

## In Focus

# Renal lesions in patients with type 2 diabetes: a puzzle waiting to be solved

Loreto Gesualdo<sup>1</sup> and Salvatore Di Paolo<sup>2</sup>

<sup>1</sup>Department of Nephrology, Dialysis and Transplantation Unit 'Aldo Moro' University of Bari, Bari, Italy and <sup>2</sup>Nephrology and Dialysis Unit, Hospital Dimiccoli, Barletta, Italy

Correspondence and offprint requests to: Loreto Gesualdo; E-mail: loreto.gesualdo@uniba.it

Three hundred sixty-six million people worldwide will be living with diabetes mellitus (DM) by 2030 ([1, 2]; <http://www.idf.org/global-diabetes-plan-2011-2021>). Prospectively, 75–150 million of these patients will develop a diabetic nephropathy (DN) or a non-diabetic renal disease (NDRD), either isolated or superimposed on DN [3, 4]. To date, the differential diagnosis between DN and NDRD remains a challenge that nephrologists are trying to win [5].

DN is a widespread microangiopathic complication of DM eventually leading to end-stage renal disease over a variable number of years [6]. The natural history of DN, as originally depicted in patients with type 1 DM and later extrapolated to type 2 DM (T2DM), would comprise an early phase of microalbuminuria, which precedes overt nephropathy, characterized by macroalbuminuria and a progressive decline of glomerular filtration rate (GFR). Indeed, T2DM patients may present with overt proteinuria (and hypertension) already at the clinical onset of diabetic disease, or remain microalbuminuric without any progression to overt nephropathy, or even display renal insufficiency with minimal or absent proteinuria, this latter phenotype being increasingly recognized worldwide [7, 8]. In fact, the Renal Insufficiency and Cardiovascular Events (RIACE) Italian Multicenter Study (pts number = 15 773), published in 2011 [7], found a 56.6% of non-albuminuric chronic renal failure among patients with T2DM.

It is likely that treatments such as the use of drugs blocking the renin angiotensin system (RAS) system or modulating dyslipidaemia and an aggressive glucose monitoring have changed the natural history of renal damage in DM shifting the microangiopathic forms of the disease towards macroangiopathic forms [9–11]. As a matter of fact, non-albuminuric renal impairment in the RIACE study was correlated with a higher prevalence of cardiovascular disease (CVD) and female

sex [7, 8]. These data suggest that T2DM patients with non-albuminuric renal impairment have a macroangiopathic phenotype and a higher CVD burden. Consequently, some questions would arise: do these patients suffer from heart disease or kidney disease? By definition, DN recognizes a microangiopathic damage characterized by the clinical appearance of microalbuminuria. Is the reduction of GFR without an increase of albuminuria sufficient to rule out the diagnosis of DN? Is the reduction of GFR a haemodynamic effect due to RAS inhibition?

The large variability in the clinical presentation of renal involvement in patients with T2DM, along with the possibility of glomerulonephritides independent from DM, make kidney biopsy a prerequisite for a correct and thorough diagnosis. However, not all nephrologists agree on the usefulness of renal biopsy, first of all because they believe that biopsy, in spite of the variability of clinical presentations, cannot but diagnose DN in the vast majority of patients with T2DM, which would render it useless and unethical, second because of the risk of major complications (haematuria, perirenal haematoma, arterial embolization and very rarely nephrectomy) [12–14]. Therefore, DN is commonly identified only on the basis of confusing clinical and laboratory data, and such diagnosis may in several cases result in misleading.

A diagnostic model to correctly identify a pure DN has been recently developed by Zhou *et al.* [15] as well as by Liang *et al.* [5]. In the first report, several clinical and laboratory parameters such as years with diabetes, systolic blood pressure values, glycosylated haemoglobin levels, the absence of haematuria and diabetic retinopathy were significantly correlated in a logistic regression analysis with pure DN with a sensitivity and specificity higher than 90%. In the second report, the authors evaluated the predictive role of clinical and laboratory data to

discriminate NDRD from pure DN in patients with T2DM. The meta-analysis of case-control studies showed that the presence of dysmorphic erythrocytes and/or erythrocytes casts in the urine sediment may better discriminate NDRD from DN than microhaematuria alone. Moreover, the authors questioned the significance of diabetic retinopathy, because it was absent in 23.6% of patients with pure DN and, conversely, was present in 17.6% of patients without DN, thus suggesting that the lack of diabetic retinopathy although predictive of NDRD does not exclude a DN. Furthermore, a shorter duration of diabetes and lower levels of HbA1C and high diastolic and systolic blood pressure may facilitate the discrimination of NDRD from DN. Such conclusions would deserve some caution, however, because the meta-analysis was mainly based on observational studies and presents the limitations due to selection and reporting biases. Overall, the above studies plead for a higher suspicion of a NDRD in patients with type 2 diabetes. Consequently, there is an urgent need for specific, rapid, non-invasive and not expensive biomarkers that can discriminate NDRD from ND forms to help nephrologists in a safe and reliable diagnosis and set the most appropriate therapy.

