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Glucagon-like-peptide-1 receptor agonists and the management of type 2 diabetes - backwards and forwards.

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Abstract

This editorial is stimulated by the article by Alqifari *et al* published in the World Journal of Diabetes (2024:). Alqifari *et al* focus on practical advice for the clinical use of glucagon-like-peptide-1 receptor agonists (GLP-1RAs) in the management of type 2 diabetes and this editorial provides complementary information. We initially give a brief historical perspective of the development of GLP-1RAs stimulated by following recognition of the 'incretin effect', the substantially greater to enteral when compared to euglycaemic glucose, and the identification of the incretin hormones, GIP and GLP-1. In addition to stimulating insulin, GLP-1 reduces postprandial glucose levels by slowing gastric emptying. GLP-1RAs were developed because native GLP-1 has a very short plasma half-life. The majority of current GLP-1RAs are administered by subcutaneous injection once a week. They are potent in glucose lowering without leading to hypoglycaemia, stimulate weight loss and lead to cardiovascular and renal protection. The landscape in relation to GLP-1RAs is broadening rapidly, with different formulations and their combination with other peptides to facilitate glucose lowering and weight loss. There is a need for more information relating to the effects of GLP-1RAs to induce gastrointestinal symptoms and slow gastric emptying which is likely to allow their use to become more effective and personalised.

Key Words: glucagon-like-peptide-1; glucose-dependent insulinotropic peptide; gastric emptying

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Core Tip: In people who are prescribed a GLP-1RA for management of type 2 diabetes you should always ask about gastrointestinal symptoms both before and after initiating

therapy. Gastrointestinal adverse effects of GLP-1RAs are common, but may not be volunteered.

INTRODUCTION

The development of agonists of the gastrointestinal hormone glucagon-like-peptide-1 (GLP-1RAs), which has revolutionised the management of both type 2 diabetes and obesity, represents a story of long-term discovery, driven as much by serendipity as targeted research, with effective, but arguably overdue, translation, the breadth of which was unanticipated.

CONCLUSION

FURTHER DEVELOPMENTS IN GLP-1RAS

The landscape in relation to GLP-1RAs is expanding rapidly. Drugs that are agonists of two or more peptides that are involved in the regulation of glycaemia and/or body weight (i.e. a GLP-1RA and at least another compound), such as tirzepatide, a combined GLP-1/GIP agonist, that has recently become available and retratutide (a combined GLP-1, GIP and glucagon agonist) that is in late phase development (3,8). Recently, and, contrary to expectation, small molecules that interact with the GLP-1 receptor and are not degraded rapidly when given orally (e.g. orforglipron), have been developed and appear effective in both glucose lowering and inducing weight loss (9). While an oral formulation of semaglutide is available, it has very low bioavailability, even with concomitant use of an absorption enhancer.

The use of GLP-1RAs is being also explored in other diverse disorders, including fatty liver disease and Parkinson's disease (10). GLP-1RAs may prove useful in the management of postprandial hypotension, a substantial fall (>20 mmHg) in systolic blood pressure after a meal, which occurs frequently (~20%) in type 2 diabetes (more commonly than orthostatic hypotension which is well recognised) and predisposes to falls (11). Postprandial hypotension currently lacks an effective treatment.

ISSUES RELATING TO THE USE OF GLP-1RAS IN TYPE 2 DIABETES THAT SHOULD BE ADDRESSED

The magnitude of the response to GLP-1RAs in type 2 diabetes in terms of both glucose lowering and weight loss is highly variable and largely unexplained – this is not surprising given the empirical design of the majority of clinical trials. This issue represents a focus of the timely review by Alqifari *et al* (12) who provide practical, and useful but, in many cases, unavoidably not evidenced-based, recommendations. Clinicians would benefit greatly by insights as to which patient should be given a GLP-1RA and which GLP-1RA.

Upper gastrointestinal symptoms are the most common adverse event of GLP-1RA therapy (particularly nausea and diarrhoea) and not infrequently (perhaps ~10%) lead to non-adherence and treatment discontinuation (3). Gastrointestinal symptoms, however, also occur frequently in people with type 2 diabetes and the obese who do not have type 2 diabetes (13). It is regrettable that in nearly all studies relating to GLP-1RAs gastrointestinal symptoms have been assessed solely using participant 'self-report', which is known to be unreliable, rather than simple, validated measures that are readily available and used extensively in the assessment of functional gastrointestinal disorders (e.g. irritable bowel syndrome and functional dyspepsia (14). The relevance of symptom indication to weight loss induced by GLP-1RAs, accordingly, still remains uncertain. The impact of GLP-1RAs to slow gastric emptying, which is integral to their capacity to reduce postprandial glycaemic excursions, also requires clarification. 'Short-acting' GLP-1RAs (i.e. exenatide BID and lixisenatide) were shown, using accurate methods, to slow gastric emptying markedly but variably that this slowing occurs in doses substantially less than used in the management of type 2 diabetes (13,15) and is predictive of the reduction in postprandial glucose (13). It was assumed (without accurate measurement) that 'longer-acting' GLP-1RAs did not have sustained effect to slow gastric emptying, but this concept has recently been shown to be incorrect – liraglutide (16), exenatide QW (17) and semaglutide sc (18) all slow gastric emptying

substantially, like 'short-acting' GLP-1RAs, variably, with longer-term administration. Gastric emptying is also frequently delayed in longstanding, complicated type 2 diabetes per se, but cannot be predicted on the basis of symptoms (13). This issue has assumed even greater importance with recent reports of retained gastric content, despite adherence to recommended periods of fasting in individuals using long-acting GLP-1RAs with cases of aspiration (19). This has stimulated recent guidelines for the use of GLP-1RAs prior to surgery/endoscopic procedures, which unavoidably lack a strong evidence base. Assessment of their effect on gastric emptying, using a precise technique, should be part of the routine development of GLP-1RAs (14).

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1	Michael Horowitz, Christopher K. Rayner, Chinmay S. Marathe, Tongzhi Wu, Karen L. Jones. "Glucagon-like peptide-1 receptor agonists and the appropriate measurement of gastric emptying", Diabetes, Obesity and Metabolism, 2020 Crossref	13 words — 1%
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