Newer diabetic medications and the kidney

By Sonali Gupta and Joseph Mattana

The prevalence of diabetes is rapidly increasing and is projected to affect more than 400 million people by 2030 worldwide. Diabetic nephropathy remains the most serious microvascular complication and most frequent cause of end stage renal disease in the United States. There has been a pressing need for new therapeutic agents to halt this expanding population and to limit the disease’s associated morbidity, mortality, and expense. Newer antidiabetic medications acting via novel pathways are gaining increased acceptance in medical practice and their renal effects have been the subject of much recent study.

Although the sodium glucose cotransporter (SGLT) inhibitor called phloretin, derived from the root bark of the apple tree, has been in use for over 150 years, it is only recently that its synthetic derivative, with a more specific and potent effect on the SGLT2 receptor in the kidney, has been approved by the FDA. Apart from its ability to cause glycosuria and better glycemic control, recent attention has been drawn to its cardio-renal profile including apparent renoprotective effects, along with optimization of body weight and blood pressure. In vitro and animal studies with empagliflozin have supported its countereacting action—by inhibiting glucose absorption in the proximal tubule—on glucose-induced inflammatory and profibrotic effects on renal tubules, thereby decreasing albuminuria, preventing hyperfiltration, and conferring renoprotective properties. Results from EMPA-REG OUTCOME (Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients), CANVAS-T2D (Canagliflozin Treatment and Trial Analysis versus Sulfonylureas), and dapagliflozin renal studies have been encouraging and support renoprotective effects (1–3). The subgroup analysis of CANVAS (Canagliflozin Cardiovascular Assessment Study) also demonstrated renal benefit of canagliflozin by targeting albuminuria, preventing deterioration in the estimated glomerular filtration rate, lowering renal replacement therapy requirement, and decreasing mortality from renal causes (4). However, questions have been raised regarding the potency of SGLT2 inhibitors in patients with established renal impairment. It is well known that renal autoregulation is impaired in diabetic kidneys and there are concerns for worsening renal function in the setting of volume depletion and the blood pressure–lowering properties of SGLT2 inhibitors. A much awaited randomized, double blind, placebo controlled trial, the CREDENCE (Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation) trial is underway and includes patients with stage 2 or 3 chronic kidney disease and macroalbuminuria who are receiving standard care including a maximum tolerated dose of an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker.

Incretin-based therapies

Incretin-based therapies are another category of diabetic drugs that have received attention for their extra-pancreatic effects beyond controlling glucose. The two classes of drugs are: 1) agonists of glucagon-like peptide 1 receptor (GLP-1R) and 2) inhibitors of dipeptidyl peptidase 4 (DPP-4). The DPP-4 inhibitors mainly act by increasing the levels of the endogenous incretin hormone GLP-1, which has known anti-inflammatory properties. DPP-4 is highly expressed in human kidneys and levels are further upregulated in the setting of diabetes (5). Targeting DPP-4 inhibition has emerged as a potential therapeutic intervention to halt diabetic nephropathy early in its course. Preliminary data from preclinical and animal studies support a role for DPP-4 inhibitors in ameliorating early signs of renal injury, which appears to be mediated independent of its glucose-lowering effects, mainly through proteolytic, antiinflammatory and anti-inflammatory actions (5).

Results from the SAVOR-TIMI 53 Trial (The Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus—Thrombolysis in Myocardial Infarction) showed that treatment with saxagliptin reduced the urinary albumin-to-creatinine ratio, with a reduction in albuminuria in patients with moderate to severe renal impairment (6). However, the TEClOS trial (Trial Evaluating Cardiovascular Outcomes With Sitagliptin) failed to show a clinically significant impact of sitagliptin on cardiovascular or renal outcomes, irrespective of the baseline glomerular filtration rate (7). Preliminary data support the stability of renal function with linagliptin and the lack of requirement for dose adjustment, even in severe renal insufficiency, although further research is needed to support these observations (8). CARMELINA (Cardiovascular and Renal Microvascular Outcome Study With Linagliptin in Patients With Type 2 Diabetes Mellitus) and MARLINA-T2D (Efficacy, Safety and Modification of Albuminuria in Type 2 Diabetes Subject With Renal Disease With Linagliptin) are two large trials that are underway and likely will provide answers to these questions.

In addition to experimental data for DPP-4 inhibitors, GLP1R agonists have also been shown to be renoprotective. Decreased albuminuria secondary to anti-inflammation and anti-oxidative properties of GLP1R agonists were shown in a rat model of diabetic nephropathy (9). Recently, the prospected secondary renal outcomes in the LEADER trial, which had shown a reduction in cardiovascular events with liraglutide in patients with type 2 diabetes mellitus, were reported (10). In this study, the effect of liraglutide on the composite renal outcome of new-onset persistent maculoundminuria, persistent doubling of the serum creatinine level, end stage renal disease, or death due to renal disease was evaluated. Fewer patients on liraglutide experienced the renal outcome, mainly due to a reduction in the new onset of persistent maculoundminuria, suggesting that liraglutide may have a favorable impact on the development and progression of diabetes-related renal disease (10).

With the excitement of having new agents to treat diabetes there are many questions to be answered, and further research is needed to evaluate their beneficial role in primary prevention of cardiovascular and renal events and to prevent renal disease onset and progression. Further clinical trials with predefined renal end points to assess the renoprotective effects of newer medications in these and other classes in patients with type 2 diabetes should provide many such answers over the coming years.

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References