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Diabetic Kidney Disease: A New Concept for an Old Problem

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Abstract

Diabetes Mellitus (DM) is a growing worldwide epidemic. It was estimated that more than 366 million people would be affected. DM has spread its presence over the world due to lifestyle changes, increasing obesity and ethnicities, among others. Diabetic nephropathy (DN) is one of the most important DM complications. A changing concept has been introduced from the classical DN to diabetic chronic kidney disease (DCKD), taking into account that histological kidney lesions may vary from the nodular or diffuse glomerulosclerosis to tubulointerstitial and/or vascular lesions. Recent data showed how primary and secondary prevention were the key to reduce cardiovascular episodes and improve life expectancy in diabetic patients. A stabilization in the rate of end stage kidney disease has been observed in some countries, probably due to the increased awareness by primary care physicians about the prognostic importance of chronic kidney disease (CKD), better control of blood pressure and glycaemia and the implementation of protocols and clinical practice recommendations about the detection, prevention and treatment of CKD in a coordinated and multidisciplinary management of the DM patient. And also the new hypoglycemic agents, - DDP4 inhibitors, GLP1R agonists, SLGT2 inhibitors-, can facilitate the management of DM and its complications in the patients with renal function impairment. Early detection of DM and DCKD is crucial to reduce morbidity, mortality and the social and economic impact of DM burden in this population.

Keywords: Diabetes mellitus; Epidemiology; Diabetic nephropathy; Diabetic kidney disease; End-stage renal disease; Multidisciplinary management

Diabetes Mellitus Epidemiology has changed in the Last Years

Diabetes Mellitus (DM) is a growing worldwide epidemic. The World Health Report in 1997 projected a continuous growth in the prevalence of DM for the next 20 years [1].

Many studies demonstrate rising prevalence of diabetes worldwide over the past decades. In 2004, Wild *et al*. estimated an increase in the global prevalence of DM from 2.8% in 2000 to 4.4% in 2030 in the world, taking into account the high percentage of undiagnosed diabetes.

That means more than 366 million people would be affected by this systemic metabolic disorder [2].

The number of diabetic American adults treated rose more than two fold between 1996 and 2007 (from about 9 million to 19 million). By age groups, the number of diabetic patients increased from 4.3 million among people aged 65 and older; 3.6 million to 8.9 million among adults aged 45 to 64 and 1.2 million to 2.4 million among people aged 18 to 44, as was reported by the Agency for Healthcare Research and Quality [3]. The total cost of DM climbed from $18.5 billion to nearly $41 billion during that time, according to the National Medical Expenditure Panel Survey.

In the year 2008, The Lancet published the global challenge of Diabetes [4]. Danaej, et al. estimated trends in mean fasting plasma glucose (FPG) and DM prevalence for adults aged 25 years and older in 199 countries and territories [5]. The authors obtained data from health examination surveys and epidemiological studies (370 country-years and 2.7 million participants). For each sex, they used a Bayesian hierarchical model to estimate mean FPG and its uncertainty. In 2008, global age-standardized mean FPG was 5.5 mmol/L for men and 5.42 mmol/L for women, having risen by 0.07 mmol/L and 0.09 mmol/L per decade, respectively. Age-standardized adult diabetes prevalence was 9.8 % in men and 9.2 % in women in 2008, up from 8.3 % and 7.5 % in 1980. The number of people with diabetes increased from 153 million in 1980, to 347 million in 2008. They recorded almost no change in mean FPG in East and Southeast Asia and Central and Eastern Europe. Oceania had the largest rise, and the highest mean FPG (6.09 mmol/L, for men; 6.08 mmol/L, for women) and diabetes prevalence (15.5 %, for men; and 15.9 %, for women) in 2008. Mean FPG and diabetes prevalence in 2008 were also high in South Asia, Latin America and the Caribbean, and central Asia, North Africa, and the Middle East. Mean FPG in 2008 was lowest in sub-Saharan Africa, East and Southeast Asia, and high-income Asia-Pacific. In high-income subregions, Western Europe had the smallest rise, 0.07 mmol/L per decade for men and 0.03 mmol/L per decade for women; North America had the largest rise, 0.18 mmol/L per decade for men and 0.14 mmol/L per decade for women. The conclusions of this study were that glycaemia and diabetes are rising globally, driven both by population growth and ageing and by increasing age-specific prevalence [5].

