

# Effects of glucagon-like peptide-1 receptor agonists on kidney function and safety in type 2 diabetes patients

Type 2 diabetes mellitus is the leading cause of chronic kidney disease (CKD) and almost 40% of type 2 diabetes patients develop diabetic kidney disease (DKD), which is characterized by reduced estimated glomerular filtration rate (eGFR) and/or increased albuminuria. Patients with DKD are at high risk of cardiovascular disease and cardiovascular death; therefore, renal protection strategies are very important for type 2 diabetes patients.

Renin–angiotensin–aldosterone system (RAAS) inhibitors are well-known, classic drugs for DKD therapy. Recently, several clinical trials have reported that some newer glucose-lowering drugs, including sodium–glucose cotransporter 2 (SGLT2) inhibitors and glucagon-like peptide-1 receptor agonists (GLP-1RAs), have beneficial effects on the kidneys in type 2 diabetes patients. Currently, there are five GLP-1RAs (exenatide, lixisenatide, liraglutide, dulaglutide and semaglutide) approved in the USA and Europe. All GLP-1RAs have shown cardiovascular benefits and safety. Most of these trials have secondary exploratory renal endpoints data, and the secondary renal outcomes from GLP-1RA cardiovascular outcome trials suggest a renal protective effect of GLP-1RA<sup>1</sup>. Based on the previous trial results, GLP-1RAs have been recommended in DKD patients if they are contraindicated for or do not tolerate SGLT2 inhibitors.

Mann *et al.*<sup>2</sup> published an article, “Effects of once-weekly subcutaneous semaglutide on kidney function and safety in patients with type 2 diabetes: a

post-hoc analysis of the SUSTAIN 1–7 randomised controlled trials” in *The Lancet Diabetes & Endocrinology* in November 2020. They carried out a post-hoc analysis of type 2 diabetes patients enrolled in Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes (SUSTAIN) 1–7 trials, to investigate the effects of once-weekly subcutaneous semaglutide 0.5 and 1.0 mg versus comparators on kidney function and safety. The main outcomes were eGFR, urine albumin-to-creatinine ratio (UACR) and reported kidney adverse events. Comparators varied between trials: a placebo was used in SUSTAIN 1, 5 and 6; sitagliptin was used in SUSTAIN 2; exenatide extended release in SUSTAIN 3; insulin glargine in SUSTAIN 4; and dulaglutide was used in SUSTAIN 7.

In SUSTAIN 1–5 and 7, in all active treatments, the declines in eGFR were observed from baseline to week 12; estimated treatment differences (ETD) compared with placebo were  $-2.15$  (95% confidence interval [CI]  $-3.47$  to  $-0.83$ ) mL/min per  $1.73\text{ m}^2$  with semaglutide 0.5 mg, and  $-3.00$  (95% CI  $-4.31$  to  $-1.68$ ) with semaglutide 1.0 mg; eGFR plateaued after 12 weeks. Also, a greater reduction in eGFR was observed from baseline to the end of treatment when semaglutide was used rather than a placebo (ETD  $-1.58$ , 95% CI  $-2.92$  to  $-0.25$  with semaglutide 0.5 mg, and  $-2.02$ , 95% CI  $-3.35$  to  $-0.68$  with semaglutide 1.0 mg). In SUSTAIN 6, there was a greater reduction in eGFR from baseline to week 16 when semaglutide was used rather than a placebo (ETD  $-1.29$ , 95% CI  $2.07$  to  $-0.51$  with semaglutide 0.5 mg, and  $-1.56$ , 95% CI  $-2.33$  to  $-0.78$  with semaglutide 1.0 mg). However, from baseline to week 104, there was no

