

Standard and novel therapeutic approaches to diabetic nephropathy

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Received for publication: 20/01/2015

Accepted: 22/01/2015

■ INTRODUCTION

Diabetes is a significant international health care problem. The prevalence of diabetes *mellitus* has reached epidemic proportions. Worldwide, around 347 million people have the disease and this number is expected to increase to 430 million by 2030. The disease comes with a financial burden. An estimated US\$548 billion was spent on this condition in 2013. The vast majority of this cost relates to the management of diabetic complications. Vascular injury and comorbidities influence the natural history of the disease, particularly in patients with type 2 diabetes *mellitus* (T2DM). The 1988-1994 NHANES III survey ($n = 14,622$) reported that kidney disease (defined as albuminuria, decreased renal function or both) was present in 42% of US patients with diabetes¹. Patients with diabetic kidney disease are at increased risk of cardiovascular events and mortality.

Diabetes is the most frequent cause of end-stage renal disease (ESRD) in developed countries, accounting for 25–40% of incident patients. The classic pattern of diabetic nephropathy involves initial microalbuminuria [urinary albumin excretion rate (UAER) 30–300 mg/24 h] that progresses to macroalbuminuria (UAER ≥ 300 mg/24 h) and is followed by a progressive decrease in renal function leading to ESRD. Around 25–35% of patients with diabetes and decreased renal function have normoalbuminuria or microalbuminuria, raising new questions about the mechanisms that contribute to kidney damage and potential therapeutic targets². Several hypotheses

have been proposed to attempt to explain progression of diabetic kidney disease in patients with normoalbuminuria or microalbuminuria. Incomplete recovery from repetitive episodes of acute kidney injury (AKI), haemodynamic changes and renal vascular disease might be contributing factors. Both hyperuricaemia and systemic inflammation are associated with progression of non-proteinuric diabetic kidney disease^{3–6}

Unless novel, effective therapeutic approaches to diabetic kidney disease are developed, the expected worldwide increase in associated cases of ESRD and cardiovascular disease will likely overwhelm health-care resources, leading to a human tragedy of major proportions

■ REFINEMENT OF STANDARD THERAPIES

■ Blood pressure control and ACEi/ARB treatment

The 2007 KDOQI guidelines for diabetes and chronic kidney disease (CKD) recommended a blood pressure target for patients with diabetic kidney disease of $\leq 130/80$ mmHg⁶. However, the 2012 KDIGO guidelines recommend a target of $\leq 140/90$ mmHg for normoalbuminuric patients with diabetes because the ACCORD study⁷ disclosed evidence of harm with tight blood pressure control in elderly patients (mean age 62 years) and in patients with comorbidities, marked

systolic hypertension or severe autonomic neuropathy. The current blood pressure target recommended by KDIGO for the management of blood pressure in diabetic patients with CKD and albuminuria is $\leq 130/80$ mmHg (8;9) By contrast, 2014 ADA guidelines recommend that blood pressure should be $<140/80$ mmHg, although in young patients or pregnant women a systolic blood pressure target of <130 mmHg could be suitable. Patients with long life expectancies are considered to be candidates for lower blood pressure goals than older patients because of the beneficial effects of lowering blood pressure on albuminuria.

Use of angiotensin converting enzyme (ACE) inhibitors or angiotensin II type 1 receptor blockers (ARBs) is the current standard strategy to control blood pressure, reduce proteinuria and slow the loss of renal function in patients with diabetic kidney disease. The revised 2014 American Diabetes Association (ADA) guidelines for standards of medical care in diabetes recommend ACE inhibitors or ARBs for the treatment of patients with microalbuminuria or macroalbuminuria⁹. In normoalbuminuric patients with T2DM and hypertension, renin-angiotensin system (RAS) blockade delays the development of microalbuminuria. However, neither ARBs nor ACE inhibitors have been shown to prevent microalbuminuria in normotensive patients with T1DM. The 2012 KDOQI guidelines for diabetes and CKD¹⁰ and the 2014 ADA guidelines⁹, therefore, do not recommend using ACE inhibitors or ARBs for the primary prevention of diabetic kidney disease in normotensive patients with normoalbuminuria.

