End-stage renal disease epidemic in diabetics: is there light at the end of the tunnel?

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The world is facing an epidemic of diabetes, especially type 2 diabetes, which appears likely to endure for decades to come. Worldwide prevalence of diabetes was estimated at 2.8% in 2000. Between 2000 and 2030, the number of adults with diabetes is expected to increase by 50–70% in developing countries and by 20% in developed countries [1, 2]. In 2030, the prevalence of diabetes is projected to be 4.4% of the world population. The most important change in this prevalence appears to be an increase in the proportion of patients older than 65 years.

This change is related to the aging of the population, especially in developed countries [1, 2], and to the burden of obesity [3] that affects the prevalence of type 2 diabetes so strongly. Unfortunately, similar trends are also observed in...
children for type 1 diabetes [4]: the number of new cases of type 1 diabetes in European children younger than 5 years is predicted to double between 2005 and 2020, and the prevalent cases younger than 15 years will rise by 70%.

However, recent data in the general population show that better primary and secondary prevention appear to be driving a trend towards decreased cardiovascular events and increased life expectancy for patients with diabetes [5]. It could, therefore, be expected that a decrease in this competing risk (early cardiovascular death) will lead to an increase in the incidence rate of end-stage renal disease (ESRD) among diabetic patients. Indeed, previous studies have observed that despite a small downward trend in all-cause ESRD incidence, the incidence of type 2 diabetic ESRD is still increasing [6, 7].

Yet, in this issue of Nephrology Dialysis Transplantation, Comas et al. offers a glimmer of hope to the nephrology community. In Catalonia, the incidence rate of ESRD due to diabetes among the general population of people with diabetes mellitus decreased from 645.6 p.m.p. in 2002 to 600 p.m.p. in 2010. This result confirms other recent data reports. In Finland, Finne et al. [8] found a lower risk of ESRD in patients diagnosed with type 1 diabetes more recently. In the USA, Burrows et al. [9] showed that from 1996 to 2006 the overall incidence of ESRD due to diabetes as the primary renal disease decreased at an average rate of 2.9% per year among the US diabetes population. Using data from the Australia and New Zealand Dialysis and Transplant Registry, Grace et al. [10] have also shown that age-specific incidence rates in most groups have stabilized in the past 2–5 years.

A variety of factors may explain the paradox of a decrease in the incidence of ESRD due to diabetes at the same time as diabetes prevalence is increasing in the general population.

First of all, it is the incidence rates that are decreasing. The number of patients with diabetes who reach ESRD is continuing to increase [11], or, from a more optimistic perspective, beginning to stabilize [10, 12]. In other words, the number of diabetic ESRD patients is increasing more slowly than the number of diabetic patients in the general population, a result that will lead to a decrease in the ESRD incidence rate over time in the diabetic population. This difference in trends between the general and ESRD populations may indicate improvements in the care of diabetic patients under treatment with renin–angiotensin system inhibitors and the aggressive glycemic control available since 1980 [13]. Nevertheless, studies of care for patients with chronic kidney disease at early stages underline that improvement is still necessary for patients with type 2 diabetes and hypertension [14, 15].

Second, some sources of bias may also need to be identified, taken into account and reduced.

If effective prevention slows down disease progression, diabetic patients may reach ESRD at a later age. The decrease in incidence might, therefore, be related to a higher proportion of patients who choose not to be treated or who are not referred to a dialysis unit. Renal replacement therapy registries do not provide estimates of these groups of patients.

Epidemiological studies based on diabetes as the primary renal disease must be interpreted with caution [16, 17]. Renal biopsies are performed in fewer than 10–20% [12, 18] of these patients; nephrologists determine the primary nephropathy by clinical evaluation. In European countries, about 30–40% of incident ESRD patients have diabetes as an associated comorbidity, but only 20% have a diagnosis of diabetic nephropathy [12, 19–21]. One-third of type 2 diabetic patients with proteinuria have histological involvement unrelated to diabetic nephropathy, and multiple diseases are possible [22]. In particular, diabetic nephropathy and hypertensive changes are likely to coexist. In the absence of a renal biopsy, the use of the primary renal disease to identify diabetic patients may result in underestimating the total number of ESRD cases among diabetic patients, as a proportion is likely to be reported as non-diabetic. Variations among nephrologists on reporting this primary renal disease can vary from a conservative approach (diabetic nephropathy only with a renal biopsy or strong evidence such as a high level of proteinuria or associated diabetic retinopathy) to a simplistic approach (coding diabetic nephropathy when diabetes is present). A decline in disease-specific incidence of diabetes-related ESRD among diabetic patients might reflect changes in diagnostic attribution over time rather than a true change in the rate of progression to diabetic nephropathy. Moreover, great variations may exist among countries: diabetes was reported as a primary renal disease in only 56% of incident ESRD patients with associated type 2 diabetes in the French Renal Epidemiology and Information Network (REIN) Registry in 2010 [12], but also in 74.1% of such patients in the Australia and New Zealand Dialysis and Transplant (ANZDATA) Registry in 1991–2005 [23]. A trend towards a more specific approach in coding the underlying nephropathy may also play a role in explaining the decreased incidence rate of diabetes-related ESRD over time.

