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Commentary
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The Latest topics of Standards of Care in Diabetes 2025: Focusing on GLP-1RA

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Abstract

The American Diabetes Association (ADA) presented the Standards of Care in Diabetes-2025 online in December 2024. The authors immediately reviewed and provided perspectives on the latest developments regarding glucagon-like peptide-1 receptor agonists (GLP-1RA). Some newly added content about GLP-1RA is included, such as its application for heart failure with preserved ejection fraction (HFpEF), obesity, metabolic dysfunction-associated steatotic liver disease (MASLD), and metabolic dysfunction-associated steatohepatitis (MASH). Concurrent use of DPP-4 inhibitors (DPP-4i) with GLP-1RA (GIP/GLP-1RA) is not recommended due to a lack of additional glucose-lowering effects beyond GLP-1RA alone. GLP-1RA is expected to demonstrate various positive clinical effects.

Keywords

American Diabetes Association, Standards of Care in Diabetes-2025, Glucagon-like Peptide-1 Receptor Agonist, Alzheimer Disease, Parkinson's Disease

Abbreviations

ADA: American Diabetes Association; GLP-1RA: Glucagon-like Peptide-1 Receptor Agonist; AD: Alzheimer Disease; PD: Parkinson's Disease

Commentary

The American Diabetes Association (ADA) Standards of Care (SoC) in Diabetes-2025 was published online in December, and the authors immediately reviewed it in detail. Chapter 9, Pharmacologic Approaches to Glycemic Treatment, particularly highlights the growing attention GLP-1 receptor agonists (GLP-1RA) have received in recent years [1].

The standard usage of GLP-1RA is described in sections 9.24–26 [2]. The key points are summarized as follows:

i) For cases with type 2 diabetes (T2D) and no evidence of insulin deficiency, GLP-1RA (dual GIP/GLP-1RA) is preferred over insulin (A).

ii) If insulin is used, the recommended treatment is a combination with GLP-1RA or GIP/GLP-1RA, which demonstrates greater effectiveness with

benefits on weight and hypoglycemic risk in T2D (A).

iii) For adults with T2D who are starting insulin, glucose-lowering agents should be continued to maintain glycemic and metabolic benefits, including cardiometabolic, renal, and weight benefits (A) [3].

In this chapter, various recommendations are provided. Among them, newly added content includes the following:

i) For T2D patients with symptomatic heart failure with preserved ejection fraction (HFpEF) and obesity, GLP-1RA is recommended for its beneficial effects on glycemic control and reduction of HF-related symptoms (A).

ii) For adults with T2D and MASLD (overweight or obesity), GLP-1RA (GLP/GIP-GLP-1RA) is recommended for its potential benefits in managing MASH or glycemic control as an adjunctive intervention for weight reduction (B).

iii) For T2D patients with MASH (biopsy-proven, high-risk fibrosis), pioglitazone or GLP-1RA (GIP/GLP-1RA) is preferred for glycemic control due to its potential beneficial effects on MASH (B) [4].

iv) Concurrent use of DPP-4 inhibitors (DPP-4i) with GLP-1RA (GIP/GLP-1RA) is not recommended due to a lack of additional glucose-lowering effects beyond GLP-1RA alone (B) [3,5].

GLP-1RAs are known for their efficacy in weight reduction for obesity, overweight, and diabetes [6]. This mechanism involves several pathways, including decreased water retention, weight reduction, and improved heart failure symptoms [7]. Consequently, GLP-1RA appears to exhibit various pharmacophysiological mechanisms [8]. Their clinical effects are summarized in **Fig-1**, highlighting three primary functions: anti-brain effects, anti-inflammation, and glucose control. Through these mechanisms, GLP-1RA may potentially treat conditions such as Alzheimer's disease, Parkinson's disease, MASLD, CKD, diabetes, cardiovascular disease, and obesity.

