Kidney Medicine

# Management of Diabetes 100 Years After the Discovery of Insulin: Nuances for the Kidney

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More than 3,000 years ago, in 1552 BCE, diabetes was first described and the association between kidney disease and diabetes was recognized.[1] Banting and Best's discovery of insulin in 1921 saved the lives of millions

**Related article, p. 173**

because before this, individuals with diabetes could only live for a few years, even following strict diets. Consequently, insulin treatment lengthened the lives of patients with diabetes, and with greater longevity, diabetic kidney disease was recognized more widely.

Diabetic kidney disease is the leading cause of kidney failure in the United States and worldwide, accounting for 45% of cases in the United States.[2] Approximately 30% of patients with type 1 diabetes mellitus (T1DM) and ~40% of patients with type 2 diabetes mellitus (T2DM) develop diabetic kidney disease.[3] The increasing prevalence of diabetic kidney disease aligns with the growing prevalence of diabetes worldwide. Currently, ~10% of the world's population (463 million people) carries a diagnosis of diabetes and the prevalence of diabetes is projected to increase to >11%, with 700 million people being diagnosed with diabetes by 2045.[4]

Traditionally, interventions that have proven useful in preventing or slowing the progression of diabetic kidney disease include strict blood pressure control, cessation of smoking, control of hyperlipidemia, restriction of protein intake, and of course, strict glycemic control. Critically, the past decade has seen tremendous advances in medications for reducing diabetic kidney disease risk and progression. In this issue of *Kidney Medicine*, Zhao et al[5] evaluate diabetes medication use among US Medicare beneficiaries between 2007 and 2016. They reported that insulin and metformin were the most often used hypoglycemic agents in Medicare patients with chronic kidney disease (CKD), an unsurprising but important finding. The authors also noted that newer glucose-lowering medication use, although low, increased significantly during the course of the study, including dipeptidyl peptidase 4 (DPP-4) inhibitors, glucagon-like peptide 1 (GLP-1) receptor agonists, and sodium-glucose cotransporter 2 (SGLT2) inhibitors.

Two landmark trials conducted in patients with early-stage T1DM and T2DM showed that intensive blood glucose control early in the course of disease demonstrates a long-lasting favorable effect on the risk for developing diabetic kidney disease.[6,7] Furthermore, in the ADVANCE-ON study, tight glycemic control with an average glycated hemoglobin level of 7.2% helped reduce the onset of kidney failure; the effects were more pronounced in earlier stages of diabetic kidney disease.[8]

It should be noted that patients with CKD have higher risk for hypoglycemia because of both reduced gluconeogenesis in the kidney and the altered pharmacokinetics of hypoglycemic drugs. For instance, in patients with CKD, the half-life of sulfonylureas and insulin is extended, which heightens the risk for hypoglycemia. In addition, little is known about the safety of metformin in CKD stages 4-5 and it is not recommended for patients with advanced CKD because of the increased risk for lactic acidosis. Therefore, it was not surprising that the use of metformin was highest in CKD stages 1-3, whereas a significant reduction in metformin use in patients with CKD stage 4 was observed in the analysis by Zhao et al.[5]

Despite current standard-of-care therapies and optimally managed patients with diabetes, a high burden of cardiovascular disease (CVD) exists in patients with CKD, accounting for high morbidity and mortality in this population. Lifestyle modification, optimization of blood glucose levels, lipid levels, and blood pressure and the use of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers have been the foundation of treatment for patients with CKD and diabetes for several decades.

