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Renal Effects of Incretin-Based Diabetes Therapies: Pre-clinical Predictions and Clinical Trial Outcomes

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Abstract

Purpose of Review—The purpose of this review is to correlate predictions based on pre-clinical data with outcomes from clinical trials that examine the effects of incretin-based diabetes treatments on the kidney. The incretin-based treatments include agonists of the glucagon-like peptide 1 receptor (GLP-1R) and inhibitors of the enzyme, dipeptidyl peptidase-4 (DPP-4). In addition, what is known about the incretin-based therapies will be compared to what is known about the renal effects of SGLT2 inhibitors.

Recent Findings—Large-scale clinical trials have shown that SGLT2 inhibitors reduce albuminuria and preserve estimated glomerular filtration rate (eGFR) in patients with diabetic nephropathy. A concise and plausible hemodynamic mechanism is supported by pre-clinical research on the physiology and pharmacology of SGLT2. Large-scale clinical trials have shown that incretin-based therapies mitigate albuminuria but have not shown beneficial effects on eGFR. Research on the incretin-based therapies has yielded a diverse array of direct effects throughout the body, which fuels speculation as to how these drugs might benefit the diabetic kidney and affect its function(s). But in vivo experiments have yet to confirm that the proposed mechanisms underlying emergent phenomena, such as proximal tubular fluid reabsorption, are the ones predicted by cell and molecular experiments.

Summary—There may be salutary effects of incretin-based treatments on the diabetic kidney, but the system is complex and not amenable to simple explanation or prior prediction. This contrasts with the renal effects of SGLT2 inhibitors, which can be explained concisely.

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Introduction

At the onset of diabetes, the kidney grows large and GFR becomes supranormal [1–3]. This early growth and hyperfunction appear to be most pronounced in the subset of patients with diabetes who proceed to develop diabetic nephropathy many years later [1, 4–9]. Current treatment for diabetic nephropathy is centered on blocking the renin-angiotensin-aldosterone system (RAAS) and is palliative. Treatment that reduces the actual incidence of diabetic nephropathy while reducing the pill burden on patients with diabetes would be preferable. Hence, it is worthwhile to consider whether a particular regimen aimed at glycemic control in diabetes might also exert "off target" effects on the kidney that forestall the onset of diabetic nephropathy or slow its progression. This consideration has gained attention during the development of sodium-glucose cotransporter 2 (SGLT2) inhibitors and incretin-based drugs for lowering blood glucose. We will discuss some of the clinical and pre-clinical data pertaining to this subject. Our principal charge is to discuss the current state of knowledge about incretin-based therapies. We will put this in context by making comparison to the current understanding of SGLT2.

SGLT2 inhibitors (canagliflozin, dapagliflozin, empagliflozin, ipragliflozin, and tofogliflozin) lower blood glucose levels by blocking reabsorption of most filtered glucose by the proximal tubule [10]. In the course of preventing glucose uptake by the early proximal tubule, acute SGLT2 blockade inevitably shifts the burden for reabsorbing a greater fraction of the filtered sodium chloride (NaCl) and fluid to later segments of the nephron and elicits a tubuloglomerular feedback (TGF) response, which suppresses hyperfiltration. These immediate effects on tubular and glomerular function have been validated in micropuncture experiments [11–12]. It has now been shown that the effect is durable and, thus, sufficient to explain the persistent, yet rapidly reversible, suppression of hyperfiltration by SGLT2 blockers in human subjects [12–15]. SGLT2 blockers likely have other effects on the kidney that will come to light through ongoing research, but this concise framework suffices to explain the main effects on renal salt handling and hemodynamics.

