Review Article ISSN 2835-6276

American Journal of Medical and Clinical Research & Reviews

Glucagon-like peptide-1 receptor agonists : A new step towards weight management

Omar, Mohamed Ahmed Raslan

Department of Internal Medicine, Burjeel Hospital Abudhabi

*Correspondence: Omar

Received: 01 Sep 2023; Accepted: 13 Sep 2023; Published: 20 Sep 2023

Citation: Omar. Glucagon-like peptide-1 receptor agonists : A new step towards weight management. AJMCRR 2023; 2(9): 1-7.

ABSTRACT

Obesity, a widely established chronic disease, presents challenges in its treatment. Unfortunately, obesity is often accompanied with a multitude of chronic maladies that substantially elevate health risks. Thus, it is critical to promote weight management in order to hinder the development of severe complications and to improve the overall patient well-being. Several approaches exist to address this condition and induce weight loss. In addition to lifestyle adjustments by physical activity and dietary modifications, some emerging medications could provide promising results in achieving a reduction in weight.

This report discusses the potential implementation of Glucagon-like peptide-1 receptor agonist (GLP-1-RA) as a therapeutic option for obesity. Specifically, it will examine the efficacy of GLP-1-RA in the promotion of weight loss in both diabetic and non-diabetic patients. Nevertheless, it is essential to highlight the potential side effects associated with the use of this drug.

KeyWords: Diabetic; Obesity; Glucagon-like peptide-1 receptor agonist (GLP-1-RA)

Introduction

One of the most prevalent diseases globally is obesity which is excessive fat accumulation that evolves gradually over time and is distributed around multiple body parts and organs, posing a great health risk. With more than four million fatalities each year, obesity is often associated with a variety of chronic diseases, amongst them hypertension, type 2 diabetes mellitus (T2DM), cerebrovascular diseases, and chronic kidney disease are most common [1]. Specifically, obesity induces the chronic excitability of the sympathetic nervous system, resulting in hypertension and increasing the risk of heart disease, stroke, and chronic kidney dysfunction [2, 3, 4]. Thus, the promotion of weight loss is crucial to lessen complications from comorbidities [5].

Obesity management principles comprise of behavioral therapy, drugs as well as bariatric surgery. One of the emerging drug therapies for obesity is the us-

age of the Glucagon-like peptide-1 receptor agonist. Glucagon-like peptide-1 "GLP-1 is a hormone responsible for increasing insulin secretion following food consumption". [6]. Whereas its receptor agonist GLP-1-RA promotes weight loss by the suppression of appetite within the hypothalamus resulting in peripheral satiety by slowing down gastric emptying, thus reducing calorie intake [7].

Glucagon-like peptide-1 receptor agonists

As indicated by Luniewski, GLP-1-RAs induce a stimulation the secretion of insulin that depends on glucose and elicit inhibition of the secretion of glucagon thereby promoting a feeling of satiety and retarding postprandial gastric emptying [Figure 1]. These combined mechanisms favor weight reduction [8,9,10–12]. Specifically, semaglutide and liraglutide are most effective at lowering glucose [13–15].In addition, the entire drug class exhibits weight loss properties and beneficial cardiovascular effects [16–18,38].

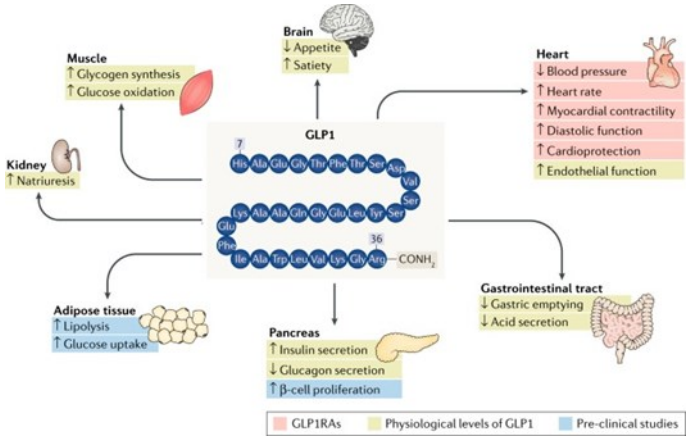

Figure 1 shows the effect of GLP-1-RAs on various body functions. Andersen, A., Lund, A., Knop, F.K. et al. Glucagon-like peptide 1 in health and disease. Nat Rev Endocrinol 14, 390–403 (2018).

