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Diabetology

NON-DIABETIC KIDNEY DISEASE IN DIABETES

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ABSTRACT The prevalence of diabetes is rising, making it a global epidemic, implicating a burden on the healthcare systems. With the rising prevalence, it is also positively associated with the increase in macrovascular & microvascular complications.

The renal involvement in diabetes, commencing to diabetic nephropathy (DN), is now the most common cause of the end-stage renal disease (ESRD) worldwide. As diabetic nephropathy is characterized by persistent proteinuria, it is also imperative to differentiate the non-diabetic renal diseases (NDRD), as diabetic patients with kidney disease, have a high prevalence of non-diabetic renal disease (NDRD). T2DM is associated with a more heterogeneous clinical course and have complex renal lesions than those in type 1 diabetes, different types of non-diabetic renal disease such as IgA nephropathy (IgAN), membranous nephropathy (MN) and mesangioproliferative glomerulonephritis (MPGN) may coexist with DN. The differentiation between DN and non-diabetic renal disease (NDRD) may not be possible without renal biopsy.

This review is focused on the prevalence and clinical staging with an emphasis on renal outcomes and the clinical course of the NDRD. It also extrapolates the clinical relevance of renal biopsy with its importance as a diagnostic tool and future perspectives in renal disease (NDRD).

KEYWORDS : Non-Diabetic Kidney Disease, Diabetes mellitus, Kidney biopsy, Diabetic nephropathy

INTRODUCTION

Today, diabetes mellitus is considered a global epidemic, affecting millions of individuals and increasing the burden on the healthcare system.

Diabetes representing dysglycemia and associated comorbidity like high blood pressure induces the risk for the development of complications like cardiovascular disease (CVD) and diabetic nephropathy (DN). Several studies show that about 30-40% of all diabetic patients represent end-stage renal disease (ESRD), and approximately 50% of all deaths in patients with type 2 diabetes mellitus (T2DM) account for CVD. Moreover, the 5-year survival time of diabetic patients on regular chronic hemodialysis is expected to be less than 50%.[1]

For many years, healthcare professionals and clinical researchers have been working in this field to better make the correct diagnosis, as a different renal disease in diabetes, with a distinct course of the disease, different therapies, and management modules with a specific prognosis. [2]

Clinicopathologically, T2DM associated renal disease has more heterogeneous renal lesions than in T1DM. [3,4] Diabetic nephropathy (DN) is considered a dangerous and mortifying complication of diabetes mellitus and a principal cause of the end-stage renal disease (ESRD) globally.[4,5]

The stages of the disease progression of DN typically commences from hyperfiltration leading to microalbuminuria to macroalbuminuria, further continuing to a slow progressive decline in renal function, ultimately ESRD. [5] Individuals with T2DM with proteinuria and diabetic retinopathy (DR) are most likely presented with diabetic nephropathy (DN); however, high frequency of non-diabetic renal disease (NDRD) has been reported in the absence of retinopathy. [6]

Furthermore, diabetic nephropathy (DN) may be considered as typically an irreversible condition, while NDRDs may be more favorable to cure with early diagnosis and treatment. Hence, the management and prognosis of NDRD and DN are distinct and different. Moreover, it is observed that non-diabetic renal disease (NDRD) like IgA nephropathy (IgAN), membranous nephropathy (MN), and mesangioproliferative glomerulonephritis (MPGN) may also coexist with DN, and therefore, the differentiation between DN and non-diabetic renal disease (NDRD) may not be possible without renal biopsy.[3,6]

The estimated prevalence of NDRD±DN in patients with T2DM is approximately in the range of 17-85% based on the geography and policies for biopsy at given institutions. In these cases, the atypical clinical features of renal involvement, especially during the short duration of diabetes warranting renal biopsy, are determined by the absence of diabetic retinopathy, rapidly decreasing renal function, and increasing proteinuria or acute onset nephrotic syndrome, and active urine sediment.[4,7,8]

Further exploring, the significant clinical clues implying NDRD includes – [2,9]

