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GLP-1 Receptor Agonists Beyond Weight Loss: Established Benefits and Unresolved Translational Questions

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GLP-1 receptor agonists have transformed the treatment of obesity and type 2 diabetes nd their therapeutic implications now extend well beyond endocrinology into cardiovascular and renal medicine, with growing interest in neurological disease. Yet the rapid translation from mechanism to widespread prescription has left several important gaps in our understanding. While large cardiovascular outcome trials have confirmed cardiorenal protection and substantial weight loss [1–7], and preclinical studies suggest neuroprotective actions, the pleiotropic nature of these agents raises a central question: do these benefits arise from direct receptor-mediated effects within individual organs, or indirectly through weight loss, improved insulin sensitivity, and broader metabolic remodeling [8,9]? Here we outline the key translational unknowns that deserve priority investigation.

Direct versus indirect organ protection

The cardiovascular benefits of GLP-1RAs are well established [1–4], but the relative contribution of direct actions on vascular endothelium (including coronary endothelium) versus systemic improvements in inflammation, blood pressure and lipid profile remains unclear. Similarly, the renal protective effect, seen in both diabetic and non-diabetic nephropathy, needs to be disentangled from haemodynamic changes [5,8,9]. Resolving this question will require more precise receptor localization studies in human tissues, complemented by tissue-specific genetic models and translational imaging approaches.

Neuroprotection: central receptor signaling or metabolic mediation?

Robust preclinical evidence suggests that GLP-1 receptor agonists can reduce pathological protein aggregation, enhance autophagy, and attenuate neuroinflammation in models of Alzheimer's disease, Parkinson's disease, and multiple sclerosis [8–10]. However, whether these observations reflect direct central nervous system actions or secondary consequences of systemic metabolic improvement remains uncertain. Furthermore, the extent to which different GLP-1 receptor agonists and newer multi-agonist compounds penetrate the blood–brain barrier remains incompletely understood. Disease-specific clinical trials with long-term follow-up will be required to determine whether these agents are truly disease-modifying rather than merely symptomatic therapies.

Gastrointestinal adverse events and perioperative risk

Nausea, vomiting and diarrhoea are the most common dose-limiting toxicities. More concerning are rare but serious events such as cholecystitis, and ileus. Delayed gastric emptying has generated concern regarding perioperative aspiration risk, although clinically significant aspiration events remain uncommon and the magnitude of risk remains uncertain. Although several professional societies have recently issued perioperative guidance, these recommendations remain based on limited prospective evidence and substantial uncertainty persists regarding optimal management strategies. Future studies should identify which patients and procedures truly warrant treatment interruption, prolonged fasting, or modified anaesthetic strategies [11,12].

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"Ozempic face" and loss of lean mass

Rapid weight loss is frequently accompanied by facial volume loss, changes in skin appearance, and reduction in lean mass. While these findings are commonly attributed to caloric deficit and adipose tissue loss, little is known about whether GLP-1 receptor signaling directly influences dermal fibroblasts, adipose-derived stromal cells, extracellular matrix turnover, or tissue regeneration. This uncertainty raises an intriguing paradox: therapies associated with substantial cardiometabolic improvement may simultaneously accelerate visible features of tissue ageing in the skin. Defining receptor expression patterns and downstream signaling pathways in cutaneous and musculoskeletal tissues therefore represents an important translational priority.

Post-treatment rebound: what is lost?

While weight regain after discontinuation is well documented, little is known about the durability of cardiovascular, renal, or potential neuroprotective benefits once treatment is stopped. Distinguishing transient pharmacological effects from true biological remodeling should become a priority for future withdrawal studies.

Conclusion

Answering these questions requires a full translational pipeline: from receptor localisation in human tissues and organoid studies, to long-term pharmacovigilance registries and pragmatic clinical trials. More broadly, GLP-1 receptor agonists have evolved from metabolic therapies into experimental tools for probing the biological links between metabolism, inflammation, ageing, and organ resilience. Understanding why these drugs work and where they work directly, may prove as important as documenting the benefits themselves.

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