Diabetic Patients

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Roughly 3% of patients worldwide with a new diagnosis of type 2 diabetes mellitus (T2DM) already have an overt nephropathy at diagnosis and about 20–30% of the remaining ones develop a complication of this kind later in life. The early identification of kidney disease in diabetic patients is important as it slows its progression, which is important not only because this reduces the need for renal replacement therapy, but also because it decreases the high rate of mortality and morbidity associated with a reduction in kidney function.

diabetic nephropathy diabetic kidney disease

1. Entity of the Problem

It is well known that type 2 diabetes mellitus (T2DM) and arterial hypertension are the two main causes of chronic kidney disease (CKD) requiring renal replacement therapy.

Globally, the prevalence of diabetes, in particular of type 2 diabetes, has quadrupled in the past three decades, and this disease is now considered the ninth leading cause of death: the estimated prevalence is currently around 10% and is rapidly growing in particular in Asian countries, closely following the obesity epidemic. T2DM accounts for about 90% of total diabetes prevalence [1].

The incidence of diabetic nephropathy in T2DM patients varies widely, depending on genetic background, lifestyle, food habits, socioeconomic status and overall diabetes care. Although genetic predisposition partly determines individual susceptibility to T2DM, obesity, an unhealthy diet and a sedentary lifestyle are important drivers of the current increase in the disease [2].

According to the timing of diagnosis, many if not most T2DM patients present at least one macro- or microvascular complication at diagnosis; most of the remaining patients will develop at least one complication during follow-up. While cardiovascular disease is the main cause of morbidity and mortality in T2DM patients, as well as in the general population of many Western countries, its relative risk is significantly increased in the presence of diabetes [3].

However, less is known about the epidemiology of kidney diseases in diabetic patients, which by itself is associated with an increased risk of mortality and morbidity [4]. Several elements account for this knowledge gap, including differences in defining kidney disease(s) in diabetic patients, differences in screening programs, and competitive mortality.

Furthermore, determining whether a death has been caused by diabetes or kidney diseases is not simple: at least in the Western world, where renal replacement therapy is available, diabetic patients rarely die of “kidney disease”. Within these limits, kidney disease is now considered one of the most important, if not the major cause of mortality and early morbidity in diabetic patients. In 2017 alone, 219,451 deaths globally were attributed to kidney disease in diabetic patients. These deaths accounted for approximately 34% of all deaths of men and 36% of women with kidney diseases. These proportions have increased since 1990, when the corresponding figures were 29% of all CKD-related deaths for men and 32% for women [5].

In a study of 15,046 diabetic patients conducted by the Kidney Research Institute of the University of Washington, CKD was present in 42.3% and 9.4% of individuals with and without type 2 diabetes, respectively. For subjects without diabetes and kidney disease (control group), the standardized cumulative all-cause mortality at 10 years was 7.7%. Standardized mortality was 11.5% for individuals with diabetes but without kidney disease (adjusted for demographics, smoking habits, blood pressure and dyslipidemia) but the combination of diabetes and CKD led to a standardized mortality rate of 31.1%, with an absolute risk difference of 23.4% compared to the control group [4].

While the definition of diabetic kidney diseases depends very largely upon the diagnostic parameters used, it is generally appreciated that 20–40% of patients with diabetes develop a clinically relevant nephropathy. These figures can be affected by different definitions (Table 1), but there is general agreement that diabetes is one of the leading causes of CKD and end-stage kidney disease worldwide. Within these limits, in recent decades the prevalence of T2DM has increased almost exponentially in patients who start renal replacement therapy [6][7].

Table 1. Definitions of diabetic and non-diabetic nephropathy in diabetic patients.

Definition	Comments
Diabetic nephropathy (DN)	Classic definition of a chronic kidney disease with a progressive increase in proteinuria and hypertension, up to end-stage kidney disease. Microvascular lesions coexist [8].
Diabetic kidney disease (DKD)	Presently the preferred definition of diabetic nephropathy. Although more widely used, it is commonly used as a synonym of DN or chronic kidney disease attributable to diabetes mellitus (as in this paper) [9].
Nephropathy in a diabetic patient	General term encompassing all types of CKD in a diabetic patient, including nephroangiosclerosis, obstructive nephropathy, etc.