Mazzucco *et al.* [4] described the renal histopathologic lesions of a large cohort of T2DM patients. They defined three classes of renal damage in patients with T2DM: the classical diabetic glomerulosclerosis (class 1), vascular and ischaemic glomerular changes (class 2), other glomerulonephritides superimposed on diabetic glomerulosclerosis (class 3a) or glomerulonephritides without diabetic glomerulosclerosis lesions (class 3b). The available literature does not allow to clearly define the rate of prevalence of the three classes of kidney damage in T2DM. In fact, the total prevalence of NDRD ranges from 10 to 85% among published studies [4, 14, 16–20]. Ethnic and geographic factors, as well as the criteria used by the nephrologists to select patients undergoing renal biopsy, may explain this wide variability. As a matter of fact, Mazzucco *et al.* [4] found that the frequency of classes 1 and 3 was strongly biased by the restricted or unrestricted biopsy policy, and these findings may explain the epidemiological controversies.

Treatments for DN and NDRD may vary widely. Primary and secondary GN, such as IgA nephropathy, minimal change disease, membranous nephropathy, as well as vasculitides and amyloidosis, either isolated or superimposed to an underlying DN, have been reported [4, 14, 16–20]. These diseases are effectively treated with immunosuppressants (corticosteroids, cyclophosphamide and monoclonal antibodies) other than the standard therapy (angiotensin converting enzyme inhibitor or angiotensin receptor blockers). Therefore, a correct diagnosis of pure DN versus NDRD is the appropriate approach for a targeted treatment.

On behalf of the Renal Pathology Society (RPS), a pathological classification of pure DN has been recently developed by an international consensus [21]. Based on glomerular lesions, four progressive classes of renal damage have been identified. Interstitial and vascular involvement have been evaluated separately. Unfortunately, the authors did not test the pathological classification system, which represents a first step towards the development of prognostic markers of DN progression, for a possible predictive role of renal outcome. Recently, Oh *et al.*

[14] and Okada *et al.* [22] tried to correlate the pathologic classification system with the clinical outcome of DN, but their conclusions, somehow conflicting, were likely limited by the small number of patients examined.

In this issue of the *Nephrology, Dialysis and Transplantation* journal, An *et al.* [23] explore the relationship between histologic changes and renal outcome in a large cohort of pure DN patients. Using the RPS classification, the authors demonstrate, for the first time, that the glomerular and tubulointerstitial lesions constituted an independent risk factor for renal outcomes, even when adjusting for clinical features. Although the glomerular and interstitial lesions correlated among each other, in several patients the severity of the latter lesions was dissociated from the degree of glomerular damage, such that tubulointerstitial damage became the only independent predictor of renal outcomes in patients with moderate to severe glomerulopathy, suggesting a central role in the development of advanced DN. Furthermore, the authors describe an association between the severity of glomerulointerstitial damage and a series of clinical features, comprising proteinuria, eGFR, anaemia, arterial blood pressure, fasting blood glucose and HbA1c. In sharp contrast, vascular lesions, present in the vast majority of patients, failed to show any significant predictive value, leading An and co-workers to suggest the necessity to redefine the vascular indexes in the pathologic classification. Indeed, their findings contrast with those reported in previous studies, showing a good correlation between glomerulosclerosis and vascular disease [14, 22, 24]. Furthermore, it might have been of interest to examine the relationship between vascular lesions and renal and cardiovascular outcome in normoalbuminuric diabetic patients, who were excluded from this study.

The authors clarify that the general indications for renal biopsy in their institution were sudden onset overt proteinuria, glomerular haematuria (dysmorphic erythrocytes and/or erythrocytes casts), as well as persistent proteinuria and increased serum creatinine. Most of these features do not associate with typical DN and would rather suggest NDRD. Unfortunately, however, this study did not convey any information on the rate of prevalence of NDRD, either isolated or superimposed on DN, among diabetic patients biopsied for the above indications. This point appears particularly intriguing, because several centres worldwide perform renal biopsy to diabetic patients only when NDRD is strongly suspected.

To date, renal biopsy remains the ‘conditio sine qua non’ for the correct diagnosis and prognosis of a renal disease. Moreover, advances in scientific knowledge have helped to characterize the pathogenetic mechanisms of a growing number of renal diseases at a molecular level. The first attempts to discover new biomarkers of DN, using omics techniques, have been published over the last few years [25–29]. To date, however, a systems biology study in T2DM with different renal lesions is still lacking. The application of the systems biology approach to body fluids and/or biopsy samples of different classes of renal injury in diabetic patients needs a correct definition of the clinical phenotype and histopathological classification to identify specific early diagnostic and prognostic non-invasive biomarkers of DN. Once discovered, these biomarkers need appropriate and well-designed validation studies.

In conclusion, patients with type 2 diabetes present several types of renal damage. These findings suggest the need for a more extensive use of the renal biopsy to better characterize the clinical phenotype. The viewpoint is to develop a logistic regression diagnostic model that, including clinical data, renal biopsy features and molecular signatures, will identify early and reliable diagnostic and prognostic non-invasive biomarkers able to distinguish NDRD from DN. The success of this approach will represent an incentive to better plan a rational therapeutic approach in T2DM patients with renal damage. Thus, further well-designed studies on differential diagnosis and prognosis of renal damage in T2DM are strongly encouraged.

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## CONFLICT OF INTEREST STATEMENT

None declared.

(See related article by An *et al.* Renal histologic changes and the outcome in patients with diabetic nephropathy. *Nephrol Dial Transplant* 2015; 30: 257–266.)

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