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The Path to Progress: Glucagon-like Peptide 1 Agonists, Individualized Care, and Overcoming Goal-Directed Medical Therapy Barriers in Diabetes and CKD

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The origin of glucagon-like peptide 1 (GLP-1) agonists (GLP-1RA) can be traced back to a shy, unassuming, slow-moving reptile found within the southwestern regions of the United States. In 1990, an endocrinologist named John Eng from the veterans' administration center in Bronx, NY, isolated exendin-4 from the venomous saliva of the famed Gila monster. Exendin-4 is an incretin hormone that stimulates insulin production during periods of high glucose loads in the Gila monster, known to consume only 3 to 4 meals per year. Exendin-4 is molecularly similar to mammalian GLP-1 and can bind to GLP-1 receptors imparting similar physiologic responses. As an incretin hormone, GLP-1 stimulates glucose-dependent insulin secretion, promotes insulin gene transcription, and inhibits glucagon release. In the stomach, it inhibits gastric emptying thereby reducing appetite. In the brain, GLP-1 promote satiety and demonstrates neuroprotective effects. Interestingly, GLP-1 is rapidly degraded within minutes whereas exendin-4 evades GLP-1 regulatory mechanisms, with a substantially longer half-life compared to its human counterpart. And the rest is history, the potential diabetes and weight loss benefits of a long-acting GLP-like therapy were clear. Following the 2005 release of the first US Food and Drug Administration-approved GLP-1RA exenatide for the treatment of type 2 diabetes, the GLP-1RAs drug industry experienced exponential growth, releasing a myriad of GLP-1RA formulations, administration routes, duration of action, and indications bringing us to the current day.

Diabetes is the leading cause of chronic kidney disease (CKD) worldwide, responsible for up to 50% of end-stage renal disease. Furthermore, CKD and diabetes have an independent and additive effect on cardiovascular (CV) risk and mortality. The Kidney Disease: Improving Global Outcomes (KDIGO) risk classification uses albuminuria and estimated glomerular filtration rate to categorize risk of progression to kidney failure, CV events, and death. However, developments in diabetes and CKD management are reshaping the therapeutic landscape with the emergence of sodium glucose cotransporter 2 inhibitors (SGLT2i), nonsteroidal mineralocorticoid receptor antagonists such as finerenone, and now GLP-1RAs, which are in addition to the age-old renin angiotensin aldosterone inhibitors. Randomized controlled trials examining GLP-1RA CV outcomes revealed improvement in CV disease in patients with type 2 diabetes and high CV risk. Although these trials were not powered for kidney outcomes, the accumulating data and multiple pooled analyses provide compelling data that GLP-1RAs provide protective kidney function benefits. The long-anticipated FLOW randomized controlled trial published in NEJM evaluating once weekly subcutaneous semaglutide versus placebo in diabetic kidney disease reported a 24% risk reduction of the primary composite end point of kidney failure, persistent ≥50% reduction in estimated glomerular filtration rate, or death from kidney or CV; finally removing any doubts that GLP-1RA has kidney protective benefits.[1]

The SUSTAIN 6 randomized controlled trial published in 2016 considered CV outcomes with once weekly subcutaneous semaglutide compared with placebo in patients

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with type 2 diabetes. In addition to positive primary end point CV outcomes, secondary outcomes revealed reduced risk of new or worsening nephropathy.[2] In a *post hoc* analysis published in Kidney International Reports, Tuttle *et al*.[3] sought to assess treatment effects of once weekly semaglutide versus placebo on kidney outcomes by KDIGO risk category and on changes in KDIGO risk category, using the SUSTAIN 6 trial patient cohorts. The values were pooled by treatment and stratified into 4 subgroups by KDIGO risk category, which included low risk, moderate risk, high risk, and very high risk. The results revealed that regardless of CKD severity, once weekly semaglutide participants experienced a positive treatment effect in the composite kidney end point. Importantly, the greatest benefit was observed at the highest risk categories. A similar trend was observed in estimated glomerular filtration rate slope, which revealed a smaller decline in the semaglutide cohort, which was numerically smaller in the highest risk categories. Participants receiving semaglutide were more likely to move to a lower KDIGO risk category and less likely to move to a higher KDIGO risk category. As expected, changes in urine albumin-to-creatinine ratio were the primary drivers for regression of KDIGO risk category in both semaglutide and placebo groups. However, uniquely identified, change in estimated glomerular filtration rate was the main driver for progression of KDIGO category in both semaglutide and placebo groups. A *post hoc* analyses SGTL2i EMPA-REG OUTCOME randomized controlled trial demonstrated similar widespread renal protective benefits across KDIGO risk categories with the greatest benefit observed in the higher risk cohorts.[4]

The 2024 KDIGO clinical practice guidelines for patients with CKD and diabetes lists the following as recommended goal-directed medical therapy (GDMT): metformin and SGLT2i, followed by nonsteroidal mineralocorticoid receptor antagonists in those with persistent albuminuria >30 mg/g despite other standard-of-care therapies, and GLP-1RA in those not achieving individualized glycemic targets despite standard-of-care therapies (1B evidence).[5] Populations that fall within the high and very high risk KDIGO categories are associated with the highest burden of disease, have the greatest risk of disease progression, and seem to benefit the greatest with rapid implementation of GDMT. Incorporating standard-of-care interventions such as GLP-1RA does not only reduce progression of kidney disease; they reduce risk of CV progression and death. Utilizing KDIGO risk categories in patient care enable practitioners to individualize CKD risk assessment, prioritizing those with greatest need and urgency in GDMT implementation.

