

New developments in diabetic nephropathy

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INTRODUCTION

Diabetes mellitus is now a health problem currently affecting 140 million people worldwide. Estimates put that figure at around 300 million by 2025¹. Diabetic nephropathy is one of the most serious complications of diabetes mellitus and is the leading cause of end stage renal disease both in the USA² and in Europe³. In Spain, diabetic nephropathy is also the leading cause of end stage renal disease⁴. Between 25-40% of patients show some degree of diabetic nephropathy as their disease progresses. The earliest clinical evidence of nephropathy in diabetes mellitus is the development of urinary albumin/creatinine ratio (ACR) above the level considered normal >30 mg/g, known as albuminuria or microalbuminuria. This indicates the presence of incipient nephropathy. If no measures are taken at this stage, it can progress to established nephropathy as manifested by urinary excretion of ACR greater than 300 mg/g or 300 mg/24 hours. This progression can be accompanied by a reduction in the glomerular filtration rate, and it can lead to end stage renal disease.

Early detection allows for early intervention in the diagnosis and treatment, preventing the progression of renal disease and cardiovascular prognosis.

We reviewed the literature published on diabetic nephropathy in the last three years. We discuss the newest features that have appeared in the field of diabetic nephropathy. The bibliography contains 34 references that have been published in the last three years on new developments in diabetic nephropathy.

