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Effects of Semaglutide on CKD in Patients With Type 2 Diabetes

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Globally, over 1 billion people suffer from type 2 diabetes, and up to 40% of these people develop chronic kidney disease (CKD) or diabetic kidney disease.[1] CKD in people with type 2 diabetes accelerates progression to end-stage kidney disease, increases the risk of cardiovascular events and mortality, and reduces the quality of life, substantially increasing the health care and economic burden. A combination of glucose-induced endothelial cell dysfunction, metabolic factors such as excess fatty acids, inflammation, carbonyl and oxidative stress, impaired autoregulation, and overactivation of the renin-angiotensin-aldosterone system contribute to driving kidney damage in people with type 2 diabetes.[2] The past decade has witnessed a paradigm shift in diabetic kidney disease management, with therapies such as sodium-glucose cotransporter-2 (SGLT2) inhibitors demonstrating not only glucose-lowering effects, but also profound benefits for kidney and cardiovascular health. Semaglutide, a glucagon-like peptide-1 receptor agonist (GLP-1 RA) with proven benefits in glucose lowering, weight loss, and blood pressure outcomes compared with placebo in people with type 2 diabetes mellitus, now enriches the treatment landscape, offering a new and promising option for kidney and cardiovascular benefits. Here, we discuss the growing body of evidence supporting renoprotective effects for semaglutide beyond its glycemic control and weight loss effects and implications for clinical practice.

Multiple GLP-1 RAs on the market have shown promising kidney benefits in large cardiovascular outcome trials involving patients with type 2 diabetes (Figure 1). Looking specifically at the semaglutide trials, the SUSTAIN-6 trial published in 2016 included 3297 participants with type 2 diabetes at high cardiovascular risk and demonstrated a significant reduction in new or worsening nephropathy with semaglutide compared with placebo (hazard ratio [HR]: 0.64; 95% confidence interval [CI]: 0.46–0.88; $P = 0.005$) as a secondary end point.[3] Subsequently, a meta-analysis of 6 landmark clinical trials, including over 22,000 participants with diabetes, found a reduction in the composite kidney outcome of macroalbuminuria, doubling of serum creatinine or ≥40% decline in estimated glomerular filtration rate, kidney failure or death because of kidney disease (HR: 0.79; 95% CI: 0.73–0.87) with GLP-1 RAs compared with placebo, but with no clear effect on the composite end point in those without new onset macroalbuminuria in this meta-analysis.[4] Notably, these trials assessed kidney effects as secondary outcomes, and the meta-analysis included only 1 semaglutide trial (SUSTAIN-6) with kidney data. Nevertheless, this meta-analysis underscored the need for a dedicated kidney outcomes trial.

The recently reported Evaluate Renal Function with Semaglutide Once Weekly (FLOW) trial, a dedicated kidney outcomes trial, provides the strongest evidence for GLP-1 RA use in CKD.[5] In this trial, 3533 people with CKD and type 2 diabetes, who were at risk for CKD progression were randomly assigned to receive subcutaneous semaglutide or matching placebo with a primary outcome of a composite of kidney failure, a sustained decrease of at least 50% in the estimated glomerular filtration rate from baseline, or death from kidney-related or cardiovascular causes. It showed that semaglutide reduced the risk of the primary outcome by 24% compared with placebo (HR: 0.76;