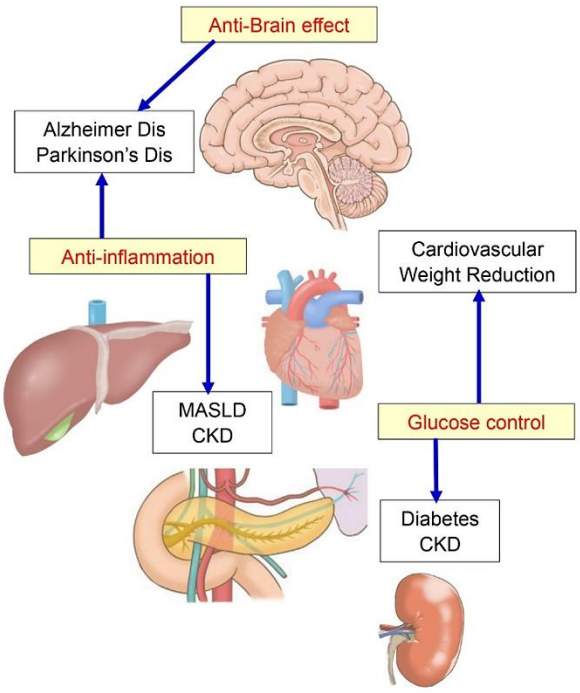

Fig-1: Various Clinical Effects of GLP-1RA

GLP-1RA has shown potential benefits for Alzheimer's disease (AD) and other neurological, psychological, and metabolic disorders [9]. It may also delay the onset of Parkinson's disease (PD) [10]. Notably, exenatide, a GLP-1RA, has demonstrated anti-inflammatory effects via microglia activation for PD [11]. In a protocol involving 447 cases divided into three groups (2.5 mg, 5.0 mg of NLY01, and placebo), total scores on the MDS-UPDRS Part 2 and 3 showed no significant changes. However, a subgroup indicated probable motor benefits in younger participants.

GLP-1RAs have also been shown to reduce the risk of death, stroke, and heart attack in patients with cardiovascular disease and CKD [12]. Obese and T2D patients exhibit a higher prevalence of HFpEF. Comparative evaluations of semaglutide versus placebo groups revealed improvements in KCCQ-CSS scores (13.7 vs. 6.4 pts) and weight reduction ratios (-9.8% vs. -3.4%) [13]. Additionally, the FLOW trial reported a 24% lower primary outcome risk for the semaglutide group (HR 0.76), with kidney-specific outcomes (HR 0.79) and cardiovascular death (HR 0.71) also favoring semaglutide [14].

GLP-1RAs may also benefit conditions like sleep apnea syndrome (SAS), MASLD, and HIV-related

complications. Moreover, they could reduce addictions to substances such as alcohol and tobacco, with several clinical trials currently underway [15]. The underlying mechanisms involve GLP-1's dual action pathways. The first pathway acts on the intestinal tract, where intestinal mucosa cells produce GLP-1, stimulating pancreatic insulin secretion and slowing digestion, leading to appetite suppression. The second pathway acts on the brain, regulating appetite, mood, and reward-related behavior.

Synthetic GLP-1RAs, such as semaglutide and tirzepatide, maintain higher blood concentrations and exhibit longer-lasting effects compared to natural GLP-1, potentially increasing their ability to reach the brain [16,17]. Unlike previous anti-obesity drugs, GLP-1RAs target both peripheral organs and brain receptors, offering broader clinical applications. However, it remains unclear to what extent GLP-1RAs penetrate the blood-brain barrier (BBB) in humans. While animal studies suggest that some GLP-1RAs can cross the BBB [18], others, like semaglutide, may not penetrate the BBB as effectively in humans [19].

Regarding GLP-1RAs' potential effects on the reward system, studies indicate they consistently decrease energy intake and influence reward-related behavior. This is linked to reduced neuro-cortical activation in response to high-reward food cues and lower calorie intake. GLP-1RAs may address reward dysfunctions related to food stimuli, T2D, and obesity. They also improve insulin resistance and may reduce anhedonia, making them potentially applicable to addiction disorders [20].

In summary, this commentary highlights the latest advancements in GLP-1RA, including the ADA SoC-2025 and its wide-ranging positive effects. GLP-1RAs influence neural pathways that control reward, taste, and salience, offering promising possibilities in medical and healthcare applications.

Conflict of Interest

The authors have read and approved the final version of the manuscript. The authors have no conflicts of interest to declare.

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