Further support for the results of Comas et al. could usefully come from studies that take into account the type of diabetes, the trends in the underlying general population and the evaluation of preventive care in the diabetic population. The differences in patient characteristics by type of diabetes and relative changes in the incidence and prevalence of diabetes in the general population and in the incidence of ESRD associated with diabetes are not likely to vary consistently between type 1 and type 2 diabetic patients over time. It is, therefore, important that epidemiology studies in ESRD populations include consideration of diabetes both as a cause of renal disease and as an associated condition or co-morbidity and that type 1 and type 2 diabetic patients be distinguished, in view of their different aetiology, management options and prognosis [23].

In comparing temporal trends, it is interesting to stratify the number of new patients with respect to demographic variation in the general population on the one hand and differences in exposure to risk factors on the other. For example, in France, between 2007 and 2011, the number of incident patients with diabetes type 2 increased by 20.9% compared with 6.7% in non-diabetic patients. Figure 1 shows the different components of the difference. In diabetic type 2 patients, an increase of 3.3% can be attributed to the aging of the general population, 2.2% to the increase in the population size and 15.4% to residual effects related to the disease. In non-diabetic patients, an increase of 3.1% can be attributed to the aging of the general population, 2.0% to the increased
population size and only 1.6% to the residual disease-related effect. This difference in the residual effect confirms the persistent impact of diabetes on ESRD incidence.

In conclusion, the reassuring results reported by Comas et al. must now be confirmed in other European populations. Epidemiologic studies are needed to improve our understanding of the decrease in ESRD in the diabetic population. After the decrease of cardiovascular mortality in patients with diabetes and ESRD is confirmed, correlation studies would be useful to evaluate the diffusion of preventive treatments such as renin–angiotensin system inhibitors.

CONFLICT OF INTEREST STATEMENT

None declared.


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FIGURE 1: Change in the number of treated ESRD patients, since 2007, in 18 French regions that contributed to the REIN registry over 2007–2011 (method from Bashir and Esteve [24]).

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Detection and progression of chronic kidney disease: does the rear-view mirror help?

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Fuelled by the pandemic of obesity and Type 2 diabetes mellitus, the prevalence of chronic kidney disease (CKD) is a major global health burden. Its prevalence in many continents already affects over 10% of the adult population. Between Europe and the United States, approximately 1 million patients currently require renal replacement therapy (RRT), including dialysis and transplantation. By 2030, it is estimated this figure will exceed 2 million [1–3]. These figures are disconcerting: the cost of managing end-stage renal disease (ESRD) and its attendant co-morbidities even today engulfs a disproportionate percentage of the health dollar and, if the above estimates are even partly correct, it is a cost which will soar in forthcoming years. However, the cost of renal disease does not commence simply when the patient reaches end-stage. With the number of pre-end-stage CKD patients estimated at >30-fold those requiring RRT, the overall drain on economic and health resources is exceptionally high, even—perhaps particularly—for those who do not eventually reach ESRD [4].

Both the numbers and costs highlight a pressing need to successfully screen and identify patients with CKD, and to define those most at risk of progression. The first, to interpret national and global health patterns as they evolve; and the second, to effect a delay in functional renal deterioration. The overwhelming challenge even for developed societies is that the numbers defy traditional attempts at targeted appraisal and intervention. However, the task is not hopeless. Several recent studies suggest that if CKD can be identified, it might be possible to slow or even prevent a fall in renal function, at least for a limited time in targeted populations exposed to intense, often novel, models of care [5–7].

Effective screening ideally requires simple, precise and affordable markers. Those that currently define CKD are the estimated glomerular filtration rate (eGFR), based on the serum creatinine and, in the initial stages, urinary protein. It is likely that future prevalence studies will incorporate proteinuria more widely as it is a strong and independent predictor of progressive functional decline [8, 9]. Nevertheless, neither its definition nor its method of detection is free from controversy. The commonly-used reagent strip or ‘dipstick’ analysis is subject to the substantial error: the reagent pads are variably sensitive (according to the manufacturer) and individual