The study of Abraham *et al*. analyzed trends in diabetes incidence over the previous four decades in USA and confirmed that the risk of new-onset diabetes continued to be higher in the 2000s compared with the 1970s [6]. With regards to Spain data, Soriguer, et al. published the Di@bet.es Study in 2011 [7]. In this population-based, cross-sectional, cluster sampling study, targeting the whole Spanish population. Five thousand and seventy-two patients participated in 100 clusters (health centers or the equivalent in each region). The patients were randomly selected with a probability proportional to population size. Participation rate was 55.8%. Study variables were a clinical and demographic structured survey, lifestyle survey, physical examination (weight, height, BMI, waist and hip circumference, blood pressure) and oral glucose tolerant test (OGTT). Almost 30% of the study population had some carbohydrate disturbance. The overall prevalence of diabetes mellitus adjusted for age and sex was 13.8% (95% CI 12.8, 14.7%), almost half of them had unknown diabetes, 6.0% (95% CI 5.4, 6.7%). The age- and sex-adjusted prevalence rates of isolated impaired fasting glucose (IFG), isolated impaired glucose tolerance (IGT) and combined IFG-IGT were 3.4% (95% CI 2.9, 4.0%), 9.2% (95% CI 8.2, 10.2%) and 2.2% (95% CI 1.7, 2.7%), respectively. The prevalence of diabetes and impaired glucose regulation increased significantly with age ($p < 0.0001$), and was higher in men than women ($p < 0.001$).

In 2012, Polonsky KS depicted a spectrum of diabetes quite different from the classical concept of DM. At that time, DM accounted for about 10% of cases, age-adjusted 6.9% of the U.S. population in 2010 [8]. Following recent data, DM patients increased from 5.6 million to 20.9 million in the general population. Nearly 27% of people over 65 years of age had DM. If the current trend continues, one in three U.S. adults could have DM in 2050 [9].

If we take all these data into account, it seems evident that DM and, specially, type 2 DM, has spread its presence over the world. The factors involved in these changes may be lifestyle changes, increasing obesity and ethnicities, among others.

In 2008, we reported the clinical and social impact of the DM and its complications in Spain, [10]. Mata, et al. estimated the global cost of DM on €2.132 per patient-year, when micro and macrovascular complications were present [11]. Lorenzo, et al. in the Canary islands in Spain—an autonomous community with a high rate of ESRD due to diabetes—, estimated that reducing the rate of ERC-5 due to diabetes in this community may lead to a decrease of 15 to 25 million € in a three year period [12].

Diabetic Nephropathy Concept may be understood as a General Concept of Diabetic Kidney Disease

Until recent years, diabetic nephropathy was defined by the evidence of a renal disturbance which is characterized by the presence of proteinuria, equal or more than 300 mg/day, in a diabetic patient. Usually, this clinical situation was accompanied by diabetic retinopathy and hypertension, leading to a progressive deterioration in the kidney function. Nevertheless, the absence of diabetic retinopathy does not exclude the diagnosis of DN. The natural history of diabetic renal disease differs between type 1 and type 2 DM. The five classical stages described in type 1 DM [13,14], may not occur in type 2 DM [15,16], because sometimes type-2 DM is diagnosed after other connected disorders as hypertension. The development of microalbuminuria and the progression to overt proteinuria are the most common clinical features. However, in contrast to the predictions of the classical model for kidney disease involvement, a considerable percentage of patients with diabetes and impaired renal filtration do not have substantially elevated urinary protein excretion rates. Many studies in recent years are describing the loss of renal function or a decline in the estimated Glomerular Filtration Rate (eGFR) in the absence of albuminuria. This fact is described as the possible existence of a non-proteinuric phenotype in DM patients [17].

Tervaert, et al. reported in 2010 a new pathology classification of the diabetic kidney lesions where the authors insisted on the existence of some forms of kidney damage with primary involvement of tubules, interstitium and/or the vessels, far away from the classical nodular or global glomerulosclerosis [18].

All these new findings lead to a change in diabetic nephropathy concept, shifting from the classical one “diabetic nephropathy” to the new one “diabetic kidney disease” (DKD).

Interestingly, O´Shaughnessy, et al. [19], in a recent review on the kidney biopsies performed in some south states of the USA, claimed the attention on the increment of diabetic glomerulosclerosis in the kidney biopsies performed in the last 30 years. That reinforce the concept that we need to pay attention to performe kidney biopsies in diabetic patients with the diagnostic suspiction of an associated non-diabetic glomerular disease or in the presence of alarm signs, - non-urologic haematuria, fast increase of proteinuria or fast decline of GFR-, in the patient with DM.

End-stage Renal Disease (ESRD) in Diabetic Patients: Has the Presence of DKD Changed in Parallel to the DM Development?

Recent data showed how primary and secondary prevention were the key to reduce CV episodes and improve life expectancy in diabetic patients [20]. Does the decrease in this competing risk lead to an increase in the rate of end stage kidney disease? The answer is probably no. In 2005, we estimated around 33,000 type 1 and 405,000 type 2 diabetic patients with some form of DN, from microalbuminuria to ERSD in Spain [21].