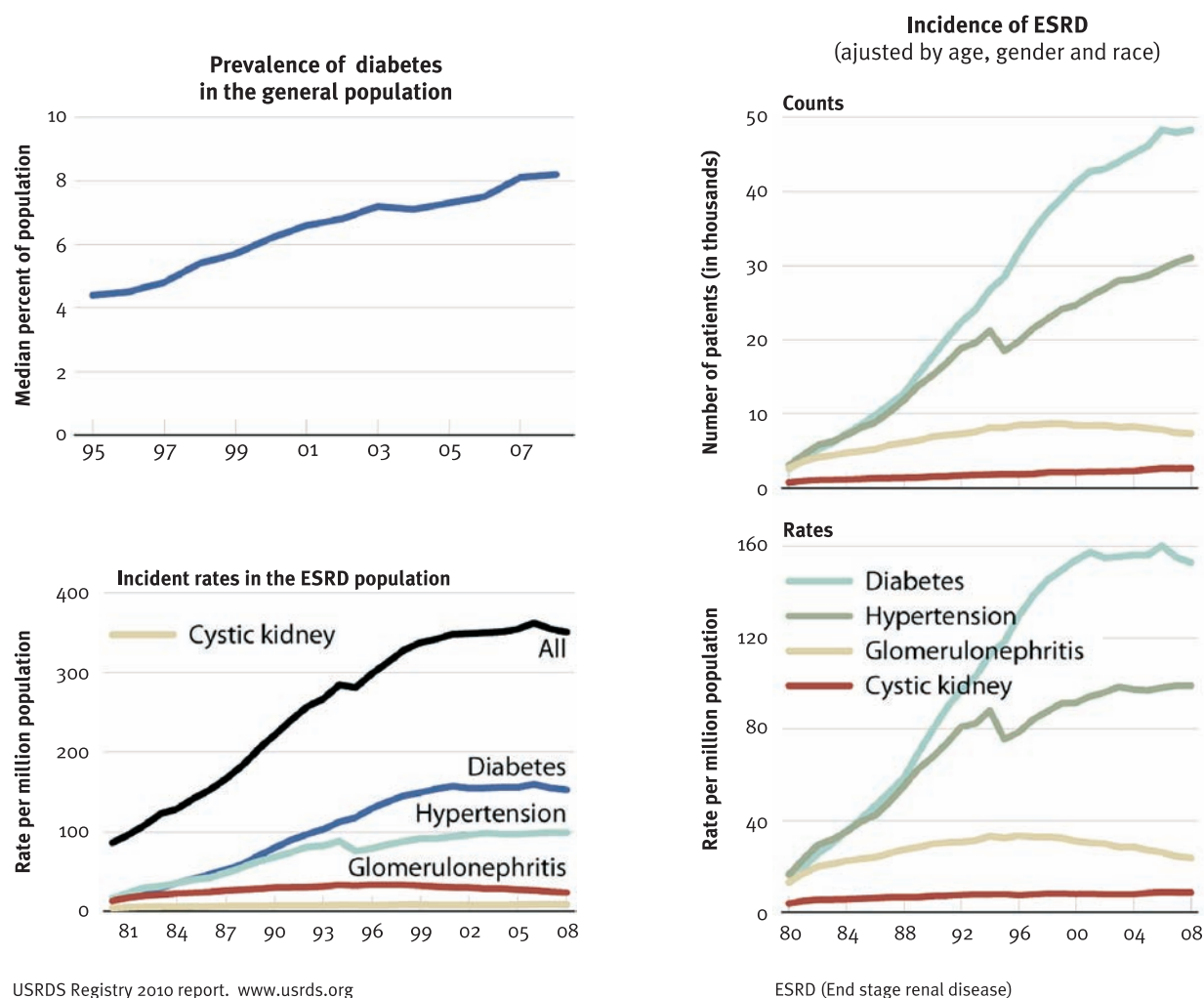
DIABETIC NEPHROPATHY. EPIDEMIOLOGY

Diabetic nephropathy (DN) is still the leading cause of end stage renal disease (ESRD) in incident patients or those that initiate dialysis or undergo transplantation.

In spite of an increase in the incidence of diabetes mellitus (DM) in the general population, a stabilisation in the rate of patients starting dialysis has been seen.

The American Registry Data of kidney patients (USRDS)² confirms this, showing a stabilisation in the overall incidence of patients with terminal renal failure, and in DN as a cause of ESRD (Figure 1). In the USA², 44% of patients have ESRD due to DN, and 21.5% in Spain⁴.

This is probably due to an awareness of the seriousness of kidney disease and cardiovascular risk factors. Equally so, improved early detection and better control of cardiovascular risk factors,



USRDS Registry 2010 report. www.usrds.org

Figure 1

especially hypertension and DM, has also had an influence. Studies conducted in the Spanish population into the prevalence of DN are scarce. In a recent study⁵, the prevalence of DN with glomerular filtration rate (GFR) less than 60 ml/min/1.73m² was 22.9%. Unfortunately, we have no data of it in Portugal. Diabetic nephropathy continues to have great epidemiological importance, with temporary stabilisation perhaps the result of work carried out in recent years to improve diagnosis and treatment of DN. However, we are still far from reaching the ideal target detection rates and treatment.

DIABETIC NEPHROPATHY. GENETICS

Genetic susceptibility is one of the determinants of progression and severity in DN. We know that only a percentage of affected patients with DM develop DN, although the same therapeutic strategy and adequate control of risk factors for progression (blood pressure, glycaemic control, obesity, smoking, dyslipidaemia) have been used for both. Some patients respond well to treatment, while others remain stable or progress to kidney failure. This suggests the existence of genetic factors related to

the development and progression of DN, as well as variations in treatment response.

Currently, there are several studies and projects in the field of DN based on the search to find the genes responsible for genetic predisposition to DN. We have followed two main search strategies: studies of candidate genes and genome scans. Candidate gene studies or association studies are based on the analysis of genes that encode proteins which play a known role in the pathophysiology of the disease, trying to find an association between variants of selected genes and disease development.

Here it has been recently reported that the development of endothelial dysfunction is favoured in patients with a deletion in intron 4 of the nitric oxide (NO) synthase endothelial, which has been associated with greater renal progression⁷. In this type of studies, those that have analysed the relationship with genotypes of angiotensin converting enzyme (ACE) (insertion/deletion, I/D) have shown conflicting results.

The other search strategy is genome scanning. It is based on the search in family relatives for the presence of a genetic component that is inherited with certain regions of the genome and the development of the disease. One of the most important initiatives employing this strategy is the Family Investigation of Nephropathy Study and Diabetes (FIND)⁸. Here the most robust evidence regarding DN points to regions on chromosomes 7 (7q21.3) 10 (10p15.3), 14 (14q23.1) and 18 (18q22.3).

In summary, genetic susceptibility is part of one of the factors that influence the development of DN. Although some genes have been identified related to alterations that favour a greater progression of DN, there are many studies with conflicting results, and we still lack studies that adequately identify those genes responsible. It is likely that the association of several genes may be the instigator of most renal progression. The identification of these genes or associations will help us identify those individuals at risk for DN as well as help us better understand their pathophysiology. However, on a daily basis, we face the clinical reality that patients with familial association of DN are more likely to develop it.