Dual blockade of the RAS (ACE inhibitor plus ARB) might decrease proteinuria more effectively than single RAS blockade (ACE inhibitor or ARB). However, this strategy is not recommended by the 2012 KDOQI, 2012 KDIGO or 2014 ADA guidelines as no additional efficacy in terms of renal function has been demonstrated and the incidence and severity of adverse effects is increased. The ALTITUDE¹¹ and VA NEPHRON-D¹² randomized controlled trials showed no beneficial effects of dual versus single RAS blockade on renal function and both studies were stopped prematurely for safety reasons.

Ongoing randomized controlled trials are now investigating the effects of combining RAS blockade with mineralocorticoid receptor antagonists (MRAs), which target aldosterone actions.

■ Metabolic control

Metabolic control in patients with diabetic kidney disease requires optimization of glucose and lipid levels. Hyperglycaemia is the driving force for diabetic complications, whereas hyperlipidaemia contributes to increased cardiovascular mortality¹³. Optimized metabolic control, new antidiabetic agents (such as incretin-based therapies), body weight reduction and statins might have a role in a holistic approach to diabetic kidney disease.

The 2014 ADA guidelines recommend an HbA1c target of $\sim 7\%$ to reduce the risk of microvascular and macrovascular complications and to avoid potentially life-threatening episodes of hypoglycaemia. However, the guidelines state that HbA1c levels of $\sim 8\%$ are admissible in patients with comorbid conditions and advanced microvascular or macrovascular disease who have difficulty in achieving tighter glycaemic control. This group might include patients with advanced-stage diabetic kidney disease.

■ Novel drugs controlling blood glucose

Treatments that target the incretin system might improve glucose control and decrease microvascular and macrovascular complications in patients with diabetes. The incretins-gastric inhibitory polypeptide (GIP) and glucagon-like peptide 1 (GLP-1) are released from gut cells in response to food intake. They suppress glucagon secretion and stimulate insulin secretion, therefore, reducing serum glucose levels¹⁴.

As integrins are degraded by dipeptidyl peptidase-4 (DPP4), agents that target the incretin system include DPP4 inhibitors and DPP4-resistant peptides that activate the GLP-1 receptor¹⁴. The DPP4 inhibitors (sitagliptin, vildagliptin, saxagliptin, linagliptin and alogliptin) and GLP-1 agonists (exenatide and liraglutide) can improve glucose and weight control in patients with T2DM and are associated with a low risk of hypoglycaemia. Data from animal models suggest that DPP4 inhibitors might improve diabetic kidney disease at doses that do not improve glycaemic control, but these observations have not yet been confirmed in humans. To shed light on this issue, randomized controlled trials comparing incretin mimetics with other antidiabetic drugs using the primary outcome of GFR or hard renal end points are required.

Inhibitors of sodium-glucose co-transporter type 2 (SGLT2), such as canagliflozin and dapagliflozin, are recently approved for treatment of type 2 diabetes. These agents lower blood glucose mainly by increasing urinary glucose excretion. Advantages of this drug class include modest weight loss of approximately 2 kg, low-risk of hypoglycaemia, and decreased blood pressure of approximately 4 mmHg systolic and 2 mmHg diastolic. These characteristics make these agents potential add-on therapy in patients with HbA1c levels close to 7%-8.0%, particularly if these patients are obese, hypertensive, and/or prone for hypoglycaemia. Overall, SGLT2 inhibitors are useful addition for treatment of select groups of patients with type 2 diabetes, but their efficacy and safety need to be established in long-term clinical trials¹⁵.

■ Body weight reduction

As obesity precedes and is strongly associated with diabetes, weight reduction is considered a first step in combating T2DM and its complications. In obese patients with T2DM, weight loss has been shown to reduce albuminuria in the early stages of diabetic kidney disease⁽¹⁶⁾. Similarly, in obese individuals with advanced diabetic kidney disease (eGFR < 40 ml/min/1.73 m² and UAE > 30 mg per day), a 12-week, very low calorie, ketogenic weight-reduction diet with encouragement of exercise led to a 12% reduction in weight, a 36% reduction in albuminuria and statistically significant reductions in serum creatinine and cystatin C levels, as well as an improvement in glycaemic control.

Bariatric surgery can reduce hypertension, albuminuria and inflammation, and might be a therapeutic option for obese patients with diabetes and macroalbuminuria¹⁷. To date, no studies have assessed the effects of bariatric surgery on albuminuria in these patients.

