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Editorial

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Beyond the Scale: The New Era of Synergy between Pharmacotherapy and Metabolic Surgery

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Editorial

Obesity is a complex chronic disease associated with a wide range of comorbidities, including high blood pressure, dyslipidemia, metabolic associated stheatosic liver disease, sleep apnea, cardiovascular diseases and certain types of cancer [1]. Its global prevalence continues to rise, imposing a substantial burden on healthcare systems finances and individuals' life expectancy and, mainly, quality of life. For decades, Metabolic and Bariatric Surgery (MBS) has been recognized as the most efficient intervention for sustained weight loss and the resolution of metabolic comorbidities in patients with severe obesity [2]. Recently, the landscape of obesity treatment has been significantly altered by the introduction of a new generation of drugs, namely Glucagon-Like Peptide-1 Receptor Agonists (GLP-1 RAs). These medications, which mimic the action of a natural gut hormone, have demonstrated a remarkable ability to induce weight loss and improve glycemic control [3]. Initially viewed as potential competitors to surgery, GLP-1 RAs are now increasingly recognized for their complementary and synergistic role with MBS, ushering in a new era in multimodal obesity treatment [4]. There is evidence that MBS combined with non-surgical approaches appears more effective than MBS alone in reducing BMI [5].

GLP-1 RAs act through multiple mechanisms that contribute to weight loss and metabolic improvement. These include increased glucose-dependent insulin secretion, suppression of glucagon secretion, delayed gastric emptying, and promotion of satiety through effects on the central nervous system [6]. Drugs such as semaglutide and, more recently, tirzepatide (a dual GLP-1/GIP agonist), have demonstrated weight losses ranging from 15% to 21% of total body weight in clinical trials, results that were previously

considered achievable only through surgical interventions [7]. This efficacy has positioned GLP-1 RAs as a fundamental therapeutic option for many patients with obesity, especially those who are not candidates for surgery or who prefer a non-surgical approach. However, their integration into the obesity treatment algorithm is more complex than a simple replacement for surgery; it is in their strategic application in conjunction with MBS that their true potential can be maximized. This interaction between GLP-1 RAs and metabolic surgery is evolving from a perspective of competition to one of collaboration, with the development of a model that can be compared to neoadjuvant and adjuvant treatment in oncology [4]. After all, neither surgeons nor endocrinologists should forget that both have strengths and weaknesses, the differences between which are now less pronounced, and that cooperation and a patient-centred approach are the most logical way forward.

The administration of GLP-1 RAs in the preoperative, or neoadjuvant, period has shown several potential benefits. Personally, we began to use it in 2017, following a very successful experience with the so called "Christine Stier "Rapid Weight Reduction" (RWR) regimen, developed as a bridging strategy for patients with extreme obesity who are initially technically/physiologically unfit for bariatric surgery" [8]. In these cases, weight loss induced by GLP1 RAs, can reduce liver volume (decreasing hepatic steatosis), improve glycemic control, and lower perioperative risks associated with surgery [9]. This strategy can facilitate the performance of surgery, making it safer and potentially leading to better long-term outcomes. However, preoperative use of GLP-1 RAs requires careful management, especially regarding their discontinuation before surgery, due to the risk of delayed gastric emptying and consequent risk of pulmonary aspiration during anesthesia [10]. After metabolic surgery, some patients may experience insufficient weight loss or weight regain over time. In these scenarios, GLP-1 RAs emerge as a valuable adjuvant tool. Studies have shown that semaglutide and tirzepatide are effective in promoting additional weight loss and improving metabolic outcomes in post-surgery patients facing these challenges, often avoiding the need for revisional surgery [11]. Tirzepatide, in particular, showed superior results compared to liraglutide and semaglutide in 6-month post-surgery studies [11]. This adjuvant approach can help sustain the benefits of surgery in the long term, addressing the complexities of obesity as a chronic disease requiring continuous management. While GLP-1 RAs have demonstrated remarkable efficacy, it is crucial to recognize that metabolic surgery still maintains its position as the most potent intervention for weight loss and comorbidity remission. A comparative study from 2025, presented at the American Society for Metabolic and Bariatric Surgery (ASMBS), revealed that sleeve gastrectomy and gastric bypass were associated with approximately five times greater weight loss than the isolated use of GLP-1 agonists after two years [12]. This difference is partly attributable to the high rates of medication discontinuation in real-world clinical practice, with up to 70% of patients stopping treatment within one year, often resulting in weight regain [12]. This evidence underscores that the choice between surgery and pharmacotherapy should not be viewed as a dichotomy, but rather as an informed decision based on individual patient characteristics, preferences, treatment adherence, and weight loss goals. The

combination of both approaches offers the potential to overcome the limitations of each individually.

The future of obesity treatment is undeniably multimodal and personalized. The integration of GLP-1 RAs with metabolic surgery represents a significant advance, allowing for more flexible approaches tailored to individual patient needs. This onco-bariatric model, which views pharmacotherapy as a complement rather than a substitute for surgery, offers the promise of optimizing perioperative safety, improving weight loss, and sustaining long-term metabolic outcomes 4. Furthermore, we need to consider the role of interventional endoscopy, which has developed new technologies such as endoscopic gastroplasty and duodenal mucosa remodeling. These new techniques have achieved promising results in controlling metabolic syndrome and are certainly worthy of a place in future multimodal algorithms **[5]**. Above all, it is important not to forget that metabolic surgery has also made strides compared to bariatric surgery. Based on well-defined pathophysiological concepts, new techniques such as the transit bipartition in its various forms or the ileal interposition have been developed. Although these techniques have not yet stood the test of time nor been validated by long-term, prospective, randomized clinical trials, they are already showing results that go far beyond merely 'promising', demonstrating the potential to set improved standards of efficacy and safety. In the future, new medicines, as well as new endoscopic technologies, are expected to be compared and combined with these new metabolic surgical procedures.

In conclusion, the role of GLP-1 agonists in metabolic surgery transcends mere competition, establishing a new paradigm of synergy. As global research continues to deepen our understanding of the mechanisms of action of GLP-1 RAs and their interaction with physiological changes induced by surgery, also guidelines are expected to evolve to further refine combined treatment strategies. Collaboration among medical specialties – surgeons, endocrinologists, gastroenterologists, nutritionists, and anesthesiologists – will be fundamental to implementing these integrated approaches and ensuring the best outcomes for patients.

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