nefrología
Revista de la Sociedad Española de Nefrología
www.revistanefrologia.com

Editorial

ERBP guideline on management of patients with diabetes and chronic kidney disease stage 3B or higher. Metformin for all?☆

Guía ERBP sobre la diabetes en la enfermedad renal crónica estadio 3B o mayor: ¿metformina para todos?

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The epidemiology of diabetes mellitus has changed in recent years

Diabetes mellitus (DM) has been a growing epidemic in recent decades. This demonstrates that the predictions of the World Health Report in 1997, which estimated a progressive growth of the disease over the following 20 years,[1] were accurate. In 2012, the prevalence of diabetes in the US was 14% (9% with known diagnosis), but a particularly remarkable and alarming piece of information is that 38% of the population was in a pre-diabetes status.[2] If this trend continues, one in three adults in the US will be diabetic in 2050.[3] The increased prevalence of DM has occurred especially at the expense of DM type 2 (DM-2), due to changes in lifestyle and an increase in obesity.[4] In the US, the cost of the DM in 2012 amounted to $245 billion, including the impact derived from lack of productivity of patients with complications. Fortunately, although from 1990 to 2010 the diabetic population in the US grew by 27%, the percentage of complications related to DM decreased: amputations, from 22.6% to 18.8%; end-stage chronic renal failure, from 13.7% to 6.1%; myocardial infarction, from 3.8% to 1.8%; and stroke, from 3.1% to 1.5%,[5] probably due to improved diagnosis and care of both DM and its complications.

The globalisation of DM is a global health problem, with increases in its incidence and prevalence, including gestational diabetes and DM type MODY (Maturity Onset Diabetes of the Young).[6,7] In Spain, the Di@bet.es study, conducted in 100 centres with a wide geographical distribution, found a glucose metabolism disorder in approximately 30% of the

DOI of original article:
http://dx.doi.org/10.1016/j.nefro.2017.06.001.

☆ Please cite this article as: Martínez-Castelao A, Górriz JL, Ortiz A, Navarro-González JF. Guía ERBP sobre la diabetes en la enfermedad renal crónica estadio 3B o mayor: ¿metformina para todos? Nefrología. 2017;37:567–571.

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population studied.[8] The prevalence of DM, adjusted for age and gender, was 13.8% (95% CI: 12.8–14.7%), and a 6% (95% CI: 5.4–6.7%) of the population was unaware of the fact they were diabetic. The socio-economic impact of DM and its complications in Spain is significant, with an overall estimated cost of €2132/patient/year in the presence of micro- and macrovascular complications.[9] A reduction in stage 5 chronic kidney disease (CKD-5) could represent savings of 15–25 million euros over three years in the Canary Islands.[10]

A more recent concept: from "diabetic nephropathy" to "diabetic kidney disease"

Until recently, diabetic nephropathy was defined as the presence of proteinuria greater than or equal to 500 mg/day in a patient diagnosed with DM. It is generally accompanied by retinopathy, hypertension and progression to advanced kidney failure. The natural history of kidney disease differs between DM-1 and DM-2.[11] DM-2 is diagnosed in some cases after onsent of hypertension or kidney failure itself, with an overlap of DM and nephrosclerosis lesions being present in the majority of cases. This makes it difficult to establish the actual time of onset of DM-2.

The presence of albuminuria and progression to proteinuria were the most common forms of clinical expression of kidney disease. However, in recent years, progression to kidney failure without developing proteinuria has been increasingly reported.[12] This therefore suggests the existence of a "non-proteinuric phenotype".[13] In 2010, Tervaert et al.[14] proposed a new histopathological classification of the renal lesions in DM, with emphasis on the finding of tubulointerstitial and/or vascular lesions in the absence of glomerular lesions as an initial form of renal impairment (Table 1). This leads to a switch from the traditional concept of diabetic nephropathy towards a more generic concept of diabetic kidney disease.[4]

Table 1 – Histopathological classification of kidney disease in diabetes mellitus.

	Description
Classes of glomerular lesions	
Class I	Thickening of the glomerular basement membrane
Class II	Mesangial expansion, moderate (IIa) or severe (IIb)
Class III	Nodular sclerosis (Kimmelstiel-Wilson)
Class IV	Advanced diabetic glomerulosclerosis
Tubulointerstitial lesions	Scores
IFTA	
No	0
<25%	1
25–50%	2
>50%	3
Inflammation	
Not related to IFTA	0
Areas without IFTA	1
Areas with IFTA	2
Vascular lesions	
Arteriolar hyalinosis	
No	0
1 area	1
>1 area	2
In large vessels	
Arteriosclerosis	
No	0
Intimal thickening lower than in mean	1
Intimal thickening greater than in mean	2
Non-diabetic glomerular lesions	

Adapted from Tervaert et al.[14]
IFTA: interstitial fibrosis and tubular atrophy.