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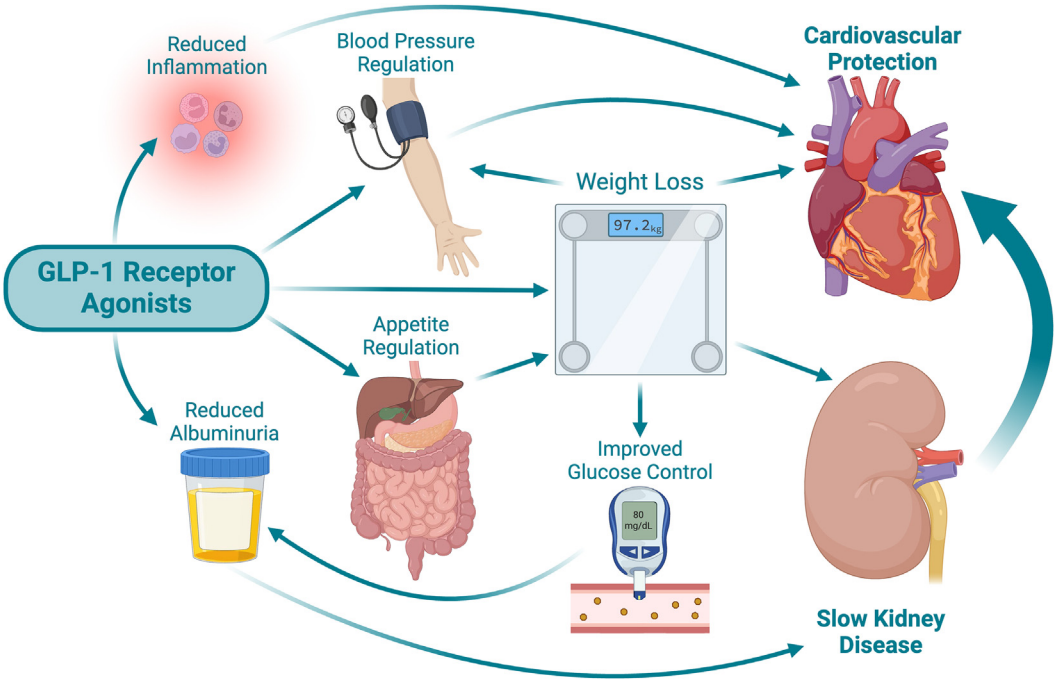

Figure 1. Effects of glucagon-like peptide-1 receptor agonist on important clinical outcomes in people with type 2 diabetes and chronic kidney disease. Figure legend created in Biorender by N Shah 2024.

95% CI: 0.66–0.88; $P = 0.0003$). These effects were consistent across outcome components and subgroups, with substantial benefits in major cardiovascular events and cardiovascular death leading to early trial termination. Although FLOW was not designed to show a direct effect on kidney failure, the results definitively demonstrate renoprotection.

The reduction in urinary albumin-to-creatinine ratio observed suggests impacts on glomerular dysfunction. In addition, the impacts of weight loss (4.1 kg greater weight loss in the semaglutide compared with placebo arm) and reductions in glycated hemoglobin levels (0.81% greater decrease in the semaglutide compared with placebo arm), are unlikely to be the sole explanation for the extensive benefits observed in the FLOW trial. The magnitude of benefit observed with semaglutide on kidney outcomes appears to surpass what would be expected solely from its effects on weight and glycemic control, when compared with other diabetes therapies achieving similar improvements in these parameters as demonstrated by this mediation analysis comparing GLP-1 RAs to SGLT2 inhibitor across 22 trials. Distinct mechanisms may be contributing to the renal benefits observed with these different drug classes, rather than simply reflecting differences in achieved weight loss or glycemic control. The lowering of systolic blood pressure but not of diastolic blood pressure in the semaglutide arm adds to the argument that there are additional renoprotective mechanisms at play beyond the effects on classic risk factors.

Several renoprotective mechanisms have been proposed, including direct antioxidant and antiinflammatory effects; reductions in renal oxidative stress, receptor for advanced glycation end-products, and receptor for advanced glycation end-product–mediated reactive oxygen species production.[6] In addition, GLP-1 receptor signaling can lead to reduced levels of angiotensin II contributing to lowering blood pressure. The natriuretic effect of GLP-1 RAs mediated through the inhibition of the sodium-hydrogen exchanger isoform 3 leads to constriction of the afferent arteriole, reducing glomerular hyperfiltration and intraglomerular pressure. Most mechanistic studies have used other GLP-1 RAs, but we anticipate that these are likely to be class effects. It is likely that the impact of GLP-1 RAs on renal hemodynamics are more complex, despite the direct vasodilating actions on the afferent arteriole.[7] Mouse models of diabetes have also shown that semaglutide reduces glomerulosclerosis and renal fibrosis suggesting an additional mechanism of protection.[8] Although semaglutide indirectly improves glycemic control, blood pressure, and weight, the FLOW trial, similar to SUSTAIN and PIONEER-6 *post hoc* analyses, found consistent renal benefits across various baseline characteristics. This suggests that GLP-1

RAs likely exert direct renoprotective effects beyond improving traditional risk factors.[9] An indirect influence on creatinine levels could be a component because of changes in muscle mass (which could occur with weight loss) which could affect creatinine generation; however, the consistency in effects observed with cystatin C–based estimated glomerular filtration rate suggests that this is less likely. Further research is needed to fully elucidate any potential independent effects on creatinine beyond glomerular filtration rate changes, and to understand the clinical implications of these effects.

