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Review

Combined Therapy of GLP-1 Receptor Agonists and Basal Insulin in Type 2 Diabetes: An Updated Review

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ABSTRACT

The combined therapy of GLP-1 receptor agonists (GLP-1RA) and basal insulin has emerged as an effective strategy for the management of type 2 diabetes mellitus (T2DM), offering benefits in glycated hemoglobin (HbA1c) reduction, weight control and a lower risk of hypoglycemia. Randomized studies and meta-analyses show that adding GLP-1RA to basal insulin provides an additional HbA1c reduction between 0.4% and 1.0%, with an average weight loss of 2.5 kg, without significantly increasing hypoglycemia. Conversely, adding basal insulin to GLP-1RA-based regimens ensures robust glycemic control and reduces the need for high doses of prandial insulin, limiting weight gain. These combinations may be administered freely (as separate drugs) or as fixed-ratio combinations (e.g., insulin degludec/liraglutide), with the latter simplifying the regimen and improving adherence. The most common adverse effects are gastrointestinal, mainly nausea, which typically subsides after the first few weeks of treatment. International guidelines already recommend intensifying treatment with GLP-1RA in patients with T2DM and high cardiovascular or renal risk, especially when glycemic control remains inadequate with basal insulin alone. Although long-term studies are still needed to evaluate the durability of benefits and major cardiovascular outcomes, current evidence supports that combined GLP-1RA and basal insulin therapy is a promising approach to improving T2DM management by maximizing efficacy and minimizing risks.

Keywords: Combined therapy; GLP-1 receptor agonist; Basal insulin; Type 2 diabetes mellitus; Glycemic control

Introduction

Type 2 diabetes mellitus (T2DM) is characterized by insulin resistance, β-cell dysfunction and increased hepatic glucose production, resulting in chronic hyperglycemia and a high risk of macro- and microvascular complications[1]. Traditionally, insulin has been the main second-line treatment for patients who do not

achieve glycemic goals with oral antidiabetic drugs. However, insulin monotherapy is often associated with weight gain and risk of hypoglycemia, which can compromise adherence and quality of life[2]. GLP-1 receptor agonists (GLP-1RA) are injectable drugs that mimic the effects of endogenous incretin, enhancing glucose-dependent insulin secretion, suppressing glucagon, delaying gastric emptying and increasing satiety. Clinical trials show that GLP-1RA such as liraglutide, semaglutide and dulaglutide reduce HbA1c by 0.8–1.5%, promote a 2–4 kg weight loss and have a lower hypoglycemia profile than insulin. However, GLP-1RA alone may not always achieve glycemic targets in patients with advanced disease, justifying the interest in combining them with basal insulin[3].

The combination of GLP-1RA and basal insulin is based on complementary mechanisms: basal insulin controls fasting glucose levels, while GLP-1RA modulates postprandial insulin secretion and suppresses glucagon, also promoting weight loss through central appetite effects[4]. Randomized prospective studies show that adding GLP-1RA to basal insulin regimens reduces HbA1c by an additional 0.4–0.8%, with weight loss of 1.5–3.0 kg and no increase in severe hypoglycemia. In contrast, adding basal insulin to GLP-1RA improves glycemic control without significant weight gain, unlike prandial insulin, which often leads to weight increases.

In addition to free combinations, fixed-ratio combination (FRC) formulations have been developed, such as insulin degludec/liraglutide (Xultophy®) or insulin glargine/lixisenatide (Soliqua®), allowing co-titration of both molecules in a single device, simplifying treatment and improving adherence. Meta-analyses indicate that FRCs offer similar HbA١c reductions to free regimens, with the added benefit of lower weight gain and reduced variability in hypoglycemic episodes. International diabetes society guidelines now include GLP١-RA and basal insulin combinations as therapeutic intensification options in patients with T٢DM not controlled with basal insulin alone, especially in the presence of cardiovascular disease or increased renal risk. However, despite robust short- and medium-term data, long-term trials are needed to assess cardiovascular and renal outcomes[5].

Objectives

This review aims to analyze current evidence on the efficacy, safety and clinical application of combined GLP-1RA and basal insulin therapy in T2DM, highlighting key findings from randomized studies, meta-analyses and guideline recommendations.

Materials and Methods

A literature review was conducted using the PubMed, SciELO, Google Scholar and ScienceDirect databases.

Discussion

The integration of GLP-1RA and basal insulin in T2DM management is based on accumulated evidence of synergy between the two drug classes. Controlled clinical trials show that adding GLP-1RA (such as liraglutide, semaglutide or dulaglutide) to basal insulin reduces HbA1c by 0.4–0.8% and body weight by up to 3 kg without significantly increasing severe hypoglycaemia. This contrasts with prandial insulin intensification, which increases hypoglycaemia and weight[6]. Comparative analyses between free regimens and FRCs show similar efficacy in HbA1c reduction, with FRCs offering practical advantages: a single device, simplified titration and better adherence reflected in lower discontinuation rates. Maiorino et al. found both approaches reduce HbA1c by around 1.0% and cause 2.0–3.0 kg weight loss, but FRCs had lower dose variability and greater patient satisfaction[7]. The main adverse events are gastrointestinal (nausea, vomiting, diarrhoea), mostly in the initial weeks of treatment and decreasing with dose stabilization. Hypoglycaemia risk remains low compared to prandial insulin due to the glucose-dependent insulin secretion of GLP-1RA. Cardiovascular changes such as increased heart rate appear not to translate into acute cardiovascular event risk, though specific trials are limited. Some subgroup analyses suggest reductions in heart failure hospitalizations, but data are preliminary.

Current guidelines recommend the combined approach, especially in patients with elevated cardiovascular or renal risk, aiming not only for glycaemic control but also for cardiorenal protection. Practical aspects and cost-effectiveness must be evaluated locally, given the higher price of GLP-1RA and combination devices. Nonetheless, the potential for reducing long-term complications may justify the initial investment, particularly in high-risk patients. FRC-facilitated adherence plays a critical role in real-world clinical effectiveness[8,9].

Conclusion

Combined therapy with GLP-1RA and basal insulin is effective and safe for patients with T2DM not achieving glycemic targets with basal insulin alone. Randomized trials and meta-analyses show an additional HbA1c reduction up to 1.0%, weight loss of approximately 2–3 kg and lower hypoglycemia rates than prandial insulin regimens. Fixed-ratio combinations offer operational advantages and improved adherence without loss of efficacy. The main adverse events are transient gastrointestinal symptoms manageable through careful titration. While definitive data on major cardiovascular and renal outcomes are still lacking, international guidelines already endorse this strategy for patients at high cardiovascular or renal risk. Cost-effectiveness analyses suggest potential long-term savings through reduced complications. In conclusion, combining GLP-1RA with basal insulin represents an advancement in T2DM treatment by aligning glycemic efficacy, weight control and hypoglycemia minimization. Long-term studies are recommended to evaluate hard outcomes and economic impact across healthcare systems.

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