Advanced kidney failure in diabetes mellitus: has the incidence of diabetic kidney disease increased in parallel to the increase in diabetes mellitus?

In 2005, with data extrapolated from the studies conducted until that year, we estimated that in Spain there could be around 33,000 patients with DM-1 and approximately 405,000 with DM-2 who could be suffering from varying degrees of kidney disease, ranging from microalbuminuria to CKD-5.[15] More recent data from registries of the Spanish Society of Nephrology and the Spanish National Transplant Organisation show that, although DM remains the leading cause of CKD-5 requiring renal replacement therapy (RRT), the percentage of patients with incidents requiring this therapy and whose primary cause of kidney failure is DM has stabilised over the last five years. Thus, data on the annual incidence from 2011 to 2015 ranged from 24 to 25%.[16] It therefore seems that a stabilisation of DM as a cause of CKD-5 is observed.

These data are confirmed in other studies, such as the End-Stage Renal Disease record in the US, which shows a stabilisation in the incidence of diabetic CKD-5 in 150 patients/pmp from 2002 to 2003,[17] and even a reduction in the period 1996–2006.[18] Moreover, the Australian and New Zealand registries of Dialysis and Transplant showed a similar stabilisation by age groups over the last five years.[19]

The apparent paradox of no increase in end-stage kidney failure caused by diabetes with growing rates of incidence and prevalence for DM may be due to the earlier diagnosis of DM and the improved control of progression factors of kidney disease associated with multidisciplinary and multifactorial intervention. The involvement of primary care physicians and physicians from other specialties, as well as consensus documents, both for DM and kidney disease in 1997 and 2002,[20,21] and for CKD in 2008 and 2014,[22,23] may have played a decisive role in our specialism. Likewise, the consensus document for the management of DM-2 in patients with CKD specified the most crucial aspects for the shared management of patients with DM and CKD.[24] In this regard, adequate control of the risk factors for progression of kidney disease, especially hypertension and glucose metabolism, are essential. In addition, greater precision in the coding of associated diseases, and of

histological data in renal biopsies, helps to reduce bias when considering the primary cause of kidney disease.

The European Renal Best Practice guideline on diabetes mellitus in advanced chronic kidney disease

The role played by scientific societies in the creation and implementation of consensus documents and clinical practice guidelines for the detection, prevention and comprehensive treatment of patients with DM and CKD is fundamental. Professionals are aware that the clinical management of patients with DM who have developed kidney failure is complex. One of these factors includes the fact that it is difficult to achieve good glycaemic control. There are currently numerous therapeutic groups for appropriate metabolic control, and we have to bear in mind that many of the drugs are excreted via the kidneys. The importance of preventing or minimising hypoglycaemic episodes is key to reducing cardiovascular morbidity and mortality.

The American Diabetes Association publishes Clinical Practice Recommendations annually, in which the appropriate advice is presented on the basis of evidence that is being generated in the management of DM. In this issue of *Nefrología* [*Nephrology*] the adaptation into Spanish of the summarised version of the '*Clinical Practice Guideline on Management of patients with diabetes and chronic kidney disease stage 3B or higher (<45 ml/min)*' of the European Renal Best Practice (ERBP) guideline is published.[24,25] The guideline contains recommendations based on the grade (1, strong; or 2, weak) and the quality of evidence (A, high; B, moderate; C, low; or D, very low). It contains three pivotal chapters, which cover aspects related to the management of glycaemic control, the management of cardiovascular risk factors and ischaemic heart disease, and the choice of the RRT. It is worth highlighting the importance attached to the management of the appropriate target HbA1c to prevent episodes of hypoglycaemia, the recommendation of dose changes according to the pharmacological group depending on the stage of CKD, as well as the impact of the different agents on mortality, cardiovascular events, risk of hypoglycaemia, changes in HbA1c and dose adaptation in advanced CKD.