The magnitude of risk reduction (24%) in major kidney outcomes in the FLOW trial is similar to the benefits observed from SGLT2 inhibitors (DAPA-CKD HR: 0.61; 95% CI: 0.51–0.72; $P < 0.001$) and finerenone (HR: 0.82; 95% CI: 0.73–0.93; $P = 0.00$) for people with diabetic kidney disease.[S1,S2] An important limitation of FLOW, as well as the SGLT2 inhibitor and finerenone trials, is that during their conduct, only renin-angiotensin-aldosterone system inhibitors were considered standard-of-care. Consequently, there is limited data to guide the use of semaglutide in combination with SGLT2 inhibitors and finerenone. The common side effects of semaglutide such as nausea, vomiting, and diarrhea, are usually mild and transient, tend to occur more frequently during treatment initiation, and the FLOW trial data shows that these effects occurred less frequently in the treatment group than the placebo group which is reassuring. Although current evidence primarily focuses on the diabetic kidney disease population, emerging data suggest potential benefits of GLP-1 RAs and SGLT2 inhibitors in nondiabetic CKD. For instance, the secondary analysis of the SELECT trial has suggested a benefit of semaglutide on kidney outcomes in individuals who are overweight or obese but without diabetes, which raises the exciting possibility that these agents could have a broader role in CKD management beyond diabetes.[1] Larger, well-designed clinical trials are needed to definitively determine their efficacy and safety in this population, and to identify which patient subgroups are most likely to benefit.

Clinicians now face the critical question of when and how best to integrate semaglutide into care, whereas policymakers must assess its potential cost savings. FLOW's robust data, alongside its cardiovascular and weight loss benefits, strongly suggest semaglutide as a potential first-line therapy for individuals with CKD and type 2 diabetes (Figure 1). Crucial research priorities include optimizing semaglutide's dosing and duration, exploring combinations with other renoprotective therapies, evaluating its efficacy in broader CKD populations, and assessing the long-term durability of its benefits. Addressing the high cost and supply challenges of semaglutide is also essential for widespread access.

Conclusion

Semaglutide has undeniably emerged as a valuable therapeutic option for managing CKD in patients with type 2 diabetes. Moving forward, research should focus on optimizing its integration into the therapeutic landscape, including determining the ideal timing and patient populations for its use. Furthermore, efforts should be made to increase the accessibility and uptake of semaglutide.

DISCLOSURE

SSK has received consulting fees from Dimerix Pharmaceuticals, Chinook Pharmaceuticals, Novartis Pharmaceuticals, and Amgen. The George Institute for Global Health and its affiliated entities work with numerous health and pharmaceutical companies in the design, implementation, and analyses of clinical research and clinical trials. It is possible that some of these companies have products relevant to the clinical space covered in this analysis; however, SSK is not aware of any possible conflicts arising from this work. VP has led or served on the Steering Committees of trials funded by AbbVie, Bayer, GSK, Boehringer Ingelheim, Chinook, Eli Lilly, Gilead, Janssen, Novartis, Novo Nordisk, Otsuka, Pfizer, Retrophin/Travere, and Tricida. VP also reports having receiving honoraria for Steering Committee roles, scientific presentations and/or advisory board attendance from AbbVie, Amgen, Astra Zeneca, Bayer, Baxter, Boehringer Ingelheim, Chinook, Durect, Eli Lilly, Gilead, GSK, Janssen, Merck, Mitsubishi Tanabe, Mundipharma, Novartis, Novo Nordisk, Otsuka, Pharmalink, Pfizer, Reata, Travere, Relypsa, Roche, Sanofi, Servier, and Tricida.

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