Incretin-based therapies have more complicated renal mechanisms of action than SGLT2 blockade. Incretin-based therapies include glucagon-like peptide-1 receptor (GLP-1R) agonists (albiglutide, dulaglutide, exenatide, liraglutide, lixisenatide), which activate GLP-1R directly, and dipeptidyl peptidase-4 (DPP-4) inhibitors (linagliptin, saxagliptin, sitagliptin, vildagliptin), which impede the degradation of endogenous GLP-1. The useful GLP-1R agonists are resistant to DPP-4. Incretin-based treatments lower blood glucose by a combination of effects that follow activation of GLP-1R at various sites. The mechanism of glucose lowering by incretin-based drugs is more complex than that for SGLT2 blockade, but it has been defined [16]. The effects of GLP-1R agonists and DPP-4 inhibitors on basic kidney function(s) are more complex than those of SGLT2 inhibitors, and they are less well-defined.

A predictive model for effects of incretin-based treatments on the kidney will be inherently more difficult to develop than a predictive model for SGLT2, because it must include more variables. SGLT2 is confirmed to exist only in the early proximal tubule, which naturally puts sodium and glucose transport in the early proximal tubule at the hub of any model of its

actions. But GLP-1R and DPP-4 are expressed throughout the body [17, 18]. Furthermore, GLP-1 fragments may be bioactive at sites other than GLP-1R while DPP-4 has many substrates other than GLP-1 with potential to impinge on the kidney through different signaling pathways [19, 20, 21]. Thus, a GLP-1R agonist or DPP-4 inhibitor may simultaneously alter the activity of multiple effectors that compete for control of a given variable. This will make the net effect of a GLP-1R agonist or DPP-4 inhibitor on that variable strongly dependent on the physiological or experimental conditions in ways that may not be obvious.

Incretins in Renal Hemodynamics and Tubular Reabsorption

To fully characterize the tonic influence of GLP-1R activity in kidney, physiology would require a potent pharmacologic GLP-1R antagonist, which does not exist, although experiments with a weak GLP-1R antagonist, exendin-(9–39), were able to establish that GLP-1 is a natriuretic factor [22]. Acute infusion of GLP-1R agonist, exenatide, causes selective renal vasodilation and diuresis in rats and wild-type mice, but not in GLP-1R knockout mice, thus conferring specificity of the agonist to GLP-1R [23, 24]. The proximal tubule contains GLP-1R and DPP-4, which presumably degrades filtered GLP-1. Intravenous exenatide acutely suppressed proximal reabsorption in micropuncture experiments, which were designed to distinguish primary effects of exenatide on proximal reabsorption from effects mediated by changes in filtered load [23]. Exenatide also suppresses proximal reabsorption when applied directly into Bowman's space by microperfusion, confirming a role for tubular GLP-1R (unpublished). GLP- 1R activation has been associated with PKA-mediated phosphorylation and potential inactivation of sodium-hydrogen exchanger 3 (NHE3) in the proximal tubule, providing a plausible mechanism for the diuretic effect [24–26].

Increases in GFR and urine output during acute exenatide infusion in rats are abrogated when systemic nitric oxide activity is clamped with a mixture of a generalized NOS inhibitor and sodium nitroprusside [27]. Analogous renal responses to acute exenatide infusion were recently reported for human subjects with and without type 2 diabetes. For example, exenatide caused nitric oxide-dependent renal vasodilation in overweight humans and reduced proximal reabsorption in humans with type 2 diabetes [28•, 29•]. The natural response to an isolated reduction in proximal reabsorption is to activate TGF and reduce GFR. For exenatide to simultaneously suppress proximal reabsorption and increase GFR, it must have an additional vascular effect to override the activation of TGF. The differential effect on humans with and without diabetes in these two recent studies could be explained if the tubular effects were to dominate the vascular effect in patients with diabetes and vice versa in patients without diabetes. This would be consistent with the overall tendency in diabetes for the proximal tubule to become the dominant controller of GFR [30–31].

Any chronic effect of GLP-1R agonist on renal function is expected to be of lesser magnitude than what is observed with acute infusion. The counter-regulatory processes that engage to mitigate the primary response to GLP-1R agonist are pertinent to predicting what role GLP-1R agonists might play in long-term renal protection. This is a subject of ongoing investigation. In humans with type 2 diabetes, there is a class effect of GLP-1R agonists to

reduce long-term blood pressure [32]. According the Guyton principle, this implies that GLP-1R agonists either reduce sodium intake or reduce the level of blood pressure required by the kidney to excrete the daily sodium intake [33].

