



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

Michael Horowitz, Lu Cai, Md Shahidul Islam

Specialty type: Endocrinology and metabolism

Provenance and peer review:

Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): A

Grade B (Very good): B

Grade C (Good): C

Grade D (Fair): 0

Grade E (Poor): 0

P-Reviewer: Alsaidan A, Saudi Arabia; Shuang W, China; Yang L, China

Received: January 28, 2024

Peer-review started: January 28, 2024

First decision: February 8, 2024

Revised: February 14, 2024

Accepted: February 23, 2024

Article in press: February 23, 2024

Published online: March 15, 2024



Michael Horowitz, Department of Medicine, University of Adelaide, Adelaide 5005, Australia

Lu Cai, Pediatric Research Institute, University of Louisville, Louisville, KY 40202, United States

Md Shahidul Islam, Department of Biochemistry, School of Life Sciences, University of KwaZulu-Natal, Durban 4000, KwaZulu-Natal, South Africa

Corresponding author: Michael Horowitz, MBBS, PhD, DSc, FRACP, AO, Director, Endocrine and Metabolic Unit, Royal Adelaide Hospital and Professor, Department of Medicine, University of Adelaide, Level 5, AHMS Corner North Tce and George St, Adelaide 5005, Australia. michael.horowitz@adelaide.edu.au

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 (GLP-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 recognition of the 'incretin effect', the substantially greater insulin increase to enteral when compared to euglycaemic intravenous 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 in obese individuals 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 both 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; Type 2 diabetes

©The Author(s) 2024. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: In people who are prescribed a glucagon-like-peptide-1 receptor agonist (GLP-1RA) for management of type 2 diabetes or obesity 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.

Citation: Horowitz M, Cai L, Islam MS. Glucagon-like-peptide-1 receptor agonists and the management of type 2 diabetes-backwards and forwards. *World J Diabetes* 2024; 15(3): 326-330

URL: <https://www.wjgnet.com/1948-9358/full/v15/i3/326.htm>

DOI: <https://dx.doi.org/10.4239/wjd.v15.i3.326>

INTRODUCTION

The development of glucagon-like-peptide-1 (GLP-1) receptor agonists (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 has been unanticipated.

BACKGROUND

The so-called ‘incretin effect’-that oral, or enteral administration of glucose leads to a much greater (50%-70%) insulin response than isoglycaemic intravenous glucose was reported in 1964 *i.e.* some 60 years ago, but already suggested by the Belgian physiologist La Barre in 1932[1]. Key milestones subsequent to 1964 have been the characterisation of the two ‘incretin’ hormones-glucose-dependent insulintropic peptide-GIP (initially termed gastric inhibitory polypeptide) (about 1973) and GLP-1 (about 1985), the demonstration that the ‘incretin effect’ is attenuated in type 2 diabetes (about 1986) reflecting a markedly diminished insulintropic effect of GIP (about 1993), which is probably the dominant incretin in health[1], and the landmark observation by Nauck *et al*[2,3] that intravenous administration of GLP-1, in pharmacological concentrations, had the capacity to normalise even markedly elevated blood glucose levels, in type 2 diabetes[2,3]. This latter observation was contrary to expectation based on the outcome of prior animal studies and, importantly, glucose lowering induced by GLP-1 was not associated with induction of hypoglycaemia[2]. The latter reflects the glucose-dependency of the insulintropic and glucagonostatic actions of GLP-1 and accounts for the safety of GLP-1RAs in relation to their low, to non-existent, potential to induce hypoglycaemia in humans[3].

