Dr. Khurana's Corner

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GLP-1 Therapy and the Kidney:
A New Tool in the Nephrologist's Toolbox

Over the course of my career in nephrology, the treatment of chronic kidney disease (CKD) has changed dramatically. For many years, our options for slowing progression were relatively limited: control the blood pressure, block the renin-angiotensin system when appropriate, improve glycemic control, reduce proteinuria, and address cardiovascular risk factors.

Today, the conversation is very different.

SGLT2 inhibitors have fundamentally changed how we approach CKD, and more recently, glucagon-like peptide-1 receptor agonists—and the broader family of GLP-1–based therapies—have emerged as another important tool. Drugs such as semaglutide and dulaglutide, along with the dual GIP/GLP-1 agonist tirzepatide, are familiar to most patients because of their effects on diabetes and weight loss. But increasingly, nephrologists are interested in them for another reason: their **potential to protect the kidney and alter the trajectory of CKD**.

From Weight-Loss Drug to Kidney Drug

The benefits of GLP-1–based therapies are probably not attributable to any single mechanism.

They improve glycemic control without causing significant hypoglycemia when used alone. They can produce substantial weight loss. They frequently lower blood pressure, improve several metabolic parameters, and reduce cardiovascular events in high-risk patients.

All of these matter enormously in CKD.

Obesity, hypertension, diabetes, cardiovascular disease, inflammation, and metabolic dysfunction often travel together in the CKD population. Treating one of these problems can indirectly help the others.

But the emerging data suggest something more important: GLP-1 therapy appears to have kidney benefits that extend beyond simply lowering the hemoglobin A1c.

FLOW Changed the Conversation

For nephrologists, the landmark study was the FLOW trial.

FLOW enrolled more than 3,500 patients with type 2 diabetes and CKD and randomized them to weekly semaglutide or placebo. The study was stopped early after an interim analysis demonstrated efficacy.

The results were impressive.

Semaglutide reduced the risk of the primary composite kidney outcome by 24%. That endpoint included kidney failure, a sustained reduction in kidney function, and death from kidney or cardiovascular causes.

Importantly, this was not simply an albuminuria study.

The kidney-specific components of the primary endpoint were also reduced, and the annual decline in eGFR was approximately 1.16 mL/min/1.73 m² slower in patients receiving semaglutide.

There were benefits outside the kidney as well. Major cardiovascular events fell by approximately 18% and all-cause mortality fell by approximately 20%.

For a patient with diabetes, obesity, cardiovascular risk and CKD—which describes a substantial portion of

the population seen in a nephrology office—those are clinically meaningful findings.

SURPASS-CVOT Adds Tirzepatide to the Cardiorenal Discussion

The next important piece of the story comes from SURPASS-CVOT, which studied tirzepatide—a dual agonist of the GIP and GLP-1 receptors—against dulaglutide in patients with type 2 diabetes and established atherosclerotic cardiovascular disease.

This was a very different design from FLOW. SURPASS-CVOT was not a placebo-controlled kidney trial; it was an active-comparator cardiovascular outcomes trial in more than 13,000 patients, with dulaglutide serving as a particularly meaningful comparator because dulaglutide already has established cardiovascular benefit.

For the primary cardiovascular endpoint—cardiovascular death, myocardial infarction or stroke—tirzepatide was noninferior to dulaglutide. That result established cardiovascular safety and efficacy in a high-risk population, but for nephrologists the prespecified kidney analysis is especially interesting.

Over a median follow-up of approximately four years, the risk of the composite major kidney outcome was 23% lower with tirzepatide than with dulaglutide: 6.0% versus 7.6% of participants experienced an event, corresponding to a hazard ratio of 0.77. The kidney composite included persistent macroalbuminuria, a sustained reduction in eGFR of at least 50%, end-stage kidney disease, or death from kidney disease.

The pattern of benefit also differed according to baseline kidney risk. In patients with low-to-moderate kidney risk, much of the advantage was driven by less new persistent macroalbuminuria. In patients with high-risk CKD, the more compelling signal was a slower decline in kidney function. In that higher-risk group, the annual eGFR slope favored tirzepatide over dulaglutide by approximately 0.93 mL/min/1.73 m^2 per year.

That is an important finding because the comparison was not against placebo. Tirzepatide demonstrated incremental kidney benefit over an active GLP-1 receptor agonist, suggesting that the magnitude of weight loss, metabolic improvement, blood-pressure effects, and possibly GIP/GLP-1 biology may translate into additional cardiorenal protection.