As it generally occurs with this type of document, the original guideline was published in July 2015,[26] with new drugs and evidence for shared management of patients with DM and kidney failure having subsequently emerged. This includes the recent results of the EMPA-REG OUTCOME trial,[27] which randomised patients with DM-2 with estimated glomerular filtration rate (eGFR) > 30 ml/min/1.73 m^2 to empagliflozin, a sodium-glucose co-transporter 2 inhibitor, or placebo added to standard treatment, and, therefore, the results would be applicable to the target population of the ERBP guideline. Unexpectedly, empagliflozin had clear benefits on cardiovascular events and survival, and it is highly possible that this will have repercussions in the near future in forthcoming clinical guidelines and in clinical practice.

More recently, Wanner et al.[28] published the results of the EMPA-REG Renal study, with data from patients in the same clinical trial. Empagliflozin delayed the progression of kidney damage and reduced the deterioration of the eGFR. Specifically, it showed a significant decrease of 46% in the relative risk for the combined endpoint of doubling of serum creatinine, starting RRT or death due to kidney failure. One of the most important factors that has been put forward as a mechanism to explain these renal benefits is the likely relationship with the decrease in glomerular hyperfiltration. The haemodynamic effect is possibly the key to explaining the benefit of empagliflozin in patients with DM-2, deterioration in kidney function and increased cardiovascular risk.

One novel aspect of the guideline is the emphasis on the use of metformin as an antidiabetic agent of choice in all stages of CKD. The guideline recommends its use, with dose adjustment, even in eGFR of 15 ml/min/1.73 m^2 and does not contraindicate it in patients on dialysis or with eGFR < 15 ml/min/1.73 m^2. The main argument is that the benefits of metformin outweigh the risks of lactic acidosis, especially if the dose is adjusted to kidney function and the patient is instructed about the risk factors. In this regard, the guideline is perhaps the most extreme manifestation of a global trend towards the use of metformin in advanced stages of CKD. The American Diabetes Association, in turn, suggests that there is observational data suggesting that metformin can be used safely with up to an eGFR of 30–45 ml/min/1.73 m^2, with dose adjustment, but it maintains CKD as a contraindication.[29] The European Medicines Agency announced in January 2016 that it was reviewing the safety and efficacy of metformin in CKD as requested by the Dutch agency, which suggested that there were significant differences among countries in the contraindications to metformin according to the eGFR and that the more stringent restrictions may not be justified.[30] The US Food and Drug Administration issued a safety communication in April 2016 indicating that it had reviewed the instructions on the use of metformin in kidney failure in order to extend its use to patients with lower eGFR.[31] The new labelling advises estimating the GFR before prescribing metformin and then periodically contraindicating the drug when the eGFR < 30 ml/min/1.73 m^2, and does not recommend starting it when the eGFR is 30–45 ml/min/1.73 m^2. If the patient was already taking metformin, and the eGFR falls below 45 ml/min/1.73 m^2, the risk/benefit ratio has to be reassessed, and if it falls below 30 ml/min/1.73 m^2, the drug should be discontinued.

Conclusions and implications for the current management of diabetic kidney disease

Despite the increase of DM in the general population, there appears to be a stabilisation in DM as an underlying cause of advanced CKD requiring RRT. Early detection, both of DM and its complications, including diabetic kidney disease, is crucial in order to reduce morbidity, especially of cardiovascular origin, and mortality, and to mitigate the serious socio-economic impact of the disease. It is also vital to reduce complications once the patient with DM has started RRT. Comprehensive multifactorial and multidisciplinary management is essential, as is being aware of and implementing the consensus documents and clinical practice guidelines, that

are amended on the basis of the evidence generated. The ERBP guideline on DM and advanced CKD represents a new step in this process of continuous improvement. However, it will be necessary to assess the impact of the recommendation to extend the indication of metformin to more advanced stages of kidney failure while it continues to be formally contraindicated by regulatory agencies, and it is possible that updates may be required in the short-term, particularly with regard to the use of sodium-glucose co-transporter 2 inhibitors.

Acknowledgements

AMC, JLG and JFNG are coordinators of the Diabetic Nephropathy Working Group (GEENDIAB) of the Spanish Society of Nephrology. All authors belong to the Kidney Disease Research Network (REDinREN) of the *Instituto de Salud Carlos III* [Carlos III Health Institute] (ISCIII): RETIC REDINREN RD16/0009/0001(AO) and RD16/0009/0022 (AMC, JLGT and JFNG). Research activity by AO and JFNG is funded by the *Programa de Intensificación de la Actividad Investigadora* [Intensification Programme of Research Activity] (ISCIII).

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