It was subsequently demonstrated (about 1997) that GLP-1 also slowed the rate of gastric emptying and this, rather than the stimulation of insulin and/or the suppression of glucagon, represented the major mechanism underlying its effect to lower postprandial glucose markedly. Accordingly, GLP-1 was shown to be an enterogastrone, as well as an ‘incretin’[4]. Altogether these observations provided a persuasive basis to support the development of drugs based on the actions of GLP-1, rather than GIP, as a glucose lowering therapy. However, it was also appreciated in about 1995, that both GLP-1 and GIP undergo rapid proteolytic degradation in plasma, by a ubiquitous enzyme, dipeptidyl peptide-4 (DPP-4), and that native GLP-1 was, accordingly, unlikely to be used therapeutically because of its short (approximately 2 min) plasma half-life[2]. To overcome the deficiency of native GLP-1 two strategies were developed and have been translated successfully to treat type 2 diabetes-DPP-4 inhibitors, designed prospectively, introduced in 2004 and now widely used, safe oral medications that they have only modest glucose-lowering capacity and are weight neutral and GLP-1RAs, resistant to degradation by DPP-4, administered for the main part subcutaneously and, as will be discussed, with potent effects to reduce elevated blood glucose levels as well as reduce body weight in obese individuals[2].

The first GLP-1RA, exenatide, introduced in 2005 for the management of type 2 diabetes, was, astonishingly, based on exendin-4 isolated from the venom of the Gila monster, *Heloderma suspectum*, a slow-moving lizard native to Southwestern United States. Exenatide exhibits approximately 50% homology to native GLP-1 and is administered subcutaneously twice a day. This has been followed rapidly by the ongoing development of ‘designer’ molecules (*e.g.* liraglutide, dulaglutide and semaglutide) with increasingly greater efficacy to improve glycaemic control, as well as reduce body weight. There are substantial differences between individual GLP-1RAs, apart from their capacity to reduce blood glucose and body weight, particularly in relation to their duration of action, where they may be classified as either ‘short’- or ‘longer’-acting[3].

LIMITATIONS OF PREVIOUS PHARMACOTHERAPY FOR TYPE 2 DIABETES

The significance of the advent of GLP-1RAs should be considered in relation to the substantial limitations in existing approaches to the management of type 2 diabetes. It was appreciated that measurement of glycated haemoglobin (Hb1Ac) was predictive of both the development and progression of the microvascular complications of diabetes, so that management should, ideally, be targeted to achieve a Hb1Ac $\leq 7.0\%$ or even less. Moreover, as a result of the seminal work by Monnier *et al*[5], it was recognised that the contribution of postprandial blood glucose excursions to Hb1Ac is

substantial, and when Hb1Ac is $\leq 7.5\%$ it is the dominant determinant. Approaches to management were also essentially 'glucocentric' with the aim of delaying, if not preventing, microvascular complications. The individual response to glucose-lowering therapy was variable and, at least in most cases, unpredictable and the approach to management was essentially empirical. The use of insulin (and to a lesser extent, sulphonylureas) was, of course, also associated with hypoglycaemia (deleterious and sometimes lethal), increased glucose variability (a potential factor in the risk of micro- and macrovascular complications) and weight gain (in individuals who are characteristically already obese). The therapeutic approaches also had limited, if any, impact on either cardiovascular or renal dysfunction, which were well recognised as major sources of morbidity and mortality. Inherent 'advantages' of GLP-1RAs were, accordingly, that they targeted the 'islet cell defects' in type 2 diabetes of excessive glucagon, and a relative reduction in insulin, secretion, their capacity to normalise both fasting and postprandial hyperglycaemia and the non-existent potential for hypoglycaemia. A further, and major, paradigm shift was the demonstration, in 2016, that liraglutide prevented cardiovascular events and was also renoprotective[6]-the majority of subsequently developed GLP-1RAs have shown similar effects[7]. It should be appreciated that these cardiovascular outcome trials, initiated in about 2008, were mandated by regulatory bodies to test the safety and efficacy of new glucose lowering drugs, and the positive outcomes were generally unanticipated. Several direct and indirect effects may account for the cardio-/reno-protective actions of GLP-1RAs, which appear unrelated to their glucose lowering effect[7].