At the same time, this deserves the same nuance we apply elsewhere in nephrology. The kidney results were prespecified but exploratory, and SURPASS-CVOT was not designed primarily as a renal outcomes trial. I therefore would not place it on exactly the same evidentiary footing as FLOW for kidney disease. But it strengthens the argument that incretin-based therapy is evolving from metabolic treatment into a genuine component of cardiorenal risk reduction.

What About Patients Without Diabetes?

This is where the story becomes even more interesting.

The SELECT trial studied patients who were overweight or obese and had established cardiovascular disease but did not have diabetes. A prespecified kidney analysis found fewer major kidney events with semaglutide: 1.8% versus 2.2% with placebo, corresponding to a 22% relative risk reduction.

Patients receiving semaglutide also experienced less decline in eGFR, with an even larger difference among participants who already had an eGFR below 60.

This raises an important question for nephrologists: Could GLP-1 therapy eventually become a treatment for CKD independent of diabetes?

We are not quite there yet.

The evidence for diabetic CKD is substantially stronger, and dedicated evidence in nondiabetic CKD remains less mature. But the direction of the data is encouraging enough that this is now an important area of investigation.

GLP-1s Do Not Replace the Rest of Kidney-Protective Therapy

One mistake would be to view these medications as substitutes for established CKD therapy.

They are better viewed as another layer of protection.

In an appropriate patient with diabetic kidney disease, treatment may now include renin-angiotensin system blockade, an SGLT2 inhibitor, appropriate use of a nonsteroidal mineralocorticoid receptor antagonist, such as finerenone, blood-pressure control, lipid management, and potentially GLP-1–based therapy.

This increasingly resembles the approach cardiologists have taken toward heart failure: instead of looking for one “best” medication, we attack disease progression through several complementary pathways. That concept is likely to become increasingly important in nephrology.

The Other Side of the Equation

GLP-1 therapy is not without drawbacks, and patients with kidney disease deserve particular attention.

The most common problems are gastrointestinal—nausea, vomiting, diarrhea, constipation and early satiety. In most patients these are manageable by starting at a low dose and titrating gradually.

In CKD, however, vomiting and poor oral intake can become more consequential.

A patient with limited renal reserve who develops significant nausea, vomiting and volume depletion can develop acute kidney injury. The drug itself is not necessarily directly nephrotoxic; rather, the combination of poor intake, gastrointestinal losses, diuretics, renin-angiotensin system blockers and other medications can create the perfect environment for a prerenal insult.

That distinction matters.

When I prescribe or encounter these medications in patients with advanced CKD, I pay particular attention to volume status, blood pressure, diuretic requirements and changes in oral intake. A patient who is doing well on therapy does not necessarily require extraordinary monitoring, but a patient who develops persistent vomiting or significant volume depletion deserves prompt reassessment.

There is also an important nutritional issue.

Weight loss is not synonymous with healthy weight loss.

Patients with advanced CKD—and particularly patients approaching dialysis or already receiving dialysis—can be vulnerable to protein-energy wasting and loss of lean muscle mass. A 30-pound weight reduction may be desirable in one patient and potentially harmful in another.

The number on the scale cannot be our only endpoint.

Advanced CKD and Dialysis

This is an area where clinical judgment becomes especially important.

For several GLP-1 agents, renal clearance is not the major pathway of elimination, and medications such as semaglutide generally do not require dose adjustment simply because the eGFR has fallen.

That does not mean that evidence is equally robust at every stage of kidney disease.

Patients with advanced CKD, and particularly those receiving dialysis, have historically been underrepresented or excluded from many of the major randomized trials. Consequently, we should distinguish between pharmacologic feasibility and proven long-term outcome benefit.

There are patients on dialysis for whom GLP-1 therapy may make excellent sense, particularly those with diabetes and severe obesity. But the risk-benefit calculation is different from that of a patient with Stage 3 CKD.

A Particularly Interesting Role: Getting Patients to Transplant

One of the most exciting applications may actually occur before transplantation.

Obesity remains a major barrier to kidney transplantation. Many transplant programs use BMI thresholds or require significant weight loss before activating a patient on the transplant waiting list.

Historically, this creates a frustrating situation.

