JDI Journal of Diabetes Investigation Open access
Official Journal of the Asian Association for the Study of Diabetes
UPDATE

# Incretin hormones: Revolutionizing the treatment landscape for kidney and liver diseases in type 2 diabetes and obesity

## INTRODUCTION

Several medications initially developed for type 2 diabetes have demonstrated therapeutic potential beyond glycemic control, particularly in obesity, kidney disease, and metabolic dysfunction-associated steatotic liver disease (MASLD). Among these, glucagon-like peptide-1 receptor agonists (GLP-1RAs) have proven effective in achieving sustained weight loss, leading to their approval for obesity treatment[1]. Furthermore, they have been shown to reduce albuminuria and preserve kidney function in chronic kidney disease (CKD), independent of their effects on body weight. Emerging trials suggest they may also alleviate liver steatosis and inflammation, key drivers of liver disease progression. This article explores the expanding role of glucagon-like peptide-1 (GLP-1)-based therapies in managing kidney disease and MASLD, highlighting their broader clinical applications (Table 1).

## GLP-1 ACTION ON THE KIDNEY

The GLP-1 receptor is widely expressed in the kidney, especially in vascular smooth muscle cells of the afferent and efferent arterioles, glomerular capillaries, endothelial cells, and juxtaglomerular cells. It is also found in proximal tubules, where it regulates sodium and water balance[2]. In CKD, circulating endogenous GLP-1 levels are elevated, possibly due to altered renal metabolism. GLP-1RAs have shown significant renal benefits, including increased natriuresis and reduced albuminuria, as demonstrated in both animal and human studies, independent of diabetes status. However, prolonged use in people with type 2 diabetes may attenuate natriuretic effects. In addition to sodium regulation, GLP-1RAs exhibit anti-inflammatory and anti-fibrotic properties that protect the kidneys. Preclinical data reveal that GLP-1 receptor activation inhibits T-cell proliferation and reduces inflammation in nephrotoxic nephritis models, mitigating kidney fibrosis and oxidative stress. These mechanisms are vital in slowing CKD progression[2]. Renoprotective benefits of GLP-1RAs extend beyond glucose lowering and include reductions in body weight, hyperinsulinemia, systemic inflammation, and oxidative stress, contributing to enhanced kidney function.

## THERAPEUTIC POTENTIAL OF GLP-1RAS IN KIDNEY DISEASE

GLP-1RAs have shown promise in slowing kidney disease progression, particularly in type 2 diabetes[3]. Most evidence comes from cardiovascular and glycemic control trials, where kidney events were secondary outcomes[4]. While these studies suggest renal benefits, definitive evidence from trials dedicated to CKD progression is needed. The FLOW (Evaluate Renal Function with Semaglutide Once Weekly) trial is a landmark study evaluating the effects of semaglutide on kidney outcomes in high-risk individuals with type 2 diabetes and CKD[5]. Over a median follow-up of 3.4 years, semaglutide reduced the risk of major kidney disease events—a composite of kidney failure, a sustained 50% or greater reduction in the estimated glomerular filtration rate (eGFR), or death from kidney-related or cardiovascular causes—by 24% compared to placebo. Additionally, semaglutide lowered kidney outcomes and cardiovascular or all-cause mortality irrespective of concurrent sodium-glucose cotransporter 2 inhibitor use[6]. These findings affirm the therapeutic potential of GLP-1RAs in managing CKD in people with type 2 diabetes.

## GLP-1 ACTION IN THE LIVER

While the liver does not directly express the GLP-1 receptor, GLP-1 influences liver disease indirectly via systemic effects[7]. Preclinical studies show that GLP-1RAs reduce hepatic steatosis by lowering inflammation and modulating lipid metabolism. These agents suppress lipogenesis by downregulating key genes, such as *SREBP-1c* and *ACC1*, critical to hepatic fat synthesis. This action decreases triglyceride accumulation in the liver, improving insulin sensitivity and reducing hepatic fat content, particularly in high-fat diet models[7,8]. Human clinical trials with GLP-1RAs, like liraglutide and semaglutide, have shown significant reductions in liver fat and markers of liver injury[9,10]. Reduced liver fat correlates with improved liver function, lower inflammatory biomarkers, and better glycemic control[11]. These effects likely stem from the systemic benefits of GLP-1RAs on weight loss and glucose regulation, offering a promising therapeutic approach for liver health.