The renal response to DPP-4 inhibitors is more subtle and complicated than the response to GLP-1R agonists. DPP-4 inhibitors suppress NHE3 activity in the OKP line of opossum kidney proximal tubule cells, suggesting these drugs should suppress proximal reabsorption by a mechanism linked to a tyrosine kinase [34]. Indeed, systemic administration of DPP- 4 inhibitors does modestly reduce proximal reabsorption in mice. However, this effect persists in mice lacking GLP-1R and does not involve phosphorylation of NHE3 [24]. Preliminary micropuncture experiments from our lab have shown that acute intravenous DPP-4 inhibition causes a slight decrease in proximal reabsorption in the rat, as others suggest should happen. But contrary to expectation, direct microperfusion of the same DPP-4 inhibitor to the neck of Bowman's space, i.e., directly into the early proximal tubule, causes a major increase in fluid reabsorption (unpublished). Thus, there are studies in mice and micropuncture data from rats that are incompatible with the current model whereby DPP-4 inhibitors act as proximal tubular diuretics by direct action on DPP-4 in the proximal tubule to affect the phosphorylation state ofNHE3. Acute vasodilatory effects of DPP-4 inhibitors in other organs are also independent of GLP-1R activation [35]. Hence, effects of DPP-4 inhibitors on salt, fluid, and blood pressure homeostasis will be more complex, variable, and difficult to explain than the effects of GLP-1R agonists. Proposed mechanisms to explain effects of DPP-4 inhibitors on albuminuria and how they could mitigate kidney injury are reviewed elsewhere in detail [36].

Renal Outcomes in Large-scale CVD Safety Trials in Patients With Type 2 Diabetes

Since 2008, the Food and Drug Administration has required new glucose-lowering therapies be proven safe from a cardiovascular standpoint [37]. This was the era when SGLT2 and incretin-based diabetes treatments were being developed. Hence, there are rigorously obtained data from large-scale clinical trials designed to measure cardiovascular disease (CVD) outcomes in patients with diabetes randomized to receive SGLT2 inhibitors and incretin-based treatments. Investigators who designed these trials all faced the same stipulation, which was to prove non-inferiority of a novel agent with respect to CVD outcomes. Hence, several of the studies are comparable in their basic design for assessing and reporting CVD outcomes of different drugs, and their findings are fairly amenable to comparison, albeit some differences in the pharmacology of particular agents or study populations have been cited.

While it was the primary objective of these trials to confirm CVD safety, some also acquired data on microvascular complications, including diabetic kidney disease, and reported these as secondary outcomes, either in the primary publication or in follow-up publications. Most reports on renal outcomes with incretin-based drugs only cite statistics on a composite renal outcome that combines some measure of albuminuria, declining estimated glomerular filtration rate (eGFR), and incident end-stage renal disease (ESRD). But while declining GFR and incident ESRD are included in the composite renal outcome, the data from these trials lack a clear signal for declining kidney function and the composite in the clinical trials

of incretin-based treatments is driven by effects on albuminuria. In contrast to the incretin-based CVD trials, the major SGLT2 trials were able to demonstrate a salutary effect on long-term GFR and report this separately from the composite renal outcome [38–39]. Prima facie, this suggests that SGLT2 blockade is more effective at mitigating loss of kidney function than are incretin-based therapies. SGLT-2 also has the advantage of a concise and plausible hemodynamic justification for improved renal outcomes, which is analogous to the original explanation given for the renal benefit of RAAS blockade [9]. The main renal outcomes of these trials are shown in Table 1.