■ DIABETIC NEPHROPATHY. PATHOGENESIS

Despite the recognition of hyperglycaemia as a prerequisite and main determinant of the development of DN, we still do not fully understand the intimate mechanisms by which hyperglycaemia leads to renal injury. Recently, there have been some studies that have helped to improve understanding the pathogenesis of DN, especially in relation to the pathways of hyperglycaemia damage.

■ The importance of hyperglycaemia and advanced glycation end products (AGEs)

The modification of various molecules by the hyperglycaemic environment, with the eventual formation of AGEs, plays an important role in DN. Elevated glucose levels exert their toxic effects within cells through their absorption by glucose transporters, activating a chain of different enzymatic reactions including sorbitol formation, increased oxidative stress, activation of protein kinase C (PKC) and hexosaminase activation. All of these enzymes and metabolic pathways will contribute to the activation of cytokines and growth factors that are actively involved in the onset and development of DN. The AGE⁹ receptor has been recently described. Its activation by the AGE has been shown to play an important part in the pathogenesis of DN and other nephropathies. The antagonism of this receptor may be a possible target strategy in the treatment of DN.

■ Renin receptor

Activation of this receptor has been associated with renal inflammation in DN, increasing the swelling produced by increased expression of tumor necrosis factor α (TNF- α) and interleukin 1 β ¹⁰. In addition, it affects the renin angiotensin-aldosterone system (RAAS). The action on the renin receptor also would enhance the anti-inflammatory response in the DN.

Nuclear hormone receptors in DN

Activation of these receptors acts to regulate carbohydrate metabolism, lipid metabolism, immune response, inflammation and fibrosis development. They

have therefore been investigated as drug targets in the treatment of various diseases. In DN, nuclear receptor activity is altered¹¹. In the case of DN, eight nuclear receptors have been found whose activation may have a renoprotective character. Among the nuclear hormone receptors are included the peroxisome proliferator-activated receptor (PPAR) (α and δ), vitamin D receptor, oestrogenic receptors, receptor hepatocyte nuclear factor 4 α and farnesoid receptor.

Agonists of PPAR- α receptors

Agonists of PPAR- α receptors such as fibrates, used in dyslipidaemia treatment, play an important role in lipid metabolism. Apart from a lipid lowering effect, they inhibit nuclear factor kappa ($\text{Nf}\kappa\text{B}$) exerting pleiotropic anti-inflammatory and anti-atherogenic effects. In the kidney, PPAR- α receptors play an important role in lipid metabolism and tubular cell toxicity in regulating blood pressure. PPAR- α is expressed primarily in the mesangium¹². Numerous and recent studies have accumulated evidence on the benefits of activating PPAR- α receptors in DN, acting on the regulation of profibrotic mechanisms, inflammatory and apoptotic in the glomerulus. In animal models with DN, activation of PPAR- α receptors with fenofibrate has been associated with a reduction in albuminuria and mesangial expansion. In the FIELD study (Fenofibrate Intervention and Event Lowering in Diabetes), administration of fenofibrate was associated with a significant reduction in the progression from normoalbuminuria to microalbuminuria to albuminuria and macroalbuminuria¹³. This suggests that activation of PPAR- α by fibrates, in addition to its effect on lipids, may represent a therapeutic potential in preventing diabetic nephropathy.

PPAR- δ receptors

R PPAR- δ receptors regulate the transcription genes responsible for insulin sensitisation, glucose metabolism, lipid metabolism, lowering blood pressure and inflammatory responses¹¹. In the kidney, these receptors are found in the glomerulus and tubule. Many studies have shown that activation of PPAR- δ receptors improves endothelial dysfunction, podocyte injury, inhibits the activation of $\text{Nf}\kappa\text{B}$, the accumulation of reactive oxygen species and macrophage infiltration in the kidney. The glitazones are