Weight loss for diabetic patients

Antihyperglycemic medication's impact on the weight of patients suffering from obesity and Type 2 Diabetes (T2DM) should be profoundly considered. Besides, the choice of drug therapy should contemplate the costs, patient preferences, and most importantly, comorbidities. Pharmacotherapy for obesity is targeted to patients meeting the following criteria (1) BMI ≥ 30 kg/m2 or (2) BMI ≥ 27 kg/m2.

It should be noted that medications used to treat obesity are complementary to the primary therapy and cannot substitute other obesity management techniques. Before and during drug therapy, patients must demonstrate a strong incentive to lose weight through proper diet and frequent exercise[8]. For instance, GLP1-RAs is proven advantageous to patients with cardiovascular diseases by lowering blood pressure and having nephroprotective and cardioprotective properties [Figure 1]. Nevertheless, it is worth noting that the dosage of GLP1-RAs recommended for weight management is different than the dose required in T2DM management [18,19].

Since patients with T2DM and obesity typically present with other comorbidities, they tend to require multiple medications. The physician attempting obesity therapy should cautiously assess these medications due to the tendency of many drugs to contribute to weight gain like antihistamines, antipsychotics, anti-depressants and hormonal drugs [20,21]. Consequently, the physician should replace the patient's drugs with ones that have a neutral impact on body weight or

even with ones that have a propensity of weight loss [8].

Weight loss for non-diabetic patients

Notably, there have been studies conducted that evaluate the effect of liraglutide, a component of the GLP-1-RAs drug class, on body weight and endurability in obese people without T2DM. For instance, the following study analyzed the efficacy and safety of all doses of liraglutide for weight loss in obese individuals without diabetes. Initially, nine randomized controlled trials were included, from amongst all doses of liraglutide for weight control in obese and nondiabetic subjects, most participants achieved about 5 to 10 percent decrease in their body weight. “examinations of all doses of liraglutide revealed that the 3.0 mg dose exhibited the most significant impact on weight reduction”. Furthermore, the decline in cardiovascular diseases risk was remarkably achieved after the administration of liraglutide.

In spite of the benefits liraglutide had revealed, adverse events were frequently reported among the subjects. In particular, the subjects experienced gastrointestinal effects at the onset of treatment and during dose escalation. “Even more precisely, the risk serious side effects such as pancreatitis, psychiatric effects and thyroid cancer especially related to the 3.0 dose, were less common yet a concern” leading to the dismissal of certain participants from the study.

Additionally, the participants of another randomized study were also with provided with liraglutide 3.0 mg. At 20 weeks since the initiation of the study, the participants eventually lost 7.2 kg of mean body weight which increased to 7.8 kg at one year. Subsequently, in a time frame of two years, participants randomized to liraglutide 2.4 or 3.0 mg (pool group) have sustained a mean reduction of body weight of 5.3 kg. Overall, subjects that had completed the entire two-year treatment period lost 7.8 kg from the time the weight loss therapy commenced [22-27].

Distinctly, out of the GLP-1-RAs, liraglutide and semaglutide are the only antihyperglycemic agents approved for weight management in obese patients without T2DM. Indeed, GLP-1RAs provide protection against the development of overt T2DM. Moreover, GLP1-RAs have a glucose-dependent mechanism of action resulting in reduced risk of hypoglycemia [28,29].

Side Effects

The utilization of drug therapy for weight management contributes to a variety of adverse effects. Specifically, individuals that use GLP1-RAs often present with gastrointestinal issues like nausea, vomiting, and diarrhea. Primarily, the side effects are more pronounced at the commencement of therapy and eventually decrease or diminish altogether over time. Besides, there is substantiated evidence suggesting that GLP-1RAs may contribute to “gallbladder disorders, pancreatitis,” cholecystitis, cholelithiasis, and thyroid disease “which are more concerning adverse effects” [30–35].