A caveat is that the placebo-treated groups in the incretin- based trials suffered fewer declines in eGFR than their counterparts in SGLT2 trials so there was less for the incretin-based treatments to improve upon. This also applies to a pooled analysis of renal disease endpoints from 13 large randomized linagliptin trials, which found a renal benefit in terms of reduced albuminuria, but lacked the power to detect effects on eGFR [40•]. Results from individual trials that reported renal endpoints are as follows:

Individual Trials of GLP-1R Agonists

SUSTAIN-6 (GLP-1R Agonist Trial): ClinicalTrials.gov **Number, NCT01720446** This study examined the effect of GLP1-R agonist, semaglutide, on cardiovascular disease (CVD) out-comes. There were fewer CVD events in subjects receiving semagutide vs. placebo (6.6 vs. 8.9%, hazard ratio 95% confidence interval (CI) 0.58 to 0.95; P<0.001 for non-inferiority; P=0.02 for superiority). New or worsening nephropathy was less in those treated with semaglutide vs. placebo (3.8 vs. 6.1%, hazard ratio CI 0.46–0.88, P=0.005) as defined by macroalbuminuria or doubling of the serum creatinine level to eGFR less than 45 ml per minute. The determinative factor was albuminuria [41•].

LEADER (GLP-1R Agonist Trial): ClinicalTrials.gov **Number, NCT01179048** This study examined the effect of GLP-1R agonist, liraglutide, on CVD outcomes. There were fewer CVD events in subjects receiving liraglutide than placebo (13.0 vs. 14.9%, hazard ratio CI 0.87–9.97, P< 0.001 for non-inferiority, P< 0.01 for superiority) [42]. New or worsening nephropathy was less with liraglutide (5.7 vs. 7.2%, hazard ratio CI 0.67–0.92, P = 0.003). Again, the improved renal outcomes were driven by lower incidence of albuminuria rather than loss of kidney function [43•].

Trials of DPP-4 Inhibitors

SAVOR-TIMI 53 (DPP-4 Inhibitor Trial): ClinicalTrials.gov **Number, NCT01107886** This study examined the effect of DPP-4 antagonist, saxagliptin, on CVD outcomes. Saxagliptin had no effect on the rate of ischemic events but increased the incidence of hospital admissions for congestive heart failure by 25% (3.5 vs. 2.8%; hazard ratio CI 1.07 to 1.51; P= 0.007). Participants treated with saxagliptin were more likely to have an improved albumin to creatinine ratio and less likely to have a worsening ratio (P< 0.001). The full effect on albuminuria was manifest within the first year of treatment, so it was likely functional. Approximately 2% of participants experienced doubling of creatinine, reached plasma creatinine concentrations > 6 mg/dl, or required renal replacement therapy in

the course of the trial, and these outcomes were not affected by saxagliptin (hazard ratio CI 0.88–1.32, $P = 0.46$) [44•].

TECOS (DPP-4 Inhibitor Trial): ClinicalTrials.gov **Number NCT00790205** This study showed that sitagliptin was noninferior to usual care with respect to CVD outcomes in participants with established CVD [45]. Ancillary data included repeated measures of eGFR, which remained stable over the 4-year study in both treatment groups and among those entering the trial with stage 3 chronic kidney disease (CKD) or normal kidney function. Albuminuria was not addressed [46•].

In a meta-analysis of 13 smaller randomized trials including ~4500 subjects, treatment with DPP-4 inhibitor, linagliptin, was associated with less new onset moderate albuminuria, but there were too few instances of CKD progression to draw conclusions about long-term effect on kidney function or kidney survival [40•].

While renal outcomes were ancillary in the foregoing CVD trials, we are aware of one published randomized DPP-4 inhibitor trial designed primarily to look at renal outcomes. This trial (MARLINA-T2D study, ClinicalTrials.gov, NCT01792518) was designed to investigate the renal effects of linagliptin in individuals with type 2 diabetes and preexisting albuminuria on RAAS blockade. After 24 weeks, linagliptin had no effect on eGFR or albuminuria. The authors were left to speculate as to why this dedicated study failed tofulfill expectations of reduced albuminuria based on large amounts of data from the earlier CVD trials [47•].

To summarize, using changes in albuminuria as a surrogate for renal disease, most, but not all, data from large randomized clinical trials point toward reduced albuminuria with incretin-based therapies, which may be an intermediate phenotype for renal preservation. In contrast, clinical trial data obtained with SGLT2 inhibitors also show preserved kidney function.