potent activators of PPAR- δ . They reduce albuminuria in DN, accompanied by reduction in glomerular hyperfiltration, and they prevent glomerulosclerosis and interstitial fibrosis, probably as they reduce the expression of TGF- β , $\text{Nf}\kappa\text{B}$ and other growth factors involved in DN¹⁴. Multiple studies and a recent meta-analysis¹⁴ have shown that treatment with glitazones has been associated with a reduction in albuminuria in DN. However, the glitazones are drugs the safety of which has been questioned, especially rosiglitazone (fluid retention, heart failure and increased distal fractures). In a recent review of nearly 40,000 patients, pioglitazone was associated with lower risk of cardiovascular events than rosiglitazone, but there are no studies that compare them with other anti-diabetic oral agents in the analysis of cardiovascular events. Therefore, in the absence of better and more specific clinical trials, we suggest restricting the use of glitazones in diabetic patients, despite the beneficial effects on DN. PPAR- δ receptors can also be activated by antihypertensive drugs. Telmisartan has been demonstrated, using laboratory animals, to produce a greater activation of these receptors.

Vitamin D receptor

Vitamin D₃ is mainly produced from sun exposure and in lesser quantities from fats and dairy products, synthesising its precursor in the skin at D₃ or cholecalciferol. After hydroxylation in the liver, it becomes the active form or calcitriol: 1, 25 (OH)₂ vitamin D in the kidneys. Equally so, it is interesting to know there is also extrarenal production of calcitriol in various tissues, such as vessels, skin and the immune system, allowing local action on them. The active form of vitamin D exerts its effects by activating the vitamin D receptor, a receptor of the nuclear receptor family, located within the cytoplasm of the cell. There are numerous organs and tissues that have receptors for vitamin D, as the endothelium, vascular smooth muscle cells, myocardium, pancreatic islet cells of the immune system, the parathyroid gland, intestinal mucosa and bone. Thus vitamin D not only acts on bone and mineral metabolism, but also plays a part in kidney and cardiovascular functions¹¹. The vitamin D receptors are expressed in various parts of the kidney (tubular cells, epithelial glomerular podocytes and mesangial cells). The administration of pharmacological doses of vitamin D and its analogues, especially paricalcitol, in animal models, prevents injuries and reduces DN glomerulosclerosis,

acting on the renin-angiotensin system (RAS) and anti-inflammatory mechanism, especially $\text{NF}\kappa\text{B}$ ¹¹. Selective activators of vitamin D receptors, such as paricalcitol, have been shown to reduce albuminuria in DN a recent clinical trial¹⁷, as well as demonstrating beneficial effects at the myocardial level. The existing evidence on the activation of these receptors will be discussed later on.

■ High doses of vitamins from group B aggravate DN

The combination of vitamins B6, B9 and B12 has been used as a treatment to reduce plasma homocysteine levels in patients with high cardiovascular risk. However, a recent clinical trial showed that the administration of these vitamins aggravates renal impairment in diabetics and increases the risk of vascular disease. This conclusion is obtained from the DIVINE study (the Diabetic intervention with vitamins to Improve nephropathy)¹⁸, a randomised clinical trial in patients with established DN (albuminuria > 300 mg/g), which compared a group treated with 2.5 mg/day of folic acid, 25 mg/day of vitamin B6, 1 mg/day of vitamin B12 versus placebo. Estimation of renal progression was performed using radioactive isotopes. The treated group showed greater progression of DN, as well as higher proportion of cardiovascular events. Although the number of patients was small (n=238), supplementation with vitamin B in high doses should be avoided in patients with established nephropathy.

■ NEW DIAGNOSTIC ASPECTS IN DIABETIC NEPHROPATHY

■ Updated ADA guidelines 2010

The detection of albuminuria in diabetic patients remains the best tool for early detection of DN. Incipient nephropathy is considered to exist when the ACR in urine is between 30-300 mg/g. The recommendations of the American Diabetes Association (ADA) guidelines of 2011 have not changed from previous ones. They recommend the following.

- Detection of urinary albumin in type 1 diabetics annually from the fifth year of diagnosis, and type 2 diabetics annually from diagnosis.

The annual detection of serum creatinine is recommended in all adults with diabetes, as well as determination of albuminuria. The determination of creatinine can be used to estimate glomerular filtration rate (eGFR) using creatinine derived formulas (MDRD or CKD-EPI). This will help to define the stages of renal disease.