1. The time-to-onset of overt proteinuria <5 years from the initial diagnosis of diabetes. Moreover, the probability of DN in T2DM might also occur in <5 years due to unawareness of the onset of diabetes, aging kidneys, and overlapping hypertensive renal injuries. Hence, this indication can be used for the renal biopsy for further confirmation.
2. The presence of prominent dysmorphic haematuria or red blood cell (RBC) casts.
3. The sudden onset or rapid progression of renal disease accompanied by massive proteinuria or renal insufficiency
4. The normal blood pressure (BP) in patients with clinical manifestation is similar to overt diabetic nephropathy.
5. The apparent absence of diabetic retinopathy or neuropathy in patients with massive proteinuria or renal insufficiency.

It is imperative to know that none of these clues indicate NDRD in T2DM patients. However, a combination of them definitely increases the positive predictive value.

Hence, the catastrophic combination of diabetes with renal complications calls for the timely intervention of nephrologists even more than diabetologists, with the patients at high risk to reduce the burden of the disease.

Screening For Chronic Kidney Disease In Type 2 Diabetes

Generally, the disease progression of chronic kidney disease with T2DM follows a similar clinical course, but with heterogeneity as that of T1DM, with the increased urine albumin excretion rate (AER) as the earliest marker and clinical evidence.

However, with diabetes being a major risk factor for the development of kidney disease and the primary cause of end-stage renal disease, evidence from Framingham Heart Study suggest that cardiovascular disease risk factors like age, sex, hypertension, smoking, body mass index, HDL cholesterol levels, and prevalent myocardial infarction or congestive heart failure contributes to the relationship between prediabetes and the development/progression of chronic kidney disease. (The fully adjusted odds of developing CKD were 0.98, 1.71, and 1.93 among those with impaired fasting glucose (IFG) or impaired glucose tolerance (IGT), newly diagnosed diabetes, or known diabetes, respectively, as compared to the normoglycemic individuals).[10]

Furthermore, the heterogeneity of the kidney disease in T2DM is shown using data from NHANES III, where it is observed that 33% of individuals with T2DM and a GFR<60 ml/min per 1.73m^2 did not have evidence of either microalbuminuria, macroalbuminuria or

retinopathy affirms that reduced glomerular filtration rate (GFR) in type 2 DM patients shall not always be due to the classic condition of diabetic glomerulosclerosis, associated with albuminuria and retinopathy. Hence, focusing solely on urine albumin excretion to screen for CKD may miss a considerable number of cases in adults with T2DM. [11,12]

As T2DM consists of heterogeneous risk factors and comorbid conditions, it is imperative for healthcare professionals to derive mandatory approaches for screening renal disease in T2DM patients for glomerular filtration rate (GFR) in addition to monitoring of urine albumin excretion (AER) and funduscopic changes that shall help in ensuring an appropriate intervention in type 2 DM patients and chronic renal insufficiency (CRI) not due to diabetic glomerulosclerosis. This shall warrant for the diagnosis of patients who follow either an albuminuric or non-albuminuric pathway to renal impairment. [11,12]

Renal Outcomes And Clinical Course Of Nondiabetic Renal Diseases In Patients With Type 2 Diabetes

It is now clear that in patients with diabetes, Non-diabetic renal diseases (NDRDs) form a significant part of disease manifestations.

In the latest study conducted by Arora P et al. (2020) with 44 patients of T2DM subjected to renal biopsy for clinical suspicion of NDRD, it was observed that 61.4% had isolated NDRD, 13.6% had NDRD superimposed on DN, and 25% had isolated DN. [13]

In patients having isolated NDRD, the most common NDRDs (≥5% of patients) were - 19.2% with minimal change disease (19.2%), followed by 11.5% with lupus nephritis, post-infectious GN (7.7%), antineutrophil cytoplasmic antibody (+) crescentic glomerulonephritis (7.7%), chronic interstitial nephritis (7.7%), membranoproliferative glomerulonephritis (7.7%), IgA nephropathy (7.7%), and HIV nephropathy (7.7%) (Shown in Fig.1). In those patients, where NDRD was superimposed on DN, 33.3% of patients had DN + chronic pyelonephritis, and 16.7% of patients each had DN + acute tubular necrosis, DN + kappa light-chain deposition disease, DN + thrombotic microangiopathy, and DN + lupus nephritis Class 3. (Shown in Fig.2) [13]