Alternative Mechanisms for Salutary Renal Effects of DPP-4 Inhibitors

Since DPP-4 has many substrates, effects of DPP-4 inhibitors are expected to be pleiotropic, and several investigators have mined these for effects that might be useful. Pre-clinical studies ascribe several properties to DPP-4 inhibitors that could be conceived as beneficial. Among these, DPP-4 inhibitors have been described as anti-fibrotic, anti-oxidant, anti-apoptotic, and anti-inflammatory [48–57]. These arguments are plausible and include molecular detail. One would imagine, given a list of potential effects this open-ended, that biological effects of DPP-4 inhibitors, once discovered, would distribute randomly between categories currently viewed as "good" and "bad." However, those findings that are published provide only optimism for the future of DPP-4 inhibitors in CKD and suggest no pitfalls. But similar properties have been imputed to dozens of other xenobiotics over the years, none of which has translated to effective treatment for human CKD. The track record of other proposed CKD treatments for which similar claims were initially made and the outcomes from randomized clinical trials with DPP-4 inhibitors militate circumspection.

Conclusions

Progress is being made through both basic science and clinical trials to establish the proper role for SGLT2 inhibitors and incretin-based therapies in human diabetes where they may improve cardiovascular and renal outcomes. At this point, the SGLT2 inhibitors enjoy an edge over incretin-based therapies with respect to renal outcomes inasmuch as SGLT2 inhibitors were clearly shown to slow the decline in eGFR in two out of two large-scale clinical trials while incretin-based drugs failed to do so in any of four similarly designed trials (see Table 1). SGLT2 inhibitors also enjoy an advantage of better coherence between the basic science and the clinical trial results. One reason for this is that the incretin-based therapies impinge on numerous factors at once, which makes their emergent properties difficult to predict.

Acknowledgments

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Table 1

Study characteristics and renal outcomes in major clinical trials of incretin-based and SGLT2 inhibitor drugs

Trial	Agent	Sample size Median time of follow-up Baseline participant characteristics	Renal endpoints	Result	P value
Sustain-6 [41•]	GLP1-R agonist Semaglutide	n = 3297 25 months ~ 60% CVD ~25% eGFR < 60	Incident albuminuria * Decline in eGFR *	2.7 vs. 4.9% 1.1 vs. 0.8%	0.001 ns
LEADER [43•]	GLP1-R agonist Liraglutide	n = 9340 46 months ~ 81% CVD ~ 25% eGFR < 60	Incident albuminuria * Decline in eGFR *	3.4 vs. 4.6% 1.8 vs. 2.1%	0.004 ns
SAVOR-TIMI 53 [44•]	DPP-4 inhibitor Saxagliptin	n = 12,360 25 months ~ 78% CVD ~ 16% eGFR < 50	Increased albuminuria * Decline in eGFR *	13 vs. 16% 2.2 vs. 2.0%	0.001 ns
TECOS [46•]	DPP-4 inhibitor Sitagliptin	n = 14,671 36 months ~ 75% CVD 23% eGFR < 60	Urine albumin/creatinine (mg/g) Rate of decline in eGFR (ml/min/year)	11.1 vs. 10.9 1.0 vs. 0.7	0.03 ns
EMPA-REG OUTCOME [15]	SGLT2 blocker Empagliflozin	n = 7020 37 months ~ 80% CVD ~ 26% eGFR <60	Incident albuminuria * Decline in eGFR *	11 vs. 16% 1.5 vs. 2.6%	<0.001 <0.001
CANVAS [39]	SGLT2 blocker Canagliflozin	n = 10,142 47 months ~ 66% CVD ~ 25% eGFR <60 ***	Incident albuminuria ** > 40% decline in eGFR **	9 vs. 13 0.5 vs. 0.9	<0.001 **** <0.001 ****

CVD cardiovascular disease, *eGFR* estimated glomerular filtration rate

* > 300 mg albumin/g creatinine or halving of eGFR to < 45 ml/min/1.73 m^2 during course of trial

** Events per 100 pt-years

*** Inferred from mean (SD) eGFR assuming normal distribution

**** Computed from 95% confidence intervals