The preferred method for albuminuria detection is the ACR in a urine sample. Given the variability of albuminuria, it will require two of three samples in 3-6 months to establish the diagnosis. In some situations albuminuria can increase, producing false positives (physical exercise in the previous 24 hr, infection, fever, congestive heart failure, very high glycaemia or very high blood pressure)¹⁹.

A minimal change was made in the 2011 ADA guidelines in terms of recommended blood pressure. Previous guidelines recommended that patients with diabetes should be treated to a systolic blood pressure < 130/80 mmHg. In the 2011 recommendations, the previous statement is maintained, but the guidelines recommended that based on patients' characteristics and response to the therapy, higher systolic or lower systolic blood pressure targets may be appropriate¹⁹.

■ Proteomics in diabetic nephropathy

Despite the importance of microalbuminuria, it is a nonspecific marker of DN. In fact, only 30-45% of microalbuminuric type 2 diabetics will develop established nephropathy in the next 10 years. On the other hand, microalbuminuria is a marker of cardiovascular risk. Therefore, it cannot be regarded as a specific marker of DN. Proteomics is the study and characterisation of the entire set of proteins expressed by a genome. Proteomics aims to identify, categorise and classify proteins with respect to their function and interactions established between them. We can characterise the functional networks which provide proteins and their dynamics, their physiological and pathological processes. Proteomic analysis of proteins in urine can identify new disease markers or identification of proteins involved in the pathogenesis of some diseases. The use of proteomics in DN is at an early stage, and it could be used as a method to predict the likely progression of the disease to more advanced stages. Great efforts have

been made using this technique (more or less complex) in the last five years to find biomarkers to detect urinary proteins (proteomics) in DN. As can be seen in detecting markers, they can predict the development of DN in normoalbuminuric patients and biomarkers of regression and progression of DN²⁰. A Danish group has recently used proteomics to detect some peptides in urine that may be markers for renoprotection in DN²¹. The monitoring allowed them to analyse various therapeutic interventions and the possible mechanism of action in improving DN, after the administration of certain drugs. Thus, the use of proteomics in analysing proteins in urine is not only a method for monitoring and predicting the evolution of DN, but can also serve to monitor the different renoprotective drugs and determine their effect on excretion of different types of proteins in urine.

Another possibility is the biomarker study using transcriptomics, which is the simultaneous study of mRNA expression levels of thousands of genes (in the case of proteomics the study was on protein expression levels). This analysis can be performed on tissue samples, such as renal biopsy. In this way one can analyse most expressed genes, learn which kidney cells are expressed and what mechanisms can affect the progression, in this case, of DN, and to detect in which situations the genes that cause disease are expressed.

■ NEW DRUG TREATMENT IN DIABETIC NEPHROPATHY

■ Blood pressure control in DN

The goal of treatment for type 2 diabetes with hypertension is to reduce the global vascular risk, trying to avoid or delay the onset of cardiovascular complications. Therefore, the therapeutic approach should aim not only to reduce high blood pressure, but also to address all factors that may play a pathogenic role in these complications.

Unfortunately, there have been no further studies to try to solve this issue in patients with DN. The guidelines of American Diabetes Association¹⁹ continue to recommend that the goal to control blood pressure should be less than 130/80 mmHg in diabetic patients,

without specific distinction for patients with nephropathy. The publication of the recently released ESH-ECH guidelines²² outlines that previous recommendations of levels of systolic blood pressure below 130/80 mmHg in diabetics and patients with high cardiovascular risk (history of cardiovascular events), no randomised clinical trials have shown a significant benefit in reducing systolic blood pressure below 130 mm Hg. Furthermore, patients in clinical trials have rarely managed to reach therapeutic goals established in the guidelines (130/80 mmHg), and giving a definitive answer is controversial because there is no compelling scientific evidence that reducing blood pressure below 130/80 mm Hg is the goal for all patients at high cardiovascular risk. A reappraisal of the guidelines from ESH-ESC suggests that in the diabetic patient, blood pressure targets should be between 130-139/80-85 mmHg. Of interest is the identification of this target in each patient, selecting those patients who benefit from a greater reduction in BP, such as those with chronic kidney disease or a greater degree of albuminuria. Therefore, in these patients the systolic blood pressure target should be closer to 130 mmHg than 139 mmHg, within the range proposed by the guidelines.