The nomenclature of kidney diseases associated with diabetes has changed remarkably in recent years. Definitions based mainly on progressive increases in proteinuria have been challenged by the increase in clinical forms with no or scant proteinuria associated with typical histological diabetic lesions.

2. Frequency of “Non-Diabetic” Kidney Disease in Diabetic Patients

As this review will discuss in greater detail, data in the literature are highly heterogeneous depending on genetic background, the patient's environment and lifestyle, the organization and quality of diabetes care and, probably most importantly, the different indications for kidney biopsy (Table 2).

Table 2. Kidney biopsy indications in a diabetic patient and most likely histological findings other than diabetic nephropathy.

Main Indication for Kidney Biopsy	Major Expected Histological Findings
Isolated microscopic hematuria	• IgA nephropathy, especially in young patients of Asian and Mediterranean origin
Rapid onset of nephrotic syndrome	• Membranous nephropathy, especially in elderly patients • Monoclonal gammopathy-related nephropathies
Progressive onset of nephrotic syndrome	• Obesity related glomerulopathy (may be difficult to distinguish from DN) • Focal-segmental glomerulosclerosis in its secondary forms • Nephroangiosclerosis/vascular involvement
Rapidly progressive or stepwise reduction in kidney function with relevant proteinuria	• Rapidly progressive glomerulonephritis • Atheroembolic disease
Rapidly progressive or stepwise reduction in kidney function with scant proteinuria	• All forms of acute kidney injury • Vascular nephropathy • Interstitial nephropathy
Non-proteinuric chronic kidney disease	• Classic nephroangiosclerosis, in particular in hypertensive patients or in patients with a history of heavy smoking

Four examples from large studies exemplify this heterogeneity.

In a pivotal study in the United States, Sharma and colleagues evaluated the clinical and histopathological characteristics of patients with type 2 diabetes who had undergone a kidney biopsy between 2011 and 2013 [10]. Of the 2642 biopsies performed, 620 (23.5%) were in diabetic patients. Kidney disease was in stage 4 or 5 in roughly half of the cases. Interestingly, results were almost evenly divided between diabetic nephropathy (37%), non-diabetic kidney disease (36%) and a combination of the above (27%). In patients with isolated, non-diabetic kidney disease, the common diagnoses of proteinuric and acute kidney diseases were represented, as expected, including focal segmental glomerulosclerosis (22%), hypertensive nephrosclerosis (18%) and acute tubular necrosis (17%), followed by IgA nephropathy (11%), and membranous nephropathy (8%). Acute tubular necrosis was more frequent in concomitance with signs of diabetic nephropathy, suggesting that a rapid deterioration in kidney function was a frequent reason for performing a kidney biopsy and that the presence of diabetic lesions may favor acute tubular necrosis. This finding is of potential clinical relevance, since it is well acknowledged that episodes of acute tubular injury are associated with a higher risk of progression to end-stage renal disease, especially in diabetic patients [11][12][13][14].

Another large study analyzing 832 renal biopsies in T2DM patients in Spain reported somewhat different data (non-diabetic nephropathy in about 50% of cases, isolated diabetic nephropathy in 39.5%, and a mixed picture in 10.8%). While all the main proteinuric nephropathies are represented, the low prevalence of acute tubular necrosis (under 5%) is evidence of different biopsy criteria [15].

A recent meta-analysis gathering data on 4876 type 2 diabetic patients with a kidney biopsy reported a very wide range of prevalence of non-diabetic lesions (up to 82.9%) [16]. IgA nephropathy was the most frequent non-diabetic histological diagnosis found in recent studies, in particular those done in Asia, although similar findings have been described in Europe [17][18][19][20].

In a retrospective series from Thailand, Kritmetapak retrospectively analyzed the data of patients with type 2 diabetes who had undergone renal biopsy between 2011 and 2015; it was found that the most frequent indication for renal biopsy was a recent and rapid onset of nephrotic syndrome (41%), followed by a rapidly progressive and unexplained decline in renal function (29%) and the presence of an active urinary sediment (21%) [17]. In this setting, isolated diabetic nephropathy was diagnosed in about half of the cases (51%), while non-diabetic kidney disease (20%) and a combination of the above (29%) accounted for the other half. Besides reporting that the kidney biopsy was prescribed at higher levels of proteinuria in cases later found to have a diabetic nephropathy, the study highlights the importance of urinary sediment analysis, which is reported as more active in patients with non-diabetic or combined kidney diseases.

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