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EDITORIAL

THE NEXT FRONTIER IN METABOLIC HEALTH: FROM GLP-1 TO MULTI-TARGET AGONISTS

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Obesity is a complex, multifactorial disease driven largely by chronic excess caloric intake, leading to adipose tissue dysfunction characterized by increased lipid release and pro-inflammatory cytokine secretion. These pathological changes contribute directly to dyslipidaemia, insulin resistance, and the development of type 2 diabetes mellitus (T2DM). The rising global prevalence of obesity has fuelled a parallel epidemic of T2DM, imposing substantial clinical and economic burdens worldwide. It is currently estimated that over 537 million individuals are living with diabetes globally, with projections suggesting this figure may rise to 783 million by 2045.[1,2] Lifestyle interventions and conventional pharmacotherapies remain central to obesity and T2DM management; however, they frequently fail to achieve sustained weight loss and long-term glycaemic control. This limitation reflects their inability to comprehensively target the multiple hormonal and metabolic pathways underlying disease progression. Consequently, there is a growing need for innovative therapeutic strategies that address several metabolic mechanisms simultaneously, in combination with lifestyle modification, to improve durability of response, reduce complications, and enable more personalised disease management.[1,2]

Glucagon-like peptide-1 receptor agonists (GLP-1RAs), including liraglutide and semaglutide, are well-established agents in the management of T2DM and obesity. Liraglutide has been shown to significantly reduce HbA1c levels and improve glycaemic control in both adults and adolescents aged over 10 years, while the approved 3 mg dose produces clinically meaningful weight loss in both clinical trials and real-world settings. In addition to its glucose-lowering effects, liraglutide improves cardiovascular outcomes and reduces liver fat content.[1,3] Semaglutide demonstrates even greater efficacy, producing more pronounced reductions in HbA1c alongside improvements in body weight, blood pressure, and lipid metabolism.[1,4] Despite their efficacy, GLP-1RA monotherapy is associated with limitations, including gastrointestinal intolerance and the development of weight-loss plateaus. These challenges can often be mitigated through dietary optimisation, physical activity, or the use of combination agonist therapies. In real-world practice, discontinuation of GLP-1RAs most commonly reflects tolerability concerns, inadequate glycaemic response, or contraindications such as a history of pancreatitis.[3]

Recent advances have led to the development of dual agonists targeting both GLP-1 and glucose-dependent insulinotropic polypeptide (GIP), such as tirzepatide. These agents provide superior glycaemic control and weight reduction compared with GLP-1 monotherapy by enhancing insulin secretion while suppressing glucagon release, thereby overcoming weight-loss plateaus.[4] Additionally, the dual agonists combining GLP-1 and glucagon, have demonstrated favourable metabolic effects, including improved glycaemic control and hepatoprotective actions through reductions in hepatic inflammation and fibrosis.[5] Dual- and triple-agonist therapies enhance satiety, increase energy expenditure, and improve lipid metabolism via mechanisms involving thermogenesis and lipolysis. Collectively, these effects translate into greater and more sustained weight loss and broader metabolic benefits compared with GLP-1 monotherapy. These agents therefore represent a significant evolution in pharmacotherapy, combining appetite suppression, delayed gastric emptying, and preserved insulinotropic effects to form a highly effective

therapeutic class for T2DM and obesity.[4,5] Although gastrointestinal adverse effects are commonly reported with GLP-1RAs, emerging evidence suggests that these effects are generally mild and manageable with dual-agonist therapies. Importantly, current data do not support an increased risk of pancreatic or thyroid cancer associated with GLP-1-based treatments. Intermediate clinical trials indicate potential cardiovascular and renal benefits; however, extended long-term studies are required to confirm the durability of these effects and their applicability across diverse populations and real-world settings.[1,5]

Future research should prioritise long-term cardiovascular outcomes, hepatic fat metabolism, and individual variability in treatment response, incorporating genetic, metabolic, and biomarker-based stratification to optimise efficacy while minimising adverse effects.[4] Integration of pharmacotherapy with personalised lifestyle interventions, including diet, physical activity, sleep optimisation, and digital health tools such as continuous glucose monitoring and mobile apps, offers a comprehensive and promising strategy for sustainable management of obesity and T2DM.

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