The ACCORD-BP study (Action to Control Cardiovascular Risk in Diabetes-Blood Pressure)²³ was recently published. It included 4,733 patients with type 2 diabetes mellitus at high cardiovascular risk, randomised into two groups (BP <120 mmHg or intensive control vs. > 140 mmHg or standard control) followed for 4.7 years. No significant differences in the objectives of the study were found (myocardial infarction, stroke or cardiovascular death). In the more intensive control group, more side effects were found, so it is not justified to achieve BP levels below 120 mmHg in these patients. Unfortunately, this study has not resolved the dilemma of what is the ideal blood pressure to achieve in patients with DN.

■ Blockage of renin angiotensin-aldosterone system (RAAS)

RAAS is a hormone system that regulates blood pressure and water (fluid) balance. When blood volume is low, juxtaglomerular cells in the kidneys secrete renin. Renin stimulates the production of angiotensin I, which is then converted into angiotensin II. Angiotensin II causes blood vessels to

constrict, resulting in increased blood pressure. Angiotensin II also stimulates the secretion of the hormone aldosterone from the adrenal cortex. Aldosterone causes the tubules of the kidneys to increase the reabsorption of sodium and water into the blood. This increases the volume of fluid in the body, which also increases blood pressure.

If the RAAS is too active, blood pressure will be too high. There are many drugs that interrupt different steps in this system to lower blood pressure. These drugs are one of the main ways to control high blood pressure (hypertension), heart failure, kidney failure, and harmful effects of diabetes. Thus, blocking this system is a major goal in renal treatment⁴³.

ACEi/ARB

Although all antihypertensive drug classes have shown potential benefit in the treatment of DN, mainly derived from blood pressure control, drugs blocking the RAAS, inhibitors of angiotensin converting enzyme (ACEi) and antagonists of angiotensin II receptors (ARBs) have shown in multiple clinical trials an additional benefit of reducing albuminuria, delaying the progression of renal disease and reducing the risk cardiovascular disease. They should therefore be considered as the first choice in diabetic patients with or without nephropathy. Some very interesting developments in the past three years have appeared using blocking RAAS in the treatment of DN.

In the last decade several clinical trials have shown evidence as to the efficacy of RAAS blockade in the prevention and treatment of DN: the BENEDICT study (trandolapril) in the prevention of onset of microalbuminuria, MICRO-HOPE studies (ramipril), LIFE (losartan), IRMA 2 (irbesartan), INNOVATION (telmisartan) and MARVAL (valsartan) in the prevention of established nephropathy, and finally the RENAAL study (Losartan), IDNT (irbesartan) and Captopril collaborative study (the latter diabetes mellitus type 1) in patients with established nephropathy to prevent progression to terminal renal failure²⁴.

Recently two studies have been completed using ARBs in preventing the appearance of microalbuminuria. The DIRECT study and the ROADMAP study.

The DIRECT study (Diabetic Retinopathy Candesartan Trial)²⁵ consists of 3 substudies, two prevention

of retinopathy in diabetes mellitus type 1 and type 2 and a third study (DIRECT-Protect-2)²⁶ for the primary prevention of microalbuminuria. The latter was performed with the ARBs-2 Candesartan in normotensive normoalbuminuric in 2725 diabetics and followed up for 4.7 years. The rate of progression to microalbuminuria in the treated group did not differ significantly from the placebo group. In addition, the event rate was so low that it is difficult to draw conclusions, unless the drug showed no significant difference in the progression of normo to microalbuminuria compared with placebo.

The ROADMAP study (The Randomised Olmesartan And Diabetes Microalbuminuria Prevention study) is a randomised clinical trial evaluating the efficacy of olmesartan in preventing microalbuminuria in type 2 diabetic patients without albuminuria and with one or more cardiovascular risk factors. Twenty-three countries participated, and it included 4,400 patients who were followed for five years. The primary end point is the appearance of microalbuminuria, and secondary the effects of olmesartan on fatal cardiovascular events and nonfatal microvascular disease (renal and retinopathy among others). The results will be published in 2011.

