Glomerular involvement in type II diabetes—is it all diabetic glomerulosclerosis?

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Introduction

The proportion of diabetic patients entering renal replacement therapy programs is increasing. It is evident that the percentage of type II (non insulin dependent) diabetes continues to increase whereas the proportion of type I diabetes remains stable. It is strange that the overall renal prognosis and survival is the same in patients with type I and type II diabetes [1] even though the former are often older by two decades than the latter.

Amongst possible explanations for this paradox one can discuss the nature of the renal disease: as a matter of fact, prognosis of diabetes strongly depends on the presence or absence of associated microangiopathic and macroangiopathic complications, particularly those affecting the renal and cardiac vasculature.

It has been known for a long time that the presence of renal signs and symptoms in a diabetic patient does not necessarily mean that he suffers from typical diffuse or nodular diabetic glomerulosclerosis. This possibility was first entertained more as an academic curiosity, but one has recently come to appreciate that it may potentially be of great prognostic importance: For the patient to have non-diabetic nephropathy implies at least theoretically that he or she might be free of microvascular or macrovascular disease. Should such non-diabetic nephropathy progress, the pace will be the one of the specific disease, i.e. different from that of diabetic nephropathy, and the patient would have a much lower risk of associated blindness, lower limb amputation, stroke and myocardial infarction [2].

Glomerulonephritis in type II diabetes

It has been claimed by Amoah that non-diabetic nephropathy was clearly more common in type II than in type I diabetes [3]. This observation was confirmed by subsequent investigators [4–10]. The spectrum of nephropathies was wide and varied from minimal change nephrotic syndrome to extra-capillary glomerulonephritis. The prevalence of glomerulonephritis (either isolated or superimposed upon diabetic glom-
erulosclerosis) seems to be higher in Asian [9-11] than in European [4-8] or American [3] patients. It is particularly high in South India where the prevalence of proliferative glomerulonephritis is very high in the non-diabetic population as well [9]. Gall et al. have recently shown that the prognosis of the patient with type II diabetes and non-diabetic nephropathy is far better than that of a patient with diabetic glomerulosclerosis [12].

Glomerular lesions secondary to interstitial and vascular nephropathies

Glomerular lesions may also result from interstitial nephropathy, e.g. papillary necrosis, or renal artery atheromatosis. Renal artery stenosis was found in 8.3% of 197 diabetic subjects in a post mortem study; all of these diabetic patients had type II diabetes [13]. On a macroscopical level, evidence of ischemia was found in 30% of the renal biopsies performed in patients with type II diabetes [8].

More recent observations in patients with type II diabetes and normal macroscopical renal morphology

In three recent series on diabetic patients who had two normal sized kidneys and who were carefully selected for prospective systematic studies, no cases of glomerulonephritis were found [14-16]. This is in agreement with observations in a post mortem study [17].

Pinel et al. [14] in contrast found 'ischemic lesions' in one out of eight microalbuminuric and three out of 22 proteinuric patients with diabetes type II [14]. Fioretto et al. [15] found 'important tubulo-interstitial and/or arteriolar lesions and/or glomerular sclerosis with minimal diabetic abnormalities' in 13 out of 35 normoalbuminuric and 14 out of 34 microalbuminuric patients. Finally, in Pima Indians with diabetes of different lengths of duration, who were either normo- or microalbuminuric, Pagtalunan et al. [16] were unable to identify structural changes associated with the appearance of microalbuminuria in a study in which biopsies were analysed using both optical and electron microscopy. In other words, glomerular lesions were present even in normoalbuminuric patients with type II diabetes of long duration.

Hypothesis

If albuminuria is present in a patient with type II diabetes, normal renal arteries and a normal excretory system (by pyelogram), two possibilities must be considered: (i) classical diabetic glomerulosclerosis of the same type that is usually observed in patients with type I diabetes or young patients with type II diabetes such as the Pima Indians, (ii) a composite of non-diabetic vascular and interstitial lesions. The latter spec-trum of morphological changes is more frequently encountered in older Caucasian patients.

It will be a task for the future to determine whether the two patterns of renal pathology have similar clinical expression, rate of progression and overall prognosis.

Consequences for clinical management

Information in literature gives very few clues when the clinician should suspect diabetic glomerulosclerosis or the above alternative lesions. Absence of diabetic retinopathy does not indicate that albuminuria is due to renal lesions other than diabetic glomerulosclerosis. Conversely, the presence of diabetic retinopathy does not exclude the possibility of superimposed glomerulonephritis [3,5,6,9,12,14].

There is a need to establish practical guidelines for how to manage the patients with type II diabetes and albuminuria of either the microalbuminuric or macroalbuminuric type. In particular it will be necessary to establish whether renal biopsy is no longer necessary when diabetes has been present for more than seven years.

As of today we feel that renal biopsy is desirable or mandatory when there is something atypical about proteinuria, e.g. sudden onset, association with hematuria, acute renal insufficiency or extra-renal manifestations [18].

Conclusions

Since patients with type II diabetes are on average older by two decades compared to patients with type I diabetes, it is not surprising to find that in addition to or instead of diabetic glomerulosclerosis other renal lesions may be present. This raises concern that prognoses may vary according to the renal histological pattern. Unfortunately, information in this respect is incomplete. Prospective studies on the natural history of these variants and their susceptibility to pharmacological intervention are clearly mandatory.

References

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De novo diabetes in dialysis patients: when diabetes is not diabetic nephropathy

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Introduction

In patients with renal failure, the presence of diabetes has nearly always been equated with the presence of diabetic nephropathy. However, in real life the situation is more complex. Figure 1 shows the possible pathogenetic relationships between diabetes and renal disease. The first possibility is that diabetes causes renal disease (diabetic nephropathy). Alternatively, renal disease may directly or indirectly cause diabetes. Finally, no cause-effect relationship may be present, in which case diabetes and kidney disease coexist independently in the same patient.

As far as the temporal relation between diabetes and kidney disease is concerned two situations may exist; first, the diagnosis of diabetes may precede the diagnosis of renal disease; second, the diagnosis of renal disease may precede the diagnosis of diabetes. In the first instance renal disease may or may not be secondary to diabetic nephropathy. In the second case (de novo diabetes) diabetes may or may not be related (directly or indirectly) to the nephropathy or to nephropathy treatment.

In this comment, I will focus on the topic of de novo diabetes in uraemic patients trying to review both the magnitude of the problem, the mechanisms potentially involved, and the consequences of diabetes on survival of RRT patients.

Dimensions of the problem

Post-transplantation diabetes mellitus is frequent, affecting 10–20% of transplanted patients [1], and it is considered to be secondary to the action of steroids (which impair non-oxidative glucose disposal) and cyclosporin A (which induces insulin resistance and decreases insulin secretion). Recently, it has been shown that post-transplantation diabetes mellitus is potentially reversible after steroid withdrawal in selected cases [2].

Whilst post-transplantation diabetes mellitus has raised the attention of clinicians and researchers, there