According to the official product characteristics of liraglutide submitted to the European Medicines Agency (EMA), the only absolute contraindication for the prescription of liraglutide is hypersensitivity

to its substituents. Moreover, due to insufficient safety data regarding pregnancy and breastfeeding, it is not recommended to administer GLP-1-RAs for women of childbearing potential. In addition, it is not advisable to administer liraglutide to patients with the following criteria (1) are 75 years old (2) are undergoing pharmacotherapy for weight management (3) are suffering from severe renal or hepatic disorder and (4) are obese due to eating or endocrine disorders. In spite of the safety issues, liraglutide is authorized to be prescribed to diabetic patients aged 10 years or more and to obese patients aged 12 years or more.

Similarly, the same protocol could be applicable for the administration of semaglutide with the exception of cholelithiasis, cholecystitis, as well as thyroid disease. Nevertheless, it is important to note that a concerning adverse effect of semaglutide is diabetic retinopathy [36,37].

Conclusion

To conclude, in response to the alarming rise in the prevalence of obesity globally, extensive research about weight loss strategies have been urged. This focus is primarily driven due to life-threatening conditions often coexisting with obesity. GLP-1-RAs, an emerging class of drugs, hold as a potential co-therapy for obesity in patients with or without T2DM. Nevertheless, its significant to consider serious adverse effects and contraindications of this medication to ensure patient safety. Still, through dose adjustments, we could control the more frquent side effects, therefore resulting in an efficient and safe weight management.

References

1. Afshin A, Forouzanfar MH, Reitsma MB, Sur P, Estep K, et al. Health effects of overweight and obesity in 195 countries over 25 years. N Engl J Med (2017) 377(1):13–27. doi: 10.1056/ NEJMoa1614362
2. Heymsfield SB, Wadden TA. Mechanisms, pathophysiology, and management of obesity. N Engl J Med (2017) 376(15):1492. doi: 10.1056/ NEJMc1701944
3. Borrelli S, Garofalo C, Mallamaci F, Tripepi G, Stanzione G, Provenzano M, et al. Short-term blood pressure variability in nondialysis chronic kidney disease patients: correlates and prognostic role on the progression of renal disease. J Hypertens (2018) 36 (12):2398–405. doi: 10.1097/ HJH.0000000000001825
4. Mallamaci F, Tripepi G, D'Arrigo G, Borrelli S, Garofalo C, Stanzione G, et al. Blood pressure variability, mortality, and cardiovascular outcomes in CKD patients. Clin J Am Soc Nephrol.: CJASN (2019) 14(2):233–40. doi: 10.2215/ CJN.04030318
5. Pratama KG, Tandarto K, Hengky A. Weight loss effect of sodium-glucose cotransporter-2 (SGLT2) inhibitors in patients with obesity without diabetes: A systematic review. Acta Endocrinol (Buchar). (2022) 18(2):216–24. doi: 10.4183/ aeb.2022.216
6. Pelle MC, Provenzano M, Zaffina I, Pujia R, Giofrè F, Lucà S, et al. Role of a dual glucose-dependent insulinotropic peptide (GIP)/ Glucagon-like peptide-1 receptor agonist

(Twincretin) in glycemic control: From pathophysiology to treatment. Life (Basel). (2021) 12 (1):29. doi: 10.3390/life12010029

7. Yumuk V, Tsigos C, Fried M, Schindler K, Busetto L, Micic D, et al. European Guidelines for obesity management in adults [published correction appears in obes facts. Obes Facts. (2015) 8 (6):402–24. doi: 10.1159/000442721

8. Luniewski, M., Matyjaszek-Matuszek, B., & Lenart-Lipińska, M. (2023). Diagnosis and non-invasive treatment of obesity in adults with type 2 diabetes mellitus: A review of guidelines. Journal of Clinical Medicine, 12(13), 4431. doi:https://doi.org/10.3390/jcm12134431

