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Review Article

The Possible Effects of Long-Term Use of Glucagon-like Peptide-1 Receptor Agonists (GLP-1RAs)

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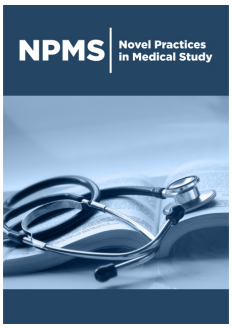

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Submission: February 03, 2025
Published: March 10, 2025

Volume 1 - Issue 4

How to cite this article: Swapnil Tripathi* and Mohamed Saleem Noormohamed. The Possible Effects of Long-Term Use of Glucagon-like Peptide-1 Receptor Agonists (GLP-1RAs). Novel Practices in Med Study. 1(4). NPMS.000518.2025.

Abstract

The rising rates of obesity and its associated health issues have led to a growing interest in effective and sustainable treatment options. Glucagon-like peptide-1 receptor agonists (GLP-1RAs) have become key pharmacological tools, impacting weight loss, metabolic health, and various systemic outcomes. Recent research highlights the role of Sirtuin 1 (SIRT1) in mediating some of the beneficial effects of GLP-1RAs, particularly in metabolic regulation and the mitigation of obesity-related complications. SIRT1 activation is critical for improving insulin sensitivity, reducing inflammation, and modulating energy metabolism, making it an essential component of obesity therapy. Given the potential impact of SIRT1 inhibition on GLP-1RA efficacy, plasma SIRT1 levels may serve as a useful biomarker for assessing patient response to treatment. This review delves into the potential long-term effects of GLP-1RAs, covering weight loss, bowel function, nutrition, cancer risk reduction, fertility, sexual health, mental well-being, diabetes management, cardiovascular health, and neurovascular conditions and the emerging role of SIRT1 in optimizing obesity therapy outcomes. By analysing recent research and incorporating data on metabolic interventions like bariatric surgery, this article aims to provide a thorough overview of the diverse benefits and challenges linked to GLP-1RA therapy.

Keywords: Obesity therapy; Bariatric surgery; Diabetes; Pharmacology

Introduction

Obesity has become a global epidemic, significantly increasing the risk of diabetes, cardiovascular diseases, and cancer [1]. Advances in pharmacology, particularly GLP-1RAs, offer a promising alternative for individuals who struggle to achieve adequate results through lifestyle modifications alone [2]. Medications like semaglutide and liraglutide replicate the action of the natural incretin hormone GLP-1, which enhances insulin secretion, curbs appetite, and delays gastric emptying [3]. Recent research has shed light on the role of SIRT1, a key regulator of metabolic processes, in obesity treatment. SIRT1 activation has been linked to improved insulin sensitivity, reduced oxidative stress, and decreased inflammation. Additionally, SIRT1 plays a role in regulating mitochondrial function and lipid metabolism, both of which are crucial for sustainable weight loss and metabolic health. Given its importance, assessing the influence of GLP-1RAs on SIRT1 activity may enhance our understanding of their long-term therapeutic potential. Metabolic and Bariatric Surgeries (MBS) have shown lasting effectiveness in promoting weight loss and influencing epigenetic factors [4]. Recent discoveries, including the involvement of long non-coding RNAs (lncRNAs) in obesity and metabolic changes following surgery, indicate a more complex metabolic interaction that is relevant to GLP-1RA therapy [5].

Weight loss

GLP-1 receptor agonists (GLP-1RAs) are among the most effective medications for managing obesity, often resulting in significant weight loss when used alongside lifestyle changes [6]. Clinical studies show that many patients experience weight reductions of over 15%, with semaglutide being particularly effective [7]. These medications work by suppressing appetite and increasing feelings of fullness, primarily through pathways in the hypothalamus [8]. Emerging evidence suggests that SIRT1 activation enhances GLP-1RA-induced metabolic benefits. SIRT1 promotes mitochondrial biogenesis and energy expenditure, facilitating sustained weight loss. Furthermore, inhibition of SIRT1 has been associated with reduced GLP-1 signalling, highlighting the importance of maintaining SIRT1 activity in patients undergoing GLP-1RA therapy. In contrast, Metabolic Bariatric Surgery (MBS) tends to produce even greater weight loss due to both anatomical and hormonal changes, including an increase in GLP-1 secretion [9]. Research indicates that bariatric surgery can lead to epigenetic modifications, particularly in long non-coding RNA (lncRNA) expression, which may enhance the long-term metabolic advantages of GLP-1RA therapy [10].

Bowel function and nutrition

GLP-1RAs also slow down gastric emptying, which can help reduce spikes in blood sugar after meals but may cause gastrointestinal side effects such as nausea, vomiting, and changes in bowel habits [11]. Fortunately, these side effects usually lessen over time with ongoing treatment [12]. When it comes to nutrition, concerns about micronutrient deficiencies are generally less significant with GLP-1RAs compared to MBS [13]. However, patients on GLP-1RAs might still need to monitor their nutritional intake to ensure they are getting enough nutrients, especially if they are consuming fewer calories [14]. SIRT1 has been implicated in gastrointestinal health, as it modulates gut barrier function and influences gut microbiota composition. This suggests that maintaining SIRT1 activity could help mitigate some gastrointestinal side effects of GLP-1RA therapy.