## THERAPEUTIC POTENTIAL OF GLP-1RAS IN MASLD

GLP-1RAs are gaining recognition for their efficacy in treating MASLD. In the phase 2 LEAN (Liraglutide Efficacy and Action in NASH) trial, liraglutide

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Received 1 October 2024; revised 7 October 2024; accepted 9 October 2024

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**Table 1** | Ongoing randomized clinical trials of incretin-based therapies for CKD and MASLD

| Medication (study name) | Mechanism of action | Trial phase | Study population | Comparator | Primary outcome | ClinicalTrials.gov ID |
|---|---|---|---|---|---|---|
| CKD | | | | | | |
| Semaglutide (REMODEL) | GLP-1 receptor agonist | Phase 3 | Adults with T2D and CKD | Placebo | • Change in kidney oxygenation<br>• Change in global kidney perfusion<br>• Change in inflammation | NCT04865770 |
| Tirzepatide (TREASURE-CKD) | Dual GIP/GLP-1 receptor agonist | Phase 2 | Adults with overweight or obesity and CKD with or without T2D | Placebo | • Change in kidney oxygenation | NCT05536804 |
| CagriSema: cagrilintide and semaglutide | Combination of DACRA and GLP-1 receptor agonist | Phase 2 | Adults with T2D, overweight or obesity, and CKD | Semaglutide, cagrilintide, or placebo | • Change in urinary albumin-to-creatinine ratio | NCT06131372 |
| Retatrutide | Triple GIP/GLP-1/glucagon receptor agonist | Phase 2 | Adults with overweight or obesity and CKD with or without T2D | Placebo | • Change in measured GFR | NCT05936151 |
| Retatrutide (TRIUMPH-OUTCOMES) | Triple GIP/GLP-1/glucagon receptor agonist | Phase 3 | Adults with obesity and established ASCVD and/or CKD | Placebo | • Time to first occurrence of a composite end points, including nonfatal MI, nonfatal stroke, CV death, or hospitalization or urgent visit due to HF<br>• Time to first occurrence of a composite end points, including EKSD, ≥40% sustained decline in estimated GFR, or CV or renal death | NCT06383390 |
| MASLD | | | | | | |
| Semaglutide (ESSENCE) | GLP-1 receptor agonist | Phase 3 | Adults with biopsy-confirmed NASH | Placebo | • Resolution of steatohepatitis and no worsening of liver fibrosis<br>• Improvement in liver fibrosis and no worsening of steatohepatitis<br>• Cirrhosis-free survival | NCT04822181 |
| Semaglutide (SAMARA) | GLP-1 receptor agonist | Phase 2 | Adults with obesity and T2D | Placebo | • Change in fibrosis due to NAFLD | NCT06005012 |
| Semaglutide | GLP-1 receptor agonist | Phase 2 | Youth with obesity, prediabetes or new-onset T2D, and NAFLD | Placebo | • Change in oral disposition index<br>• Change in PDFF | NCT05067621 |
| Survodutide | Dual GLP-1/glucagon receptor agonist | Phase 3 | Adults with overweight or obesity and confirmed or presumed NASH | Placebo | • Relative reduction in liver fat content of at least 30% assessed by MRI-PDFF<br>• Relative change in body weight | NCT06309992 |
| Pemvidutide (IMPACT) | Dual GLP-1/glucagon receptor agonist | Phase 2 | Adults with biopsy-confirmed NASH | Placebo | • Proportion of subjects achieving NASH resolution with at least a 2-point reduction in NAS without worsening of fibrosis<br>• Proportion of subjects achieving at least one stage improvement in liver fibrosis without worsening of NASH | NCT05989711 |