> **This may prove to be one of the most practical applications of GLP-1 therapy in advanced kidney disease: not merely treating obesity, but removing obesity as a barrier to transplantation.**

We tell a patient with kidney failure that transplantation offers the best long-term renal replacement therapy, but then tell that same patient that he or she must lose substantial weight before becoming eligible. Losing weight while living with advanced kidney disease or undergoing dialysis can be extraordinarily difficult.

GLP-1 therapy may give us another option.

Early observational experience is encouraging. Recent reports of semaglutide use in obese dialysis patients have demonstrated clinically meaningful weight loss, with substantial numbers of previously ineligible patients subsequently becoming eligible for transplant listing.

This may prove to be one of the most practical applications of GLP-1 therapy in advanced kidney disease: not merely treating obesity, but removing obesity as a barrier to transplantation.

That is a very different clinical endpoint than lowering an A1c.

What About After Kidney Transplantation?

Post-transplantation is equally intriguing.

Kidney transplant recipients commonly struggle with weight gain, diabetes, hypertension and cardiovascular disease. Corticosteroids and calcineurin inhibitors can compound these metabolic problems.

GLP-1 therapy therefore has obvious theoretical advantages.

The emerging observational literature suggests that GLP-1 receptor agonists can improve weight and glycemic control in kidney transplant recipients without a consistent adverse signal for graft function. Recent pooled analyses have also been reassuring regarding tacrolimus exposure, although the evidence remains far less robust than the randomized data available in non-transplant CKD.

This is an important distinction.

We should not take evidence from the general CKD population and automatically assume that it applies identically to transplant recipients. Delayed gastric emptying, gastrointestinal intolerance, fluctuating volume status and the narrow therapeutic window of immunosuppressive medications all deserve attention.

For now, I view GLP-1 therapy after transplantation as a promising and increasingly reasonable option in selected patients—not as a universal transplant protocol.

Can GLP-1 Therapy Actually Improve Kidney Function?

Patients frequently ask whether these medications can "make my kidneys better."

That question requires some nuance.

Chronic kidney disease usually represents structural injury that cannot simply be reversed by medication. We should therefore be cautious about describing GLP-1 therapy as regenerating or repairing damaged kidneys.

The better way to think about it is preservation of remaining kidney function.

If a patient's eGFR would otherwise decline several points each year and treatment slows that decline substantially, the patient's laboratory numbers may not dramatically "improve." But dialysis might be postponed for years.

For the patient, that is an enormous benefit.

The goal of modern CKD therapy is increasingly not simply to improve today's creatinine. It is to change the slope of kidney-function decline over the next five, 10 or 15 years.

> **GLP-1–based therapy should no longer be thought of simply as diabetes treatment—or even simply as weight-loss treatment.**

Where I Think This Is Going

We are entering an era in nephrology in which CKD is becoming increasingly treatable.

That statement would have sounded optimistic 20 years ago.

Today we have therapies that attack CKD progression through several different mechanisms. SGLT2 inhibitors changed our expectations. Finerenone added another pathway. Semaglutide has now demonstrated dedicated kidney-outcome benefit in FLOW, while SURPASS-CVOT extends the cardiorenal story to tirzepatide. GLP-1–based therapies increasingly appear capable of adding meaningful renal, cardiovascular and metabolic protection in appropriately selected patients.

The next question will be how effectively we combine them.

There are still unanswered questions. We need better randomized evidence in nondiabetic CKD, dialysis patients and transplant recipients. We need to understand the long-term consequences of substantial weight and lean-mass loss in advanced CKD. We need better strategies for managing gastrointestinal intolerance and volume depletion. And cost and access remain significant real-world barriers.

But the direction is increasingly clear.

GLP-1–based therapy should no longer be thought of simply as diabetes treatment—or even simply as weight-loss treatment.

For nephrologists, it represents something considerably more interesting: another opportunity to intervene earlier, reduce cardiovascular risk, slow the loss of kidney function and, in selected patients, potentially help create a bridge to transplantation.

For a specialty that historically spent much of its time managing the consequences of irreversible kidney disease, the ability to meaningfully change its trajectory is a welcome shift.

The future of nephrology is increasingly about preserving kidney function before we ever have to replace it. GLP-1–based therapy appears poised to become an important part of that future.

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KDIGO Clinical Practice Guidelines for Diabetes Management in Chronic Kidney Disease.

Emerging observational studies and pooled analyses evaluating GLP-1 receptor agonists in dialysis patients, kidney-transplant candidates, and kidney-transplant recipients.



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