significant difference in eGFR reduction between semaglutide and the placebo (ETD 0.07, 95% CI  $-0.92$  to  $1.07$  with semaglutide 0.5 mg, and 0.97, 95% CI  $-0.03$  to  $1.97$  with semaglutide 1.0 mg; Table 1). In SUSTAIN 1–5, at the end of treatment, semaglutide had a greater reduction in UACR compared with the placebo (estimated treatment ratios 0.74, 95% CI 0.64–0.85 for semaglutide 0.5 mg, and 0.68, 95% CI 0.59–0.78 for semaglutide 1.0 mg). In SUSTAIN 6, at the end of treatment, there was a greater reduction in UACR with semaglutide compared with the placebo (estimated treatment ratios 0.75, 95% CI 0.66–0.85 for semaglutide 0.5 mg, and 0.66 95% CI 0.58–0.75 for semaglutide 1.0 mg). There was no difference in the incidence of renal adverse events between the treatment groups and the trials.

In SUSTAIN 1–5 and 7, in the semaglutide groups, eGFR initially decreased and then remained until the end of treatment. The initial decrease in eGFR might be due to dehydration. However, there was no difference in reported acute kidney failure, probably due to dehydration, between semaglutide and comparators. In addition to semaglutide, a slow decrease has been reported after an acute decrease in eGFR in other medications, such as RAAS inhibitors and SGLT2 inhibitors. This might reflect hemodynamic changes with a decrease in intraglomerular pressure. The initial decrease in eGFR observed with these drugs might play a role in attenuating the progression of kidney disease in the long term. The effect of SGLT2 inhibitors on eGFR has been shown to be reversible. Reduced UACR by semaglutide was observed overall across all SUSTAIN trials. A greater reduction in UACR was observed in patients with baseline

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**Table 1** | Changes and estimated treatment differences in estimated glomerular filtration rate in Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes 1–7 used in report form by Mann *et al.*<sup>2</sup>

	SUSTAIN 1-5 and SUSTAIN 7					SUSTAIN 6				
	Semaglutide 0.5 mg (n = 1,332)	Semaglutide 1.0 mg (n = 1,734)	Placebo (n = 2,62)	Stagliptin 100 mg (n = 407)	Exenatide extended release 0.2 mg (n = 405)	Insulin glargine U100 (n = 360)	Dulaglutide 0.75 mg, 1.5 mg (n = 598)	Semaglutide 0.5 mg (n = 823)	Semaglutide 1.0 mg (n = 819)	Placebo (n = 1,644)
SUSTAIN 1–5 and SUSTAIN 7: baseline to week 12; SUSTAIN 6: baseline to week 16										
Change in eGFR (mL/min per 1.73 m <sup>2</sup> )	–2.6	–3.4	–0.4	–2.7	–3.3	–1.6	–1.9	–2.1	–2.4	–0.9
ETD, semaglutide vs placebo (95% CI)	–2.15 (–347 to –0.83)	–3.00 (–4.31 to –1.68)	NA	NA	NA	NA	NA	–1.29 (–2.07 to –0.51)	–1.56 (–2.33 to –0.78)	NA
SUSTAIN 1–5 and SUSTAIN 7: week 12 to week 30; SUSTAIN 6: week 16 to week 104										
Change in eGFR (mL/min per 1.73 m <sup>2</sup> )	0.2	0.4	–0.2	0.3	0.8	0	0.2	–2.9	–1.7	–4.2
ETD, semaglutide vs placebo (95% CI)	0.33 (–0.92 to 1.59)	0.56 (–0.70 to 1.81)	NA	NA	NA	NA	NA	1.29 (0.30 to 2.28)	2.44 (1.45 to 3.44)	NA
SUSTAIN 1–5 and SUSTAIN 7: baseline to week 30; SUSTAIN 6: baseline to week 104										
Change in eGFR (mL/min per 1.73 m <sup>2</sup> )	–2.5	–2.9	–0.9	–2.5	–2.4	–1.9	–2.2	–5.0	–4.1	–5.1
ETD, semaglutide vs placebo (95% CI)	–1.58 (–2.92 to –0.25)	–2.02 (–3.35 to –0.68)	NA	NA	NA	NA	NA	0.07 (–0.92 to 1.07)	0.97 (–0.03 to 1.97)	NA

CI, confidence interval; eGFR, estimated glomerular filtration rate; ETD, estimated treatment difference; NA, not analysed; SUSTAIN, Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes.

microalbuminuria or macroalbuminuria than in normoalbuminuria. A decrease in UACR might lead to improving renal outcomes, such as a reduced risk of end-stage kidney disease. Take together, this post-hoc analysis suggests that semaglutide might be expected to have renoprotective effects.

