather independent of the type of underlying glomerular lesions, but consistently predicted by the level of urinary protein excretion. This series included 30 patients with typical diabetic glomerulopathy, 23 with aspecific chronic changes predominantly of the nephroangiosclerotic type, and 12 with non-diabetic glomerular disease superimposed on diabetic lesions. Patients with urinary protein excretion ≤ 2 g/d had stable serum creatinine and 100% kidney survival at 5 years, whereas those with proteinuria > 2 g/d had a 92% risk of progression to ESRD over the same period. Among these patients, the risk was even more reliably predicted by quantification of a global score for tissue injury at renal biopsy (i.e. the sum of the scores of glomerular sclerosis, glomerular ischaemia, arteriosclerosis, arteriolar hyalinosis, interstitial fibrosis, and tubular atrophy). Patients with a high histologic score (> 13) progressed to ESRD with a median kidney survival time of only 1.6 years, whereas those with a score < 7 never doubled their serum creatinine over the follow-up period [21]. Nonetheless, these results need to be confirmed by prospective studies.

In conclusion, the development of renal insufficiency in a diabetic patient should not be attributed to diabetic glomerulosclerosis without considering further diagnostic work-up. A critical analysis of a patient with diabetes mellitus and renal insufficiency should be made, including kidney biopsy, to exclude the possibility of a non-diabetic, potentially treatable glomerulonephritis [22].

REFERENCES