9. Matyjaszek-Matuszek, B.; Szafraniec, A.; Porada, D. Pharmacotherapy of obesity—State of the art. Endokrynol. Pol. 2018, 69, 448–457. [CrossRef]

10. Thrasher, J. Pharmacologic Management of Type 2 Diabetes Mellitus: Available Therapies. Am. J. Med. 2017, 130, S4–S17. [CrossRef]

11. Pi-Sunyer, X.; Astrup, A.; Fujioka, K.; Greenway, F.; Halpern, A.; Krempf, M.; Lau, D.C.W.; le Roux, C.W.; Violante Ortiz, R.; Jensen, C.B.; et al. A Randomized, Controlled Trial of 3.0 mg of Liraglutide in Weight Management. N. Engl. J. Med. 2015, 373, 11–22. [CrossRef] [PubMed]

12. Pedersen, S.; Manjoo, P.; Wharton, S. Canadian Adult Obesity Clinical Practice Guidelines: Pharmacotherapy in Obesity Management. Available online: https://obesitycanada.ca/guidelines/pharmacotherapy

13. Pratley, R.E.; Aroda, V.R.; Lingvay, I.; Lüdemann, J.; Andreassen, C.; Navarria, A.; Viljoen, A. Semaglutide versus dulaglutide once weekly in patients with type 2 diabetes (SUSTAIN 7): A randomised, open-label, phase 3b trial. Lancet Diabetes Endocrinol. 2018, 6, 275–286. [CrossRef] [PubMed]

14. Htike, Z.Z.; Zaccardi, F.; Papamargaritis, D.; Webb, D.R.; Khunti, K.; Davies, M.J. Efficacy and safety of glucagon-like peptide-1 receptor agonists in type 2 diabetes: A systematic review and mixed-treatment comparison analysis. Diabetes Obes. Metab. 2017, 19, 524–536. [CrossRef] [PubMed]

15. Frias, J.P.; Wynne, A.G.; Matyjaszek-Matuszek, B.; Bartaskova, D.; Cox, D.A.; Woodward, B.; Li, Y.G.; Tham, L.S.; Milicevic, Z. Efficacy and safety of an expanded dulaglutide dose range: A phase 2, placebo-controlled trial in patients with type 2 diabetes using metformin. Diabetes Obes. Metab. 2019, 21, 2048–2057. [CrossRef]

16. Marso, S.P.; Bain, S.C.; Consoli, A.; Eliaschewitz, F.G.; Jódar, E.; Leiter, L.A.; Lingvay, I.; Rosenstock, J.; Seufert, J.; Warren, M.L.; et al. Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. N. Engl. J. Med. 2016, 375, 1834–1844. [CrossRef]

17. Marso, S.P.; Daniels, G.; Brown-Frandsen, K. Liraglutide and cardiovascular outcomes in type 2 diabetes. N. Engl. J. Med. 2016, 375, 311–322. [CrossRef]

18. Gerstein, H.C.; Colhoun, H.M.; Dagenais, G.R.; Diaz, R.; Lakshmanan, M.; Pais, P.; Probstfield, J.; Riesmeyer, J.S.; Riddle, M.C.; Rydén, L.; et

al. Dulaglutide and cardiovascular outcomes in Type 2 diabetes (REWIND): A double-blind, randomised placebocontrolled trial. Lancet 2019, 394, 121–130. [CrossRef]

19. Care, D.; Suppl, S.S. Obesity management for the treatment of type 2 diabetes: Standards of medical care in diabetes—2020. Diabetes Care 2020, 43 (Suppl. S1), S89–S97. [CrossRef]

20. American Diabetes Association. 9. Pharmacologic approaches to glycemic treatment: Standards of medical care in diabetes—2020. Diabetes Care 2020, 43 (Suppl. S1), S98–S110. [CrossRef]