Cancer reduction

Emerging evidence indicates that GLP-1 Receptor Agonists (GLP-1RAs) might offer protective benefits against certain types of cancer, especially those associated with obesity, like colorectal and breast cancer [15]. These benefits are believed to stem from mechanisms such as weight loss, enhanced insulin sensitivity, and anti-inflammatory effects [16]. SIRT1 plays a role in tumor suppression by regulating DNA repair and apoptosis. Increased SIRT1 activity has been linked to reduced cancer progression, suggesting that GLP-1RA-induced SIRT1 activation may contribute to the observed reduction in cancer risk among GLP-1RA users. Research on Long Non-Coding RNAs (lncRNAs) in patients who have undergone bariatric surgery has uncovered their regulatory roles in pathways related to tumor development [17]. It is possible that similar epigenetic changes could occur with prolonged use of GLP-1RAs, which calls for further research [18].

Fertility and sexual function

Hormonal imbalances caused by obesity frequently disrupt fertility and sexual health [19]. By facilitating weight loss and enhancing insulin sensitivity, GLP-1RAs can help restore levels of reproductive hormones, leading to improved fertility outcomes for both men and women [20]. Furthermore, better endothelial function and reduced inflammation may also have a positive effect on sexual function [21]. Additionally, SIRT1 has been shown to regulate gonadal function and reproductive aging, suggesting that GLP-1RA-induced SIRT1 activation may further enhance fertility benefits.

Mental health

The psychological advantages of GLP-1 Receptor Agonists (GLP-1RAs) primarily arise from enhanced self-image and a decrease in the stigma associated with obesity [22]. Weight loss is also associated with a reduction in symptoms of depression and anxiety [23]. Additionally, GLP-1 may have neuroprotective properties, indicating possible benefits for cognitive health in neurodegenerative conditions related to obesity [24].

Diabetes mellitus

GLP-1RAs are recognized as effective antidiabetic medications, as they improve glycemic control by boosting insulin secretion, inhibiting glucagon, and facilitating weight loss [25]. Research indicates significant decreases in glycated hemoglobin (HbA1c) levels, with some patients experiencing long-term remission from diabetes [26]. Bariatric surgery has demonstrated impressive rates of diabetes remission, which are associated with alterations in GLP-1 secretion and epigenetic factors like Long Non-Coding RNAs (lncRNAs) [27]. These results highlight the potential for synergistic effects when combining GLP-1RA therapy, especially in patients facing severe insulin resistance [28].

Cardiovascular disease

GLP-1 Receptor Agonists (GLP-1RAs) help lower cardiovascular risk by enhancing lipid profiles, decreasing blood pressure, and providing direct anti-inflammatory benefits [29]. Clinical trials like LEADER and SUSTAIN-6 have shown a reduction in cardiovascular mortality and events among high-risk groups [30]. Metabolic Bariatric Surgery (MBS) also offers significant cardiovascular advantages, partly through improved lipid metabolism and decreased systemic inflammation [31]. Investigating the role of Long Non-Coding RNAs (lncRNAs) in cardiovascular improvements after surgery may shed light on ways to boost the effectiveness of GLP-1RAs [32].

Neurovascular disease

Neurovascular diseases, such as stroke, are strongly associated with obesity and diabetes [33]. GLP-1RAs have demonstrated potential in lowering stroke risk by enhancing endothelial function, reducing inflammation, and decreasing atherogenic risk factors [34]. Preliminary studies indicate that GLP-1 may have neuroprotective effects, which could help lessen ischemic damage [35].

SIRT1 and GLP-1RA therapy

SIRT1 is a Nicotinamide Adenine Dinucleotide (NAD+)-dependent deacetylase that plays a pivotal role in metabolic regulation. Studies indicate that GLP-1RA therapy can activate SIRT1, contributing to improved insulin signalling, mitochondrial biogenesis, and anti-inflammatory responses. This mechanism is particularly relevant for obesity-related complications such as insulin resistance, Non-Alcoholic Fatty Liver Disease (NAFLD), and cardiovascular diseases. SIRT1 activation through GLP-1RAs has been shown to enhance mitochondrial function and protect against oxidative stress, which are crucial factors in metabolic syndrome and obesity. Furthermore, some research suggests that SIRT1 inhibition may negatively impact the effectiveness of GLP-1RA therapy, making it important to assess SIRT1 levels in patients undergoing treatment. Measuring plasma SIRT1 could provide valuable insights into individual responses to GLP-1RAs and help optimize therapeutic strategies.

Challenges and future directions

While GLP-1 Receptor Agonists (GLP-1RAs) have shown significant effectiveness, they do not work the same for everyone. Differences in individual responses may be linked to genetic factors, including variations in the GLP-1 receptor gene [36]. Additionally, there is still a lack of comprehensive long-term safety data, especially concerning potential cancer risks and rare side effects [37]. Future studies should investigate epigenetic factors, such as how GLP-1RAs influence Long Non-Coding RNAs (lncRNAs), to identify new therapeutic targets [38]. Also, a focus on further elucidating the molecular interactions between GLP-1RAs and SIRT1 is required. Furthermore, combining GLP-1RAs with other interventions, like bariatric surgery, may improve results for patients dealing with severe obesity [39].

Conclusion

GLP-1RAs offer a groundbreaking method for addressing obesity and its associated complications. Their benefits go beyond just weight loss, positively impacting metabolic, cardiovascular, and neurological health [40]. The activation of SIRT1 emerges as a crucial factor in enhancing GLP-1RA efficacy, suggesting that monitoring SIRT1 levels may improve personalized treatment approaches [41-45]. By integrating knowledge from bariatric surgery and epigenetic studies, we can deepen our understanding and use of GLP-1RAs, leading to more personalized strategies for managing obesity.

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