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EDITORIAL

Is there a role for glucagon-like peptide-1 receptor agonists in the management of diabetic nephropathy?

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Abstract

Chronic kidney disease constitutes a major microvascular complication of diabetes mellitus. Accumulating data suggest that glucagon-like peptide-1 receptor agonists (GLP-1 RAs) might have a role in the management of diabetic kidney disease (DKD). GLP-1 RAs appear to reduce the incidence of persistent macro-albuminuria in patients with type 2 diabetes mellitus. This beneficial effect appears to be mediated not only by the glucose-lowering action of these agents but also on their blood pressure lowering, anti-inflammatory and antioxidant effects. On the other hand, GLP-1 RAs do not appear to affect the rate of decline of glomerular filtration rate. However, this might be due to the relatively short duration of the trials that evaluated their effects on DKD. Moreover, these trials were not designed nor powered to assess renal outcomes. Given than macrolbuminuria is a strong risk factor for the progression of DKD, it might be expected that GLP-1 RAs will prevent the deterioration in renal function in the long term. Nevertheless, this remains to be shown in appropriately designed randomized controlled trials in patients with DKD.

Key Words: Diabetic nephropathy; Type 2 diabetes mellitus; Glucagon-like peptide-1 receptor agonists; Liraglutide; Dulaglutide; Semaglutide

Core Tip: Glucagon-like peptide-1 receptor agonists prevent the development of persistent macroalbuminuria in patients with type 2 diabetes mellitus. However, it is unclear whether they delay the decline in glomerular filtration rate in this population. Long-term trials are needed to clarify the role of these agents in the management of diabetic nephropathy.

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INTRODUCTION

Chronic kidney disease (CKD) constitutes a major microvascular complication of diabetes mellitus (DM) and occurs both in type 1 and type 2 DM (T2DM)[1]. The prevalence of diabetic nephropathy is 50% in patients with type 1 DM and 30%-50% in patients with T2DM[2]. Diabetic kidney disease (DKD) is characterized by specific structural and functional changes in the kidneys of patients with DM. These changes result in a clinical presentation that includes hypertension, increased urinary albumin excretion and progressive deterioration in kidney function[1]. It has been estimated that DKD is the leading cause of end-stage renal disease (ESRD) and 30%-40% of patients with DKD are expected to develop ESRD[3]. More specifically, patients with higher levels of albuminuria, quick deterioration of glomerular filtration rate (GFR), uncontrolled hypertension, long duration of DM, presence of microvascular complications and positive family history of DKD are at higher risk of DKD progression to ESRD[4]. Importantly, DKD is associated with increased cardiovascular morbidity and mortality[4]. It has been shown that proteinuria and impaired GFR are independently associated with higher risk of adverse cardiovascular outcomes in patients with T2DM[5]. The main goals of treatment of DKD are to delay the deterioration of kidney function and to prevent cardiovascular events. Lifestyle measures (*i.e.*, diet and exercise), strict glycemic control and blood pressure control using renin–angiotensin–aldosterone system inhibitors are the cornerstone of DKD treatment[6].

Accumulating data suggest that glucagon-like peptide-1 receptor agonists (GLP-1 RAs) might have a role in the management of DKD. GLP-1 is secreted by the L-cells of small intestine after food intake and regulates glucose homeostasis[7]. GLP-1 RAs are divided into short-acting (exenatide, liraglutide and lixisenatide) or long-acting (albiglutide, dulaglutide, exenatide long-acting release and semaglutide)[8]. GLP-1 RAs induce substantial reductions in glucose levels without the risk of hypoglycemia and also reduce cardiovascular morbidity[9]. Notably, several randomized, placebo-controlled trials in patients with T2DM and established cardiovascular disease, CKD or multiple cardiovascular risk factors reported a beneficial effect on DKD. In the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial (n = 9340), liraglutide reduced the incidence of the composite renal outcome (new-onset persistent macroalbuminuria, persistent doubling of the serum creatinine level and an estimated GFR ≤ 45 mL/min/1.73 m^2, the need for continuous renal-replacement therapy with no reversible cause of the renal disease, or death from renal disease) by 22% compared with placebo during a median follow-up of 3.8 years[10]. This reduction was driven by the lower incidence of new-onset persistent macroalbuminuria whereas the other endpoints did not differ between patients treated with liraglutide and placebo[10]. Liraglutide also reduced the incidence of new-onset microalbuminuria by 13%[10]. Even though GFR declined and albuminuria increased during follow-up in both groups, these changes were smaller in patients treated with liraglutide[10]. In the Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes (SUSTAIN-6, n = 3297), once-weekly semaglutide reduced the risk of new or worsening nephropathy (defined as a new onset of persistent macroalbuminuria, or persistent doubling of serum creatinine level and creatinine clearance) by 36% compared with placebo during a median follow-up of 2.1 years; this benefit was primarily due to the prevention of persistent macroalbuminuria[11]. In the Researching Cardiovascular Events with a Weekly Incretin in Diabetes (REWIND) trial (n = 9901), once-weekly dulaglutide reduced the incidence of the renal component of the composite microvascular outcome (defined as first occurrence of new macroalbuminuria, a sustained decline in estimated GFR ≥ 30% from baseline, or chronic renal replacement therapy) by 15% compared with placebo during a median follow-up of 5.4 years[12]. Again, this benefit was due to a decreased risk of new macroalbuminuria in patients treated with dulaglutide whereas the incidence of sustained decline in GFR and chronic renal replacement therapy did not differ between the 2 groups[12]. In a smaller randomized study in 577 patients with moderate-to-severe DKD, dulaglutide had

similar effects on albuminuria with insulin glargine but was associated with higher GFR at 52 wk[13]. In a recent meta-analysis of 7 placebo-controlled, cardiovascular outcome trials in patients with T2DM (n = 56004), treatment with GLP-1 RAs reduced the risk of the composite renal outcome by 17%; again, this benefit was only due to a reduction in the incidence of macroalbuminuria by 24%[14].

In addition to the glucose-lowering action of GLP-1 RAs, several other mechanisms appear to underpin the effects of these agents on renal function[15]. GLP-1RAs lower blood pressure both due to weight loss and due to direct effects on the kidney[15]. Indeed, it has been reported that GLP-1 RAs promote natriuresis and diuresis due to the inhibition of the sodium–hydrogen exchanger 3, which is located in the renal proximal tubular cells[16,17]. In addition, preclinical models suggest that GLP-1 RAs exert anti-inflammatory effects and decrease oxidative stress in the kidneys[18,19].

CONCLUSION

In conclusion, GLP-1 RAs appear to reduce the incidence of persistent macroalbuminuria in patients with T2DM. On the other hand, these agents do not appear to affect the rate of decline of GFR. However, this might be due to the relatively short duration of the trials that evaluated these effects. Moreover, these trials were not designed nor powered to assess renal outcomes. Given than macrolbuminuria is a strong risk factor for the progression of DKD[5,20], it might be expected that GLP-1 RAs will prevent the deterioration in renal function in the long term. However, this remains to be shown in appropriately designed randomized controlled trials in patients with DKD. The FLOW trial (NCT03819153) is currently evaluating the effects of semaglutide *vs* placebo on the progression of renal impairment in patients with DKD and is expected to be completed in 2024[21].

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