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**Table 1** (*Continued*)

| Medication (study name) | Mechanism of action | Trial phase | Study population | Comparator | Primary outcome | ClinicalTrials.gov ID |
|---|---|---|---|---|---|---|
| Efinopegdutide (MK-6024-013) | Dual GLP-1/glucagon receptor agonist | Phase 2b | Adults with biopsy-confirmed NASH | Semaglutide or placebo | • Percentage of participants with NASH resolution without worsening of fibrosis<br>• Percentage of participants who experienced an adverse event<br>• Percentage of participants discontinuing study medication due to an adverse event | NCT05877547 |
| Efinopegdutide (MK-6024-017) | Dual GLP-1/glucagon receptor agonist | Phase 2a | Adults with compensated cirrhosis due to MASH | Placebo | • Change in liver fat content<br>• Percentage of participants who experienced an adverse event<br>• Percentage of participants discontinuing study medication due to an adverse event | NCT06465186 |
| DD01 | Dual GLP-1/glucagon receptor agonist | Phase 2 | Adults with overweight or obesity with MASLD or MASH | Placebo | • Proportion of subjects who achieve at least 30% liver fat reduction measured by MRI-PDFF | NCT06410924 |
| Efocipegtrutide | Triple GIP/GLP-1/glucagon receptor agonist | Phase 2 | Adults with biopsy-confirmed NASH | Placebo | • Proportion of subjects who achieve resolution of steatohepatitis on overall histopathological reading and no worsening of liver fibrosis | NCT04505436 |

ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; CV, cardiovascular; DACRA, dual amylin and calcitonin receptor agonist; ESKD, end-stage kidney disease; GFR, glomerular filtration rate; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1; HF, heart failure; MASH, metabolic dysfunction-associated steatohepatitis; MASLD, metabolic dysfunction-associated steatotic liver disease; MI, myocardial infarction; MRI, magnetic resonance imaging; NAFLD, nonalcoholic fatty liver disease; NAS, NAFLD activity score; NASH, nonalcoholic steatohepatitis; PDFF, protein density fat fraction; T2D, type 2 diabetes.

significantly reduced steatosis and hepatocyte ballooning, without affecting lobular inflammation[9]. In another phase 2 trial, semaglutide showed further improvement, with a 59% resolution of nonalcoholic steatohepatitis (NASH), defined as mild residual inflammatory cell infiltration and no hepatocyte ballooning, though its effects on fibrosis were limited[10]. Tirzepatide, a dual GLP-1 and glucose-dependent insulinotropic polypeptide receptor agonist, demonstrated even greater potential. In the SYNERGY-NASH trial, 44%–62% of individuals with metabolic dysfunction-associated steatohepatitis (MASH) and moderate-to-severe liver fibrosis (F2 or F3) achieved MASH resolution, while over 50% experienced a one-stage fibrosis improvement[12]. Survodutide, a dual GLP-1 and glucagon receptor agonist, also showed histologic improvement in MASH without worsening fibrosis in 43%–62% of individuals with MASH and fibrosis (F1 through F3)[13]. In East Asian populations, MASLD tend to develop at lower body mass indexes. Although the pathophysiology in these individuals remains unclear, metabolic dysregulation appears to play a significant role[14,15]. Further studies are needed to evaluate whether GLP-1RAs are effective in this population.

## CONCLUSION

Incretin-based therapies, particularly GLP-1RAs, have shown significant potential beyond diabetes and obesity, offering benefits in managing CKD and MASLD. These agents reduce inflammation, fibrosis, and metabolic dysfunction, providing kidney and liver protection. Emerging dual and triple agonists, such as tirzepatide, survodutide, or retatrutide, offer new avenues for addressing metabolic and fibrotic processes. While current evidence is promising, further studies are required to optimize their application and evaluate their long-term effects across diverse populations.

## DISCLOSURE

Young Min Cho, as an Editorial Board member of the *Journal of Diabetes Investigation*, was excluded from all editorial decisions regarding the acceptance of this article to avoid potential conflicts of interest. The authors declare no other conflicts of interest.

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Doi: 10.1111/jdi.14336


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