ACE2 as a therapeutic target in DN

In RAAS, angiotensin I is converted into angiotensin II by the effect of angiotensin converting enzyme (ACE). A homologue of ACE, the ACE 2, angiotensin I and angiotensin II to angiotensin 1-7, a peptide that antagonises the effects of angiotensin producing opposite effects (vasodilatation, decreased cell proliferation and direct antagonism of angiotensin II). ACE 2 is in the kidney, liver, adipose tissue and pancreas. This peptide is elevated in the pancreas in diabetes, and in the early stages of DN. It is postulated to be a compensatory response to diabetes and DN²⁷. Deletion of ACE2 in experimental models is associated with worsening of DN. The empowerment of ACE 2 using genetic or pharmacological intervention is postulated as an attractive therapeutic target in DN, as well as in complications of DM.

Direct renin inhibitors

This class of drugs has led to a new therapeutic option for hypertension and diabetic nephropathy. Its mechanism of action is by competitive renin antagonism.

The only representative of this group currently is aliskiren. The mechanism of action on the opening of the RAAS cascade and reduced plasma renin activity is a fact that differentiates it from ACE inhibitors and ARBs, making this drug an attractive option. The renoprotective effect is demonstrated to be of great relevance in diabetic patients in the study AVOID (Aliskiren in the Evaluation of Proteinuria in Diabetes). Patients already receiving optimal treatment with ARBs (100 mg of losartan) showed additional antiproteinuric effect when aliskiren was added (150 mg initially and 300 mg at week 12), achieving additional antiproteinuric effect in proteinuria between 17-20%, already evident at the fourth week of treatment²⁸. Thus aliskiren is an excellent therapeutic option in patients who receive treatment with an ARB. The only contraindication to its use is the presence of hyperkalaemia before treatment as it also works by blocking the RAAS. However, in published studies, this effect has not been more prevalent than in the placebo group. Confirmation of this superior renoprotective effect requires further studies with more patients and longer follow-up times to be considered as an excellent alternative in the treatment of hypertensive patients, especially in diabetics with albuminuria. In addition, more morbidity and mortality studies are needed to generalise the drug for the treatment of cardiovascular risk and to determine the effect of prorenin and high plasma renin concentrations during treatment. The study ALTITUDE (Aliskiren Trial in Type 2 Diabetes Using Cardio-Renal Disease Endpoints) has included 8,600 type 2 diabetics and will answer this question upon its completion in 2012.

Aldosterone in DN

There are several mechanisms by which aldosterone may act by promoting renal injury. These mechanisms differ little from the effects of aldosterone in cardiovascular disease. In addition to the classic effects of promoting sodium retention and volume expansion, aldosterone promotes inflammation, production of cytokines, growth factors and endothelial dysfunction, which acts on the renal vasculature, glomeruli and tubules and favours the emergence of proteinuria²⁹.

In recent years clinical trials have been published in DN with small numbers of patients in whom the addition of eplerenone³¹ and spironolactone³⁰ is associated with a significant reduction in albuminuria. Recently there have been several studies in experimental animals that have shown the benefit of aldosterone

in DN, but it is noteworthy that in the past three years, only a clinical trial has been published, and this was carried out with only 81 patients. This study compares three arms (spironolactone 100 mg, losartan 100 mg and placebo) in patients with overt DN receiving an ACE inhibitor (lisinopril, 80 mg/day). The addition of spironolactone achieved a reduction in proteinuria of 34% ($p=0.007$) compared to placebo, while only 17% was noted with losartan. ($P=ns$). Thus the addition of spironolactone was associated with greater renoprotection than placebo despite equal blood pressure control, although this was not the case when losartan was associated³². Potassium levels were significantly increased with both losartan and spironolactone versus placebo. Potassium was detected ≥ 6 mEq/L in 7% of placebo group, 37% of the losartan group and 52% of the spironolactone group. These hyperkalaemia figures limit the use of aldosterone in patients with DN and especially with renal failure, in spite of the benefit of reducing proteinuria.

Vitamin D receptors Activators Selective vitamin D receptor

Under section 3.3.4 it was mentioned that the selective activation of the vitamin D receptor has been shown to be an additional therapeutic target in dealing with DN.