■ Lipid management

Patients with T2DM have an increased prevalence of lipid abnormalities, which contribute to their high risk of cardiovascular disease^{9,18}. The dyslipidaemia pattern in diabetes includes hypertriglyceridemia, low HDL levels and increased levels of small, dense LDL particles and oxidized LDL cholesterol¹⁸. The 2013 KDIGO guide-lines for lipid management in CKD

recommend that all adults with diabetes and CKD should be treated with a statin or a statin plus ezetimibe regardless of their LDL cholesterol levels.

Overall, the evidence for beneficial effects of statins in patients with diabetes and a moderate or high risk of cardiovascular disease are convincing. Numerous trials have confirmed the cardiovascular benefits of this therapy. Evidence from some small trials suggests that statin treatment might also delay the progression of diabetic kidney disease.

The present recommendations for glycaemic, blood pressure and lipid controls are depicted in Table 1

Table 1

Recommendations for glycaemic, blood pressure and lipid control for most adults with diabetes. KDOQI, KDIGO and ADA (2007, 2012 and 2013)

Glycaemic control HbA1c	<ul style="list-style-type: none"> - Around 7% to reduce the risk of micro and macro vascular complications and to prevent episodes of hypoglycaemia - Around 8% in patients with comorbidities including advanced DKD
Blood pressure control	<ul style="list-style-type: none"> - In patients with diabetes and normoalbuminuria ≤ 140/90-80 mmHg and microalbuminuria ≤ 130/80 mmHg
Lipid control	<ul style="list-style-type: none"> - LDL-c ≤ 100mg/dL: All adults patients over 50 years with CKD should be treated with a statin or a statin plus ezetimibe regardless of their LDLc

■ NOVEL APPROACHES BEYOND METABOLIC CONTROL

In the past few years, a series of randomized controlled trials that investigated new approaches to diabetic kidney disease have provided negative or inconclusive data or were terminated due to safety concerns or a lack of efficacy (Table 2).

■ Nrf2 activators

Bardoxolone methyl is a synthetic triterpenoid that activates the nuclear factor erythroid 2-related factor 2 (Nrf2) transcription pathway and inhibits nuclear factor κB (NF-κB)¹⁹. The BEAM phase II placebo bardoxolone therapy increased eGFR by 5.8–10.5 ml/

Table 2

Clinical trials of add-on therapies to RAS blockade in DKD

Therapy
Nrf2 activator
Vitamin D receptor activator
Endothelin receptor antagonists
Antifibrotic therapies
AGE/RAGE inhibitor
Glycosaminoglycans
Antioxidants
Protein kinase C- β inhibitors
Mineralocorticoid receptor blockers
Xanthine oxidase inhibitor
Anti-inflammatory agents
MMP/ADAM inhibitors
JAK1 and JAK2 inhibitor
Dopamine receptor antagonist
5-HT-2A and 5-HT-2B antagonist
Adoptive transfer
Inhibitors of epidermal growth factor ligands
Vitamin B1

min/1.73 m² at 24 weeks, and this improvement persisted at week 52. However, the BEACON phase III randomized controlled trial, which aimed to confirm the efficacy and safety of bardoxolone methyl, was terminated early due to safety concerns²⁰.

■ Vitamin D receptor (VDR) activators

In humans, vitamin D deficiency is associated with inflammation, immune dysfunction, endothelial dysfunction and cardiovascular disease.

Interestingly, podocytes express VDRs and their activation can directly decrease the inflammatory response of these cells to high glucose level²¹. In animal models of diabetes, VDR deficiency increased albuminuria, whereas treatment with the VDR activators calcitriol or paricalcitol had antiproteinuric and anti-inflammatory effects^{21,22}. Paricalcitol has some clinical advantages over the natural VDR ligand calcitriol in terms of adverse effects on serum calcium and phosphorus levels. However, the VITAL phase III randomized controlled trial, which investigated the anti-proteinuric effect of paricalcitol (1 μ g or 2 μ g per 24 h) as an adjuvant therapy to RAS blockade in 281 patients with T2DM and stages 2–4 CKD, showed no significant difference between the intervention and placebo

groups in the primary end point of percentage change in UACR at 24 weeks (between-group difference for paricalcitol versus placebo of –15%, 95% CI –28% to 1%, $P = 0.071$)²³. At 24 weeks, the secondary outcome of 24-hour albuminuria decreased significantly in the 2 μ g paricalcitol group (–717 mg versus –463 mg in the placebo group), with a sustained reduction in UACR (–18% versus –28% for placebo, $P = 0.014$). However, 2 μ g paricalcitol was poorly tolerated.

