

COMMENTARY

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The transformative breakthroughs in GLP-1 research recognized by the 2024 Lasker~DeBakey award

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The 2024 Lasker~DeBakey Clinical Medical Research Award has honored three pioneering scientists—Joel Habener, Svetlana Mojsov, and Lotte Bjerre Knudsen—for their groundbreaking contributions to the understanding and therapeutic application of glucagon-like peptide-1 (GLP-1) in the treatment of obesity. This recognition not only highlights their individual achievements but also underscores a significant shift in the landscape of metabolic disease treatment. The work of these researchers serves as a model for how basic science can translate into impactful clinical therapies, ultimately enhancing patient care and improving public health outcomes.

1 The discovery of GLP-1

The journey began with Habener and Mojsov's identification of the physiological roles of GLP-1, a hormone initially discovered as an incretin, which is released by the gut (Drucker et al 1986) (Fig. 1). It is processed from proglucagon in a cell-specific post-translational processing (Mojsov et al 1986; Philippe et al 1986), includes at least two forms: GLP-1(1-37) and GLP-1(7-37). GLP-1(7-37) significantly stimulated insulin secretion, suggesting it plays an important role in insulin secretion (Mojsov

et al 1987). Their research also elucidated GLP-1's multifaceted functions beyond glucose regulation, including its role in appetite suppression and energy balance. These findings revealed that GLP-1 is not merely a glucose-regulating hormone but a key player in the complex neuroendocrine network that governs food intake and body weight.

The physiological effects of GLP-1 include stimulating insulin secretion in a glucose-dependent manner (Holz et al 1993), inhibiting glucagon release, and slowing gastric emptying. Furthermore, GLP-1 acts on central nervous system receptors in the paraventricular nucleus of the hypothalamus and the central nucleus of the amygdala to promote satiety and reduce food intake (Turton et al 1996) (Fig. 1), and also acts on receptors in pancreatic β -cells, myocytes in the sinoatrial node, and Brunner's glands in the duodenum (Knudsen et al 2014). These comprehensive understandings laid the groundwork for exploring GLP-1 as a therapeutic target for obesity—a condition that significantly contributes to the global diabetes epidemic and associated comorbidities.

2 Transformative therapeutics

Lotte Bjerre Knudsen's work at Novo Nordisk marked a pivotal transition from scientific discovery to clinical application. By leveraging the physiological properties of GLP-1, she and her team developed a class of medications—GLP-1 receptor agonists—that effectively promote weight loss in individuals with obesity. Their work began with modifying GLP-1 with fatty acids of more than 12 carbon atoms to extend its action. They found that compounds with linear fatty acids up to 16 carbon atoms in the C-terminal region without a notable loss in

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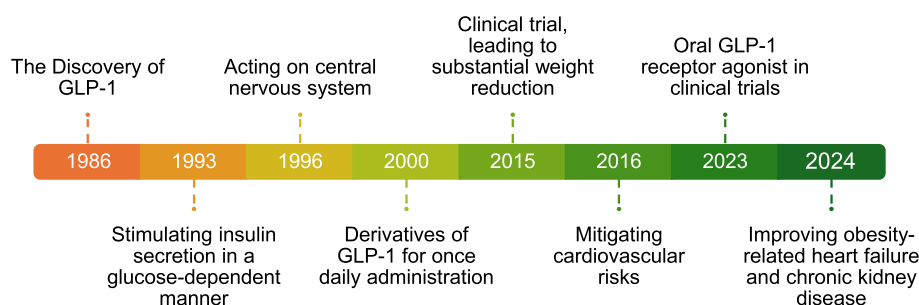


Fig. 1 Breakthroughs in GLP-1 research

potency (Knudsen et al 2000). In these medications, liraglutide and semaglutide have demonstrated remarkable efficacy in clinical trials, leading to substantial weight reductions (Pi-Sunyer et al 2015; Wilding et al 2021) by suppressing appetite and reducing energy intake (Friedrichsen et al 2021) (Fig. 1).

The introduction of these therapies represents a paradigm shift in obesity treatment. Traditionally, obesity management focused on lifestyle modifications, including dietary restrictions and increased physical activity. However, such approaches often yield limited results, as they fail to address the underlying biological mechanisms driving weight gain. GLP-1-based therapies offer a pharmacological intervention that targets these mechanisms directly, allowing for more effective management of obesity. Knudsen's work found that liraglutide was internalized by proopiomelanocortin (POMC)/cocaine- and amphetamine-regulated transcript (CART) neurons and indirectly inhibits neuropeptide Y (NPY) and agouti-related peptide (AgRP) neurons through Gamma Amino Butyric Acid (GABA) dependent signaling. This mechanism is likely crucial for mediating liraglutide-induced weight loss (Secher et al 2014).

Clinical studies have shown that patients treated with GLP-1 receptor agonists not only experience significant weight loss but also improvements in associated health markers, such as blood pressure and lipid profiles. The profound impact on weight management and metabolic health has positioned these drugs as game-changers in the treatment landscape for obesity and type 2 diabetes.