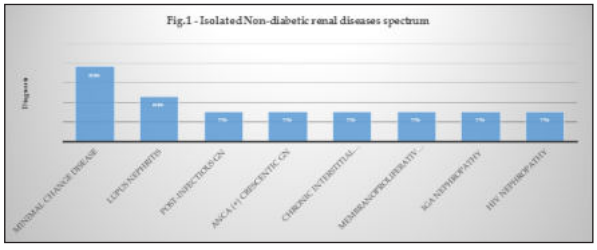

Fig.1 - Isolated Non-diabetic renal diseases spectrum. ANCA = Antineutrophil cytoplasmic antibodies; GN = Glomer ulonephritis; HIV = Human immune deficiency virus; IgA = Immunoglobulin A (Adapted from Arora P. et al, 2020) [13]

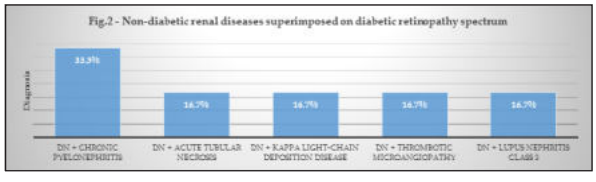

Fig.2 - Non-diabetic renal diseases superimposed on diabetic retinopathy spectrum. DN = Diabetic retinopathy (Adapted from Arora P. et al, 2020) [13]

Similar results were observed in a single-center retrospective study conducted by Kanodia K. V. et al. (2013) on 152 diabetic patients grouped into - Group-I (isolated NDRD, 35 (23.03%), Group-II (NDRD superimposed on underlying DN, 35 (23.03%), and Group-III (isolated DN, 82 (53.95%), with the standard clinical presentation of Nephrotic syndrome (NS).

The most likely histological types of NDRD were acute tubulointerstitial nephritis (38.57%) followed by benign nephro sclerosis (15.72%), membranousnephropathy (10%), IgA nephropathy (7.14%), and membranoproliferative glomerulonephritis (7.14%). Moreover, factors like shorter duration of diabetes, hematuria, absence of retinopathy, low serum complement levels, and nephrotic range proteinuria emerged as the predictors of NDRD. [14]

The literature summary for Diabetic nephropathy (DN) with non-diabetic renal disease (NDRD) in diabetic patients is presented in Table 1 (Adapted from Zhuo, L, 2013) [15]

Table 1 - Diabetic nephropathy (DN) with non-diabetic renal disease (NDRD) in diabetic patients – Literature Summary

Pathological types	Prevalence (%)
Glomerular diseases	
IgA nephropathy	14.1%
Mesangial proliferative glomerulonephritis	10.0%
Post-infectious glomerulonephritis	10.0%
Membranous nephropathy	6.8%
Immune complex-trapping glomerulonephritis	5.5%
Crescentic glomerulonephritis	3.6%
Focal segmental glomerulosclerosis	3.2%
Minimal change glomerulopathy	1.4%
Membrano-proliferative glomerulonephritis	1.4%
Lupus glomerulonephritis	1.0%
Fibrillary glomerulonephritis	0.5%
Necrotizing focal glomerulonephritis	0.5%
Hepatitis-related nephritis	0.5%
Vascular	
Hypertensive changes and arterionephrosclerosis	8.6%
Atheroembolic renal disease	1.0%
Thrombotic microangiopathy	0.5%
Tubulointerstitial	
Tubulointerstitial nephritis	22.7%
Pyelonephritis	2.3%
Toxemia of pregnancy	0.5%
Other	6.4%