In summary, when added to RAS blockade, VDR activators might have antiproteinuric effects in selected patients with T2DM. However, no evidence that these agents slow the progression of CKD exists to date.

As the patent for 1 μ g paricalcitol capsules expired on 24 December 2013 and the patent for 2 μ g paricalcitol capsules has expired on 24 June 2014²⁴ randomized controlled trials to investigate whether VDR activators preserve renal function are unlikely to be funded in the next few years.

■ Inhibitors of AGE formation

Advanced glycation end products (AGEs) accumulate in patients with diabetes²⁵ and might activate the receptor for AGEs (RAGE), cause protein dysfunction and impair collagen turnover²⁴. Pimagedine (also known as aminoguanidine) inhibited the formation of AGEs and slowed the progression of diabetic complications in animal models²⁶. However a phase III randomized controlled trial in patients with T2DM was terminated because of adverse effects²⁷ and the drug is no longer under development.

Pyridoxamine, the natural form of pyridoxine (vitamin B6), also prevents AGE formation. Two phase II randomized controlled trials have evaluated this agent in patients with T1DM or T2DM without affecting urinary albumin excretion the primary outcome of change in serum creatinine level from baseline at week 52.

■ ONGOING TRIALS

■ Endothelin-receptor antagonists

Endothelins are small vasoactive peptides with pleiotropic actions that contribute to hypertension,

albuminuria, insulin resistance, inflammation, fibrosis and endothelial dysfunction²⁸. The predominant isoform, endothelin-1, activates the endothelin-1 receptor (ETA) and the endothelin B (ETB) receptors ETB1 and ETB2. The ETA/ETB receptor antagonist bosentan prevented severe proteinuria and renal function impairment in experimental models of immune-complex nephritis²⁹. The pathological effects of endothelin-1, including vaso-constriction, proteinuria, inflammation, cellular injury and fibrosis, are likely mediated by the ETA receptor, whereas ETB receptors generally exert a natriuretic effect²⁸⁻³¹. Thus, use of ETA-selective drugs would not be expected to be associated with fluid retention. However, even very selective ETA blockers, such as sitaxsentan (ETA:ETB blockade 6,000:1) and avosentan cause fluid retention in patients to a similar degree as less-selective ETA-receptor blockers^{5,28-31}. This finding is probably the result of effects of these agents on the proximal tubule, which lead to sodium retention by the kidney; however the mechanism has not been fully elucidated.

At present, the compound more advanced on clinical trials is atrasentan. This is a more-selective ETA-receptor antagonist (ETA:ETB receptor selectivity 1,200:1) than avosentan. In a phase II randomized clinical trial, atrasentan in addition to RAS blockade significantly reduced UACR (by 42% and 35%, respectively) compared with placebo (reduction of 11%). Peripheral oedema was observed in 18% patients in the low-dose atrasentan. The SONAR phase III randomized controlled trial is now assessing the effect of atrasentan versus placebo as adjuvant to RAS blockade in patients with T2DM, eGFR 25–75 ml/min/1.73 m² and UACR 300–5,000 mg/g³². The primary outcome is time to the first occurrence of a composite renal end point (doubling of serum creatinine levels or the development of ESRD).

■ Mineralocorticoid receptor antagonists

The RAS component aldosterone is a steroid hormone that activates the mineralocorticoid receptor. In addition to a role in the regulation of sodium balance, aldosterone has direct pro-inflammatory and pro-fibrotic action³³. MRAs are potent antiproteinuric agents in humans³⁴.

Two phase II randomized clinical trials are currently investigating the antialbuminuric effects of the novel

MRAs, MT-3995 and BAY 94-8862, as add-on therapy to RAS blockade in patients with diabetic kidney disease. However, the need to administer MRAs in the early phase of disease because of concerns regarding the risk of hyperkalaemia in patients with decreased renal function is likely to limit the investigation of their effects on hard end points and their regulatory approval for diabetic kidney disease.