However, patients with T2DM and CKD are more likely to die of CVD than progress to kidney failure.[9] Thus, recent studies in this population have focused on therapies that not only slow the progression of kidney disease in patients with diabetes, but also on decreasing the risk for CVD. Newer therapies such as GLP-1 receptor agonists, DPP-4 inhibitors, and SGLT2 inhibitors represent exciting therapies for managing T2DM and slowing the progression of diabetic kidney disease.[10-12] Furthermore, SGLT2 inhibitors and GLP-1 receptor agonists have demonstrated significant reductions in both cardiovascular and kidney adverse outcomes in patients with T2DM and CKD.[10-15] These drugs represent a paradigm shift in the management of diabetes by not only affecting glycemia but also improving cardiovascular and kidney outcomes in these patients beyond what would be expected by their effects on glycemia. Although Zhao et al demonstrate a statistically significant upward trend for the use of the newer glucose-lowering medication classes, DPP-4 inhibitors, GLP-1 agonists, and SGLT2 inhibitors, their uptake through 2016 was modest, with only 3% to 7% of the population using these newer agents.[5] These data highlight the need for increased efforts to use these medications in patients with diabetes who are at the greatest risk for CVD and CKD progression while also highlighting the need for frequent

updating of these analyses to ensure that patients with CKD have access to and are using these agents.

Zhao et al did not evaluate the use of other medications in patients with diabetes and CKD, such as angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, other antihypertensive agents, statins, or lifestyle management. Moreover, they did not evaluate clinical outcomes in these patients using these hypoglycemic agents or adherence to therapies or adverse effects to these medications. All these factors play an important role in the optimal management of diabetes in patients with CKD.

Because patients with diabetes and CKD have a multisystem disease, they require treatment from a multidisciplinary team of health care professionals. Pharmacists can contribute to the multidisciplinary care team by using their knowledge of medications and their experience and training to help manage patients' medication needs. With the fast-growing number of diabetes medications on the market, pharmacists play a key role in suggesting medications with greater efficacy and fewer side effects and that will be beneficial for other diseases the patients may be experiencing (such as kidney disease and CVD), while minimizing costs. Patients with diabetes visit their pharmacists 2 to 8 times more frequently than they do with their physicians.[16] Several meta-analyses have shown that glycemic control is improved after pharmacist interventions.[17,18]

Moreover, a recent systematic review examined the effect of pharmacist interventions on cardiovascular risk reduction in 15 randomized trials in 9,111 patients with diabetes and found significant reductions in blood pressure (−6.2/−4.5 mm Hg), low-density lipoprotein cholesterol levels (−0.31 mmol/L), and body mass index (−0.9 kg/m$^2$).[19] Finally, a recent study found that higher rates of medication reconciliation in patients with diabetes treated by primary care practices at two academic medical centers was associated with fewer hospitalizations and emergency department visits.[20]

Pharmacists also have an important role in promoting adherence to medication because patients are more likely to take medications if they understand its purpose, how they should take it, and possible adverse effects they can expect. Pharmacists can help patients obtain a patient-friendly pack and can educate patients on mobile applications to assist with medication reminders. Furthermore, pharmacists can help educate patients in administering insulin, monitoring blood glucose levels, helping with lifestyle changes, and "sick day" management.

Finally, the burden of polypharmacy and its impact on adherence is significant in patients with diabetes, CKD, and CVD. This may be a limiting factor when deciding on appropriate regimens that satisfy both the need for optimal glycemic control and CVD and CKD benefit. Therefore, health care providers should focus on minimizing polypharmacy and de-prescribing agents that have no benefit.

Since insulin's discovery, we have made significant advances in improving the management of diabetes. Although Zhao et al[5] explore hypoglycemic agent use between 2007 and 2016, unanswered questions remain in the management of diabetes for patients with CKD. In the last 5 years, clinical trials have focused on both managing CVD and slowing kidney disease progression, in addition to glycemic control in patients with diabetes. However, translating the use of these newer agents into routine practice remains an unknown. Recent studies with SGLT2 inhibitors, GLP-1 agonists, and DPP-4 inhibitors will undoubtedly change clinical practice. Therefore, a collaborative approach among health care providers is needed to integrate these newer therapies into practice to provide the best possible outcomes for patients with diabetes and CKD.

## ARTICLE INFORMATION

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