Unfortunately, the known benefit of GLP-1RA and other GDMT in CKD and diabetes has not translated into widespread implementation of these practices. A cross-sectional study in the veterans' health administration between 2019 and 2020 revealed that 10.7% and 7.7% of patients were prescribed an SGLT2i or a GLP-1RA, respectively.[6] Data from the centers for disease control and prevention show that older adults, women, and non-Hispanic White patients are more likely to be prescribed SGLT2i, GLP-1RA, or DPP-4 inhibitor compared to other ages, male gender, and race/ethnicities; however, they were still only prescribed in 21.3%, 17.8%, and 20.4% of those cohorts, respectively.[7]

Reasons for the lackluster adoption of these important GDMT is multifaceted. Frequently cited barriers include limited kidney disease education among patients and providers, low CKD awareness, clinical inertia, polypharmacy, cost, disparities in underserved populations, lack of public policy on health equity, and fragmented care.[8] Surmounting these barriers will take a coordinated effort between health systems and communities, interdisciplinary care; and local, national, and global initiatives aimed to educate and create CKD awareness.

At the level of the provider, patients often receive fragmented care caused by the siloed care models found in many health care delivery systems, where providers practice independent of one another. In the setting of advanced diabetic kidney disease, where primary care physicians, nephrologists, cardiologists, and other specialists provide overlapping care, providers can fall victim to "stay in your lane" mentalities. This is a form of clinical inertia whereby crucial GDMT such as SGLT2i and GLP-1RA can be delayed. In any disease with increasing complexity, clinical inertia is magnified. We call it a "medical complexity care conundrum" when increased disease complexity and comorbid conditions necessitate an increased number of involved specialists. With increased complexity, primary care physician and specialist care responsibility overlap whereby everyone, or no one is responsible, and deferral of patient management decisions is common. In addition, increased subspecialist visit frequency competes with time and motivation to attend primary care physician visits. The sum effect is a greater number of physicians involved in patient care; however, an overall reduction in coordinated care whereby patient

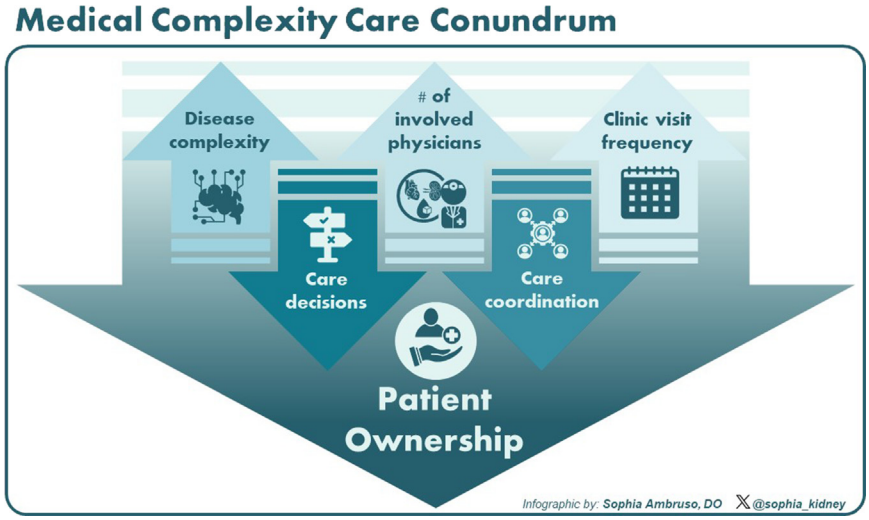

Figure 1. The medical complexity care conundrum is a phenomenon observed with increasing disease complexity, which results in a proportional increase in the number of physicians (primary care physician and specialists) providing patient care. Competing appointment time, siloed medical care, and "stay in your lane" mentalities result in fragmented care and clinical inertia whereby delays in care decisions, reduced care coordination, and a loss of patient ownership occurs.

ownership is not claimed (Figure 1). Using the example of diabetes management in diabetic kidney disease, optimized glycemic control and GDMT can be delayed for months to years while waiting for another provider to begin or adjust therapy. As nephrologists, we should acknowledge that we have a responsibility to close this gap, dismantle "stay in your lane" mentalities and expand patient care roles such as diabetes management, which includes GLP-1RA therapies. Furthermore, we can begin tearing down the familiar compartmentalized care platform and build interdisciplinary care models aimed to provide a team-approach for optimized GDMTs.

DISCLOSURE

SLA is a scientific advisor to AstraZeneca. MRW is a scientific advisor to Bayer, AstraZeneca, CLS Vitor, NovoNordisk, and Boehringer Ingelheimer.

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