■ Targeting inflammation

Chemokines secreted by stressed kidney cells activate receptors in inflammatory leukocytes and drive infiltration of leukocytes into the kidney³⁵. Targeting MCP-1, or its receptor CCR2, has been shown to reduce albuminuria and podocyte injury and increase eGFR in experimental models of diabetic kidney disease³⁵⁻³⁷. (Ongoing phase II randomized controlled trials are exploring the safety, tolerability and effect on albuminuria of the CCR2 antagonist CCX 140-B and the CCR2/5 antagonists PF-04634817³⁸ and BMS-813160³⁹).

Activation of Janus kinase (JAK)–signal transducer and activator of transcription (STAT) signalling is another pathway for hyperglycaemia-induced kidney injury. Dysregulation of the JAK–STAT pathway has been documented in human progressive diabetic kidney disease.

Overexpression of the intracellular negative regulators of JAK–STAT signalling, suppressors of cytokine signalling (SOCS)-1 and SOCS-3, is also protective in experimental diabetic kidney disease⁴⁰. The oral JAK1 and JAK2 inhibitor baricitinib, which is being developed for rheumatoid arthritis, might also have renoprotective effects. An ongoing phase II randomized clinical trial is testing baricitinib as an adjuvant to RAS blockade in 250 patients with diabetic kidney disease and macroalbuminuria (UACR 300–5,000 mg/g). The primary outcome is change from baseline UACR at 24 weeks of treatment.

■ Other compounds

There are a number of experimental and clinical data suggesting that other compounds, such as xanthine oxidase inhibitors, anti-TGF-Beta antibodies and phosphodiesterase inhibitors, could have a role in

the prevention and treatment of diabetic nephropathy. In fact, small clinical trials are currently in progress to explore and extend the potential therapeutic involvement in those patients⁴¹

■ CONCLUSIONS

Despite major advances in the knowledge of molecular and cell signalling pathways involved in kidney injury, few new drugs are coming into the market to treat diabetic kidney disease. Failure rates of new agents in randomized controlled trials are very high, exceeding 90% overall and 50% for phase III trials.

Several problems with testing new approaches to therapy in diabetic kidney disease impair the ability to identify therapeutic agents and might have contributed to the paucity of clinical advances in the past 10 years. Renal disease in T2DM might be heterogeneous both in terms of the underlying cause of kidney injury and of the stage of the disease. Since diabetic kidney disease is a clinical diagnosis, in the absence of a gold-standard diagnostic test (such as kidney biopsy), there is no certainty that patients enrolled in diabetic kidney disease trials have the disease. Inclusion criteria in diabetic kidney disease trials vary widely from the presence of diabetes plus reduced GFR to diabetes and various ranges of eGFR, serum creatinine levels and albuminuria. The issue of disease heterogeneity is tightly linked to regulatory problems regarding acceptable end points. Given the difficulty of performing randomized controlled trials with hard end points, most studies focus on albuminuria as a first step towards taking a decision to go ahead with further studies. However, albuminuria and decline in renal function might be dissociated and studies targeting more robust end points, such as measured GFR or progression to ESRD are sorely needed.

Only one ongoing study is aimed at achieving regulatory approval for a novel therapy (atrasentan) for diabetic kidney disease; however, safety concerns and the limited study population mean that this therapy is unlikely to represent a breakthrough for the wider diabetic kidney disease population. We hope that the outstanding advances in knowledge of the molecular and cellular mechanisms involved in organ injury in diabetic patients will pave the way

for the design of novel drugs and trials in the years to come. It is expected that, besides a better control of blood glucose, we will have a number of drugs to treat the complications of diabetes.

■ ACKNOWLEDGEMENTS

This work was supported by grants from the Spanish Ministry of Science (SAF 2012-38830 to C.G.-G.), Fondo de Investigaciones Sanitarias (FIS PSo9/00447, FIS P110/0072, P114/00386, P113/00047, FIS/PIE13/00051, ISCIII-RETIC REDinREN/RD06/0016 and 12/0021), Spanish Society of Nephrology, Comunidad de Madrid S2010/BMD-2378 and PRIORITY, as well as ISCIII Juan Rodés to B.F.-F., Programa Intensificación Actividad Investigadora (ISCIII/Agencia Laín-Entralgo/CM) to A.O, and Diabetes kidney connect (Health-F2-2013-602422) and e-PREDICE (FP7-HEALTH-2011-279074) to J.E.

Conflict of interest statement: The authors declare no conflict of interests.

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