Paricalcitol, a selective activator of the vitamin D receptor, reduces parathyroid hormone in patients with secondary hyperparathyroidism with lower incidence of adverse effects than calcitriol (hypercalcaemia and hyperphosphataemia)³³.

The administration of pharmacological doses of selective activators of vitamin D receptors such as paricalcitol in DN animal models has shown a reduction in albuminuria, inflammation and nephroangiosclerosis³⁴ independent of blood pressure control. Recently, the same group of researchers have shown in a rat model with type 2 (leptin receptor KO mice) that administration of paricalcitol can improve the effectiveness of receptor antagonists of angiotensin II associated with better prevention of the progression of DN on type 2 DM³⁵. These studies suggest that the beneficial effects of activation of vitamin D receptor in experimental DN may be due to its action on the RAS. However, paricalcitol appears to have several mechanisms of action in DN in which the activation of the vitamin D receptor is involved in

suppressing renin transcription, has antiproliferative and antifibrotic effects and improves podocyte cytoskeleton and histological lesions of DN³⁶.

Two previous studies have shown the benefit of paricalcitol in the reduction of albuminuria in the ND³⁷⁻³⁸, but a clinical trial has been recently published – the VITAL study (Selective Vitamin D receptor activator, paricalcitol, for Albuminuria Lowering study)¹⁷, designed to evaluate the effects of adding to ACE inhibitors or ARBs Paricalcitol in patients with DN on the further reduction of albuminuria. This study has shown that 2 mg/day of paricalcitol added to conventional therapy (ACE inhibitors or ARBs) reduce albuminuria in patients with DN. The authors suggest that paricalcitol administration restores the physiology of receptor activation of vitamin D in chronic kidney disease and may achieve benefits in cardio-renal markers such as albuminuria.

One issue that remains to be discussed is the effect of the suppression of parathyroid hormone (i-PTH) in patients with normal renal function, and therefore without secondary hyperparathyroidism. However, this therapeutic strategy can help to reduce the residual risk in DM and this encourages further studies to demonstrate other cardiovascular benefits shown in experimental animals.

■ Other therapeutic targets for study

There have been several studies in experimental models and in small groups of patients, but clinical trials have been published in recent years. These studies include those made with antifibrotic agents (neutralizing TGF- β , protein kinase inhibitors, β). Other molecules being tested are inhibitors of endothelin and bardenoxolone.

Inhibitors of endothelin

Endothelial dysfunction, characterised by an imbalance between vasodilator and vasoconstrictor factors derived from endothelium, plays an important pathogenic role in diabetic microangiopathy. Endothelin-1 (ET₁) is one of the most potent endogenous vasoconstrictor with pleiotropic actions related to DN, including proinflammatory and profibrotic activity, the inhibitory effects on nitric oxide production and increased production of components extracellular matrix. Inhibition

of ET-1 by blocking its receptors is a potential strategy in the treatment of DN. Avosentan studies (ET_A receptor antagonist of ET₁) showed reduction in albuminuria. A clinical trial was recently published (the ASCEND study)³⁹ in which 1692 patients were randomised to different doses of avosentan or placebo – patients who were already under treatment with ACE inhibitors or ARBs. Despite the strong avosentan anti-proteinuric effect in patients with DN, this treatment was associated with a significant volume overload and heart failure in a high percentage of patients, so this was not a viable therapeutic option due to its low profile. However further tests are being developed with molecules such as atrasentan with fewer side effects.

Pentoxifylline

Pentoxifylline has been available for many years with prescription, in peripheral arterial occlusive and other circulatory disorders as well as skin ulcers. It has an anti-inflammatory mechanism of action by inhibiting TNF- α gene transcription and interleukins that modulate inflammatory process present in DN. Some studies have demonstrated reduction in albuminuria in ND⁴⁰. Most studies have included a small number of patients. A meta-analysis⁴¹ has shown recently that the available data from the studies (a total of 476 patients) suggest that pentoxifylline reduces albuminuria in patients with DN. To confirm these findings requires clinical trials with a significant number of patients and long-term results. At this time, one of these trials is underway in Spain, which may have data available next year⁴².

Other molecules under study are bardenoxolone acting through an inflammatory mechanism and increasing the glomerular filtration in pilot studies. Next year the first results of clinical trials will be available.

Conflict of interest statement. None declared.

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