Data from the Spanish Society of Nephrology (S.E.N.), recorded in the annual renal registry, also showed a stabilization of DM as a cause of CKD requiring renal replacement therapy (RRT) in the last four years (incidence: 24.97% in 2011, 23,1 % in 2015). Although DM continuous to be the first cause of ESRD in Spain—as in the whole world-we have observed a clear stabilization of ESRD due to DM compared to other causes of CKD-5 [22,23].

Such findings were confirmed in recent studies. The ESRD report in U.S.A. showed a stabilization of the percentage of ESRD in almost 190 p.m.p., from 2002 to 2003 [24]. Besides, Burrows, et al. reported 2.9% annual decrease in overall incidence of ESRD due to DM, from 1996 to 2006 [25]. When considering the data from Australia and New Zealand Dialysis and Transplant (ANZDATA) Registry Grace, et al. also described the stabilization in age-specific incidence rates in most groups during the past 5 years [26].

Many factors may explain this paradox, a decrease in ESRD secondary to diabetic nephropathy and an increase in the rates of DM in the general population concurrently. An earlier diagnosis and better management of this pathology based on a multidisciplinary approach of the different professionals involved may be an explanation. The earlier and better control of CKD progression risk factors as well as the widespread utilization of renin-angiotensin-aldosterone blockers (RAAB) plays a decisive role.

In addition to that, other factors have probably influenced the decline in the incidence in both diabetic nephropathy and ESRD of the other etiologies. These

factors include the increased awareness by primary care physicians about the prognostic importance of CKD and its consequences.

It is noteworthy that a better control of risk factors for DKD progression has been achieved by primary care doctors in the last decade, especially regarding blood pressure and glycaemic control [27]. And also the scientific societies have played an important role in the dissemination of protocols and clinical practice recommendations about the detection, prevention and treatment of chronic kidney disease and DKD which undoubtedly have influenced the stabilization of the incidence [28-31].

The stratification of new incident patients according to demographic variations is another interesting point to take into account. Increasing age, population size and residual disease-related effect are factors connected to ESRD incidence in DM [32].

The Treatment with the Novel Hypoglycemic Agents in Patients with DKD

An elevated risk for hypoglycemia is a key point for the management of the DM patients with impaired renal function. New drugs for the management of hyperglycaemia have appeared and facilitate the more sure management in our patients. The dipeptidyl-peptidase-4 inhibitors (DPP4i) have dramatically changed the management of type 2 DM patients and, especially, the management of those patients with an estimated GFR below 60 mL/min/1,73 m2. And also in some studies, TECOS SAVOR-TIMI sitagliptin and saxagliptin have demonstrated to be able to reduce the CV risk in type-2 DM patients [33,34].

Very recently the introduction of the Sodium-Glucose co-transporter 2 inhibitors, - cana, empa and dapaglyflozin-, has shown to be effective for the management of DM. The EMPA-REG OUTCOME study the renal EMPA-REG OUTCOME study or the CANVAS program results have shown important decrease in the vascular risk of the DM patients, as well as beneficial effect on the development of new incident nephropathy or in the progression from micro to macroalbuminuria or the decline of eGFR, as was the case in the Renal EMPA-REG OUTCOME study [35-37].

And also other incretin drugs with agonist GLP1 Receptor effects, as liraglutide or semaglutide have demonstrated to be able to reduce the CV risk in diabetic patients as well as also beneficial effects on microalbuminuria [38,39].

Conclusions and Implications

Despite the growing DM population, a slowdown in DKD progression seems to be evident. Early detection of both DM and DKD are crucial to reduce complications, morbidity and mortality as well as the social and economic impact of DM burden in this population. The early application of these recommendations may also lead to improve the survival of these patients once they are under RRT.

The new hypoglycemia drugs offer the possibility to optimize the global management of the DM patient, decreasing the CV risk and facilitating the management of glucose metabolism in these patients. Many questions do not have still enough evidence, - as is the safety administration of some of these new drugs in the patient with an eGFR less than 30 mL/min/1,73 m2-, the increase number of ketoacidosis episodes or fractures in high-risk DM patients or some other adverse events, but we will probably obtain some new evidences in the next future.

There is still a long way towards improvement, but the observed trend probably reflects that an earlier application of preventive measures and treatment and, very importantly, a coordinated and multidisciplinary management of the patient with DM, with an earlier implementation of guidelines and clinical recommendations, are the key for the equity in the access to the therapeutic options that may have a positive impact on patients' outcomes.

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