3 Future directions

Looking ahead, the future of GLP-1 research appears promising. Emerging studies are exploring the potential of GLP-1-based therapies in diverse populations and comorbidities, such as patients with type 2 diabetes or cardiovascular diseases. At present, it has been proved that liraglutide and semaglutide can mitigating cardiovascular risks (Fig. 1) (Marso et al 2016; Wilding et al. 2021), and may mitigate atherosclerosis through

anti-inflammatory mechanisms (Rakipovski et al 2018). Semaglutide can also improve heart failure-related symptoms and inflammation in patients with obesity-related heart failure with preserved ejection fraction (HFpEF), and decrease the risk of major kidney disease events and cardiovascular-related mortality in patients with type 2 diabetes and chronic kidney disease (Butler et al 2024; Perkovic et al 2024) (Fig. 1). These studies highlight the broad effect of GLP-1-based therapies and its potential application value.

In addition to agonists only target to GLP-1 receptors, agonists with multiple targets now are being developed. Tirzepatide is the agonist of GLP-1 receptor and glucose-dependent insulinotropic polypeptide (GIP) receptor, which can reduce body weight and improve cardiac metabolism by subcutaneous injection once a week (Jastreboff et al 2022). Retatrutide is the agonist of GLP-1 receptor, GIP receptor, and glucagon (GCG) receptor, which can reduce body weight and improve blood glucose by subcutaneous injection once a week (Rosenstock et al 2023).

In consideration of the reduced compliance of peptide GLP-1 receptor agonists due to subcutaneous injection, oral micromolecular GLP-1 receptor agonists such as orforglipron have already in clinical trials, which can reduce body weight and improve cardiac metabolism in adults with obesity (Wharton et al 2023) (Fig. 1).

Additionally, researchers are investigating combination therapies that incorporate GLP-1 receptor agonists with other pharmacological agents. For instance, pairing GLP-1 agonists with Sodium-dependent glucose transporters 2 (SGLT-2) inhibitors—a class of medications that help lower blood sugar by preventing glucose reabsorption in the kidneys—may enhance treatment efficacy and improve patient outcomes. Such integrative approaches could pave the way for more comprehensive obesity management strategies.

The exploration of GLP-1's mechanisms also present opportunities for novel therapeutic developments. For example, ongoing research aims to identify new analogs

or formulations of GLP-1 that may offer improved dosing regimens, reduced side effects, or enhanced efficacy. The potential for long-acting GLP-1 receptor agonists could improve patient adherence and further optimize treatment outcomes.

Moreover, as understanding of GLP-1 biology expands, researchers are also investigating its effects on the gut-brain axis. The interplay between gut hormones and neurological pathways could unveil new insights into appetite regulation and obesity treatment. Such discoveries may lead to innovative interventions that target not just weight loss, but overall metabolic health.

4 Implications for public health

The impact of GLP-1 therapies extends beyond individual patient outcomes. The obesity epidemic is a pressing public health challenge, with significant economic and societal costs. According to the World Health Organization, obesity prevalence has nearly tripled since 1975, and it is associated with increased risks of developing chronic diseases such as type 2 diabetes, cardiovascular disease, and certain types of cancer. The economic burden of obesity-related healthcare costs is staggering, emphasizing the urgent need for effective interventions.

By offering a new strategy for weight management, GLP-1 receptor agonists hold the potential to reduce the prevalence of obesity-related complications. As healthcare systems grapple with the burdens of these conditions, the availability of effective pharmacotherapy can alleviate some of the strain on medical resources. The successful implementation of GLP-1-based therapies could lead to decreased hospitalization rates, lower healthcare costs, and improved quality of life for patients.

Moreover, the success of GLP-1 drugs serves as a testament to the importance of continued investment in metabolic research. The recognition of Habener, Mojsov, and Knudsen by the Lasker-DeBakey Award reinforces the idea that foundational scientific research can lead to transformative clinical applications that improve population health. It also highlights the necessity for sustained funding and support for research initiatives that focus on understanding complex metabolic processes.

5 Challenges and considerations

Despite the tremendous promise of GLP-1-based therapies, challenges remain. Accessibility and affordability of these medications are critical concerns, particularly in low- and middle-income countries where obesity prevalence is rising. Ensuring equitable access to effective treatments is essential for addressing the global obesity epidemic.

Moreover, ongoing education and training for healthcare providers regarding the benefits and limitations of

GLP-1 therapies are vital. As new treatment modalities emerge, clinicians must be equipped to navigate patient conversations about options, expectations, and adherence strategies.

Long-term safety and efficacy data are also essential. While current studies demonstrate promising results, understanding the long-term effects of GLP-1 receptor agonists will be crucial for establishing their role in chronic obesity management. Continuous monitoring of patient outcomes and post-marketing surveillance will help ensure that these therapies are used safely and effectively.

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Authors' contributions

J.K.Y. designed the work. Y.-F.Z. and J.K.Y. wrote the initial draft of this paper. All the authors participated in editing content of this paper and approved the final version.

Data availability

Not applicable.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

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