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 retatrutide (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 mm Hg) in systolic blood pressure after a meal, which occurs frequently (approximately 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 about 10%) lead to non-adherence and/or 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 induction 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) have been shown, using accurate methods, to slow gastric emptying markedly but variably. 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 and, 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].

FOOTNOTES

Author contributions: Horowitz M conceptualised and wrote the first draft of the editorial; Islam MS and Cai L made revisions and editorial corrections before submission; All authors have read and approved the final manuscript.

Conflict-of-interest statement: Horowitz M, Cai L and Islam MS have no conflict of interest within this article.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <https://creativecommons.org/licenses/by-nc/4.0/>

Country/Territory of origin: Australia

ORCID number: Michael Horowitz 0000-0002-0942-0306; Lu Cai 0000-0003-3048-1135; Md Shahidul Islam 0000-0003-0309-9491.

S-Editor: Fan JR

L-Editor: A

P-Editor: Chen YX

REFERENCES

- Creutzfeldt W. The [pre-] history of the incretin concept. *Regul Pept* 2005; **128**: 87-91 [PMID: 15780427 DOI: 10.1016/j.regpep.2004.08.004]
- Nauck MA, Müller TD. Incretin hormones and type 2 diabetes. *Diabetologia* 2023; **66**: 1780-1795 [PMID: 37430117 DOI: 10.1007/s00125-023-05956-x]
- Nauck MA, Quast DR, Wefers J, Meier JJ. GLP-1 receptor agonists in the treatment of type 2 diabetes - state-of-the-art. *Mol Metab* 2021; **46**: 101102 [PMID: 33068776 DOI: 10.1016/j.molmet.2020.101102]
- Horowitz M, Nauck MA. To be or not to be--an incretin or enterogastrone? *Gut* 2006; **55**: 148-150 [PMID: 16407380 DOI: 10.1136/gut.2005.071787]
- Monnier L, Colette C, Dunseath GJ, Owens DR. The loss of postprandial glycemic control precedes stepwise deterioration of fasting with worsening diabetes. *Diabetes Care* 2007; **30**: 263-269 [PMID: 17259492 DOI: 10.2337/dc06-1612]
- Marso SP, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JF, Nauck MA, Nissen SE, Pocock S, Poulter NR, Ravn LS, Steinberg WM, Stockner M, Zinman B, Bergenstal RM, Buse JB; LEADER Steering Committee; LEADER Trial Investigators. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med* 2016; **375**: 311-322 [PMID: 27295427 DOI: 10.1056/NEJMoa1603827]
- Solini A, Tricò D, Del Prato S. Incretins and cardiovascular disease: to the heart of type 2 diabetes? *Diabetologia* 2023; **66**: 1820-1831 [PMID: 37542009 DOI: 10.1007/s00125-023-05973-w]
- Frias JP, Davies MJ, Rosenstock J, Pérez Manghi FC, Fernández Landó L, Bergman BK, Liu B, Cui X, Brown K; SURPASS-2 Investigators. Tirzepatide versus Semaglutide Once Weekly in Patients with Type 2 Diabetes. *N Engl J Med* 2021; **385**: 503-515 [PMID: 34170647 DOI: 10.1056/NEJMoa2107519]
- Nauck MA, Horowitz M. Non-peptide, once-per-day oral orforglipron to compete with established peptide-based, injectable GLP-1 receptor agonists. *Lancet* 2023; **402**: 429-431 [PMID: 37369233 DOI: 10.1016/S0140-6736(23)01201-1]