CLINICAL COURSE AND PROGNOSIS

A prospective cohort study conducted on 46 patients by Soleymanian T et al. (2015) showed that the patients with NDRD have a lesser prevalence of diabetic retinopathy (5%), shorter duration of diabetes, higher range of proteinuria, and better kidney survival. Moreover, One, three, and five-year cumulative kidney survival was higher in NDRD patients compared to DN and DN+NDRD groups (p=0.016) (Shown in Figure 3), despite having a similar baseline eGFR in NDRD and DN groups. [4]

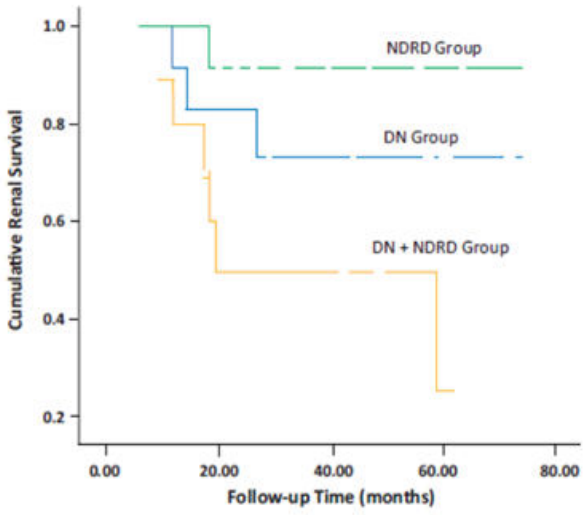

Fig. 3 - Cumulative renal survival in three groups (DN Group, NDRD Group, DN+NDRD Group) (Adapted from Soleymanian T et al., 2015) [4]

A retrospective analysis by Byun J. M. et al. (2013) showed that amongst 110 patients with type 2 diabetes, who were presented with NDRD had a better renal outcome, probably have resulted from the specific treatment modalities including, utilization of aggressive disease-specific treatments like steroids and immunosuppressants. [7]

Clinical Relevance Of Renal Biopsy Studies In Type 2 Diabetes And Future Perspectives

The importance of renal biopsy has been firmly established for

diagnosing and treating NDRD; however, renal biopsy is also emerging as an essential diagnostic tool in T2DM patients for the following reasons - 1. Renal prognosis, 2. Understanding of the different clinical phenotypes, 3. Understanding of the responses elucidated by various therapies, thus allowing a tailored approach, 4. Reassuring many T2DM patients with microalbuminuria that they have minimal DN lesions and hence, are at low risk of substantial loss of GFR in the near future.

As discussed above, the heterogeneity of renal lesions has an essential influence on the progression of the disease and is likely to be responsible for the different clinical presentations in type 2 diabetes. For the prognosis and management of the disease states, renin-angiotensin system blockers, known to suppress albuminuria and mask albuminuria progression, have been suggested. The use of new glucose-lowering agents like SGLT2 inhibitors has also been demonstrated to reduce albuminuria and, importantly, GFR loss and ESRD. The cardiovascular outcome trials with these drugs have shown a significant reduction in major adverse cardiovascular events, hospitalization for heart failure, and renal events.

Furthermore, to understand and extrapolate the mechanisms responsible for the nephroprotective effects of the drug classes, renal biopsies could be fundamental and helpful in discovering new and more targeted nephroprotective agents.[16]

Summary

In the epidemic of Type 2 Diabetes, the renal involvement is quite heterogeneous and many a time overlooked and designated as having diabetic nephropathy. However, renal biopsy is emerging as an essential diagnostic tool for various reasons like understanding renal prognosis, different clinical phenotypes, responses elucidated by various therapies, and many others. Along with that, renal biopsies from type 2 diabetic patients with renal disease comprise a heterogeneous group of disease entities, some of which are remittable and in some cases, treatable.

In T2DM subjects, manifesting renal involvement, having a short duration of diabetes, and absence of retinopathy are independent predictors of non-diabetic renal disease (NDRD). From various studies, it has been recognized that patients with NDRD are associated with better renal outcomes and prognosis. Therefore, it has warranted the need for renal biopsy in type 2 diabetic patients with risk factors of NDRD for accurate diagnosis, prompt initiation of disease-specific treatment, and ultimately, better renal outcomes.

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