The mechanisms of potential renoprotective effect of GLP-1RA are less acknowledged. It is well recognized that GLP-1RA can control risk factors for CKD, such as blood pressure, glucose, insulin levels and weight loss. This might indirectly be related to the beneficial effects of GLP-1RA on the kidney. In addition, recent evidence suggests that GLP-1RA might have direct action on the kidney<sup>3</sup>. Proposed mechanisms include its natriuretic and diuretic properties associated with sodium–hydrogen exchanger 3 localized to the brush border of the renal proximal tubule. A decrease in urinary sodium reabsorption and increased proximal urinary sodium excretion have been observed when some GLP-1RAs are injected into type 2 diabetes patients<sup>1</sup>. GLP-1RA is also thought to reduce RAAS activation. In the previous experimental studies, GLP-1RA was shown to decrease renal RAAS activation markers, including angiotensin II<sup>4</sup>. Additional possible mechanisms include the reduction of renal hypoxia. Although many experimental studies to date have already shown the beneficial effect of GLP-1 on renal ischemia, no clinical trials have proven this benefit<sup>3</sup>. There are also studies suggesting that GLP-1 has anti-oxidant and anti-apoptotic properties. In an animal study, liraglutide administration delayed progression of DKD by reducing the levels of glomerular superoxide, along with decreased mesangial expansion and increased renal nitric oxide levels<sup>5</sup>. GLP-1 metabolites were associated with decreased expression of renal tubular injury markers and reduced tubulointerstitial damage by decreasing the accumulation of macrophages and T cells in the kidney<sup>6</sup>. Finally, a possible mechanism is the anti-atherogenic effect of GLP-1RA by its anti-inflammatory and anti-ischemic


activities<sup>7</sup>. This property makes it possible to have a protective effect against glomerular atherosclerosis, which shares the same predictors and mediators as macrovascular disease.

There are several dedicated kidney outcome trials to evaluate the effects of SGLT2 inhibitors on kidney function – Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE), Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD) and The Study of Heart and Kidney Protection With Empagliflozin (EMPA-KIDNEY). In CREDENCE, canagliflozin showed renoprotective properties by reducing the risk of kidney results by 30% compared with a placebo. In DAPA-CKD, dapagliflozin appeared to have renoprotective properties, and the hazard ratio of death from renal causes or end-stage kidney disease was 0.56 versus a placebo. However, to date, no designated GLP-1RA clinical trial has been published to evaluate renal outcomes as the primary end-point. To investigate the effect of GLP-1RA on kidney function, dedicated renal outcome trials and head-to-head comparison studies are required. There is an on-going placebo-controlled trial of injectable semaglutide on renal outcome – Effect of

Semaglutide Versus Placebo on the Progression of Renal Impairment in Subjects With Type 2 Diabetes and Chronic Kidney Disease (FLOW; NCT03819153). The American Diabetes Association guidelines recommend the use of GLP-1RA in CKD and type 2 diabetes patients for whom SGLT2 inhibitors are inadequate. Additional long-term trials of GLP-1RA with primary renal end-points are required to support this guideline. Considering the renoprotective effects of both GLP-1RA and SGLT2 inhibitor through sodium–hydrogen exchanger 3, future clinical trials using GLP-1RA and SGLT2 inhibitors together for DKD will give us very interesting results.

#### DISCLOSURE

The authors declare no conflict of interest.

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