- Baggio LL, Drucker DJ. Glucagon-like peptide-1 receptor co-agonists for treating metabolic disease. *Mol Metab* 2021; **46**: 101090 [PMID: 32987188 DOI: 10.1016/j.molmet.2020.101090]
- Jones KL, Rigda RS, Butfield MDM, Hatzinikolas S, Pham HT, Marathe CS, Wu T, Lange K, Trahair LG, Rayner CK, Horowitz M. Effects of lixisenatide on postprandial blood pressure, gastric emptying and glycaemia in healthy people and people with type 2 diabetes. *Diabetes Obes Metab* 2019; **21**: 1158-1167 [PMID: 30623563 DOI: 10.1111/dom.13633]
- Alqifari S, Alkomi O, Esmail A, Alkhawami K, Yousri S, Muqresh MS, Alharbi N, Khojah AA, aljabri A, Allahham A, Prabakar K, Alshareef H, Aldhaeefi M, Alrasheed T, Alrabiah A, Albishi LA. Practical Guide: Glucagon-like peptide-1 and dual glucose-dependent insulinotropic polypeptide and glucagon-like Peptide- receptor agonists in diabetes mellitus. *World J Diabetes* 2024; **15**: 331-347 [DOI: 10.4239/wjcd.v15.i3.331]
- Jalleh RJ, Jones KL, Rayner CK, Marathe CS, Wu T, Horowitz M. Normal and disordered gastric emptying in diabetes: recent insights into (patho)physiology, management and impact on glycaemic control. *Diabetologia* 2022; **65**: 1981-1993 [PMID: 36194250 DOI: 10.1007/s00125-022-05796-1]
- Jalleh RJ, Jones KL, Nauck M, Horowitz M. Accurate Measurements of Gastric Emptying and Gastrointestinal Symptoms in the Evaluation of Glucagon-like Peptide-1 Receptor Agonists. *Ann Intern Med* 2023; **176**: 1542-1543 [PMID: 37931267 DOI: 10.7326/M23-2019]
- Linnebjerg H, Park S, Kothare PA, Trautmann ME, Mace K, Fineman M, Wilding I, Nauck M, Horowitz M. Effect of exenatide on gastric emptying and relationship to postprandial glycemia in type 2 diabetes. *Regul Pept* 2008; **151**: 123-129 [PMID: 18675854 DOI: 10.1016/j.regpep.2008.07.003]
- Maselli D, Atieh J, Clark MM, Eckert D, Taylor A, Carlson P, Burton DD, Busciglio I, Harmsen WS, Vella A, Acosta A, Camilleri M. Effects of liraglutide on gastrointestinal functions and weight in obesity: A randomized clinical and pharmacogenomic trial. *Obesity (Silver Spring)* 2022; **30**: 1608-1620 [PMID: 35894080 DOI: 10.1002/oby.23481]
- Jones KL, Huynh LQ, Hatzinikolas S, Rigda RS, Phillips LK, Pham HT, Marathe CS, Wu T, Malbert CH, Stevens JE, Lange K, Rayner CK, Horowitz M. Exenatide once weekly slows gastric emptying of solids and liquids in healthy, overweight people at steady-state concentrations. *Diabetes Obes Metab* 2020; **22**: 788-797 [PMID: 31903712 DOI: 10.1111/dom.13956]
- Jensterle M, Ferjan S, Ležaič L, Sočan A, Goričar K, Zaletel K, Janež A. Semaglutide delays 4-hour gastric emptying in women with polycystic ovary syndrome and obesity. *Diabetes Obes Metab* 2023; **25**: 975-984 [PMID: 36511825 DOI: 10.1111/dom.14944]
- Kobori T, Onishi Y, Yoshida Y, Tahara T, Kikuchi T, Kubota T, Iwamoto M, Sawada T, Kobayashi R, Fujiwara H, Kasuga M. Association of

glucagon-like peptide-1 receptor agonist treatment with gastric residue in an esophagogastroduodenoscopy. *J Diabetes Investig* 2023; **14**: 767-773 [PMID: [36919944](#) DOI: [10.1111/jdi.14005](#)]



Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA

Telephone: +1-925-3991568

E-mail: office@baishideng.com

Help Desk: <https://www.f6publishing.com/helpdesk>

<https://www.wjgnet.com>