21. Matuszek, B.; Szafraniec, A.; Porada, D. Pharmacotherapy of obesity—State of the art. Endokrynol. Pol. 2018, 69, 448–457. [CrossRef]

22. Astrup, A.; Rössner, S.; Van Gaal, L.; Rissanen, A.; Niskanen, L.; Al Hakim, M.; Madsen, J.; Rasmussen, M.F.; Lean, M.E.; NN8022-1807 Study Group. Effects of liraglutide in the treatment of obesity: A randomised, double-blind, placebo-controlled study. Lancet 2009, 374, 1606–1616. [CrossRef] [PubMed]

23. Kanwal, S.; AlEmadi, E.A. Liraglutide for Weight Management, Critical Analysis of Efficacy and Side effects in Nondiabetic, individuals with obesity: A Comprehensive Systematic Review. Middle East J. Fam. Med. 2021, 19, 72–83.

24. Field, B.C.T.; Wren, A.M.; Cooke, D.; Bloom, S.R. Gut Hormones as Potential New Targets for Appetite Regulation and the Treatment of Obesity. Drugs 2008, 68, 147–163. [CrossRef]

25. Zander, M.; Madsbad, S.; Madsen, J.L.; Holst, J.J. Effect of 6-week course of glucagon-like peptide 1 on glycaemic control, insulin sensitivity, and β-cell function in type 2 diabetes: A parallel-group study. Lancet 2002, 359, 824–830. [CrossRef]

26. Garber, A.J. Incretin-based therapies in the management of type 2 diabetes: Rationale and reality in a managed care setting. Am. J. Manag. Care 2010, 16 (Suppl. S7), S187–S194. [PubMed]

27. Isidro, M.L.; Cordido, F. Drug treatment of obesity: Established and emerging therapies. Mini-Rev. Med. Chem. 2009, 9, 664–673. [CrossRef] [PubMed]

28. Matyjaszek-Matuszek, B.; Szafraniec, A.; Porada, D. Pharmacotherapy of obesity—State of the art. Endokrynol. Pol.; 2018; 69, pp. 448-457. [DOI: https://dx.doi.org/10.5603/EP.2018.0048]

29. FDA. FDA Approves New Drug Treatment for Chronic Weight Management, First Since 2014. Available online: https://www.fda.gov/news-events/press-announcements/fda-approves-new-drug-treatment-chronic-weightmanagement-first-2014

30. Storgaard, H.; Cold, F.; Gluud, L.L.; Vilsbøll, T.; Knop, F.K. Glucagon-like peptide-1 receptor agonists and risk of acute pancreatitis in patients with type 2 diabetes. Diabetes Obes. Metab.; 2017; 19, pp. 906-908. [DOI: https://dx.doi.org/10.1111/dom.12885]

31. Monami, M.; Nreu, B.; Scatena, A.; Cresci, B. Safety issues with glucagon-like peptide-1 receptor agonists: Pancreatitis, pancreatic cancer, and cholelithiasis. Data from randomised con-

trolled trials. Diabetes Obes. Metab.; 2017; 19, pp. 1233-1241. [DOI: https://dx.doi.org/10.1111/dom.12926]

32. Knudsen, L.B.; Madsen, L.W.; Andersen, S.; Almholt, K.; De Boer, A.S.; Drucker, D.J.; Gotfredsen, C.; Egerod, F.L.; Hegelund, A.C.; Jacobsen, H. et al. Glucagon-like peptide-1 receptor agonists activate rodent thyroid C-cells causing calcitonin release and C-cell proliferation. Endocrinology; 2010; 151, pp. 1473-1486. [DOI: https://dx.doi.org/10.1210/en.2009-1272]

33. Bezin, J.; Gouverneur, A.; Pénichon, M.; Mathieu, C.; Garrel, R.; Hillaire-Buys, D.; Pariente, A.; Faillie, J.-L. GLP-1 Receptor Agonists and the Risk of Thyroid Cancer. Diabetes Care; 2022; 46, pp. 384-390. [DOI: https://dx.doi.org/10.2337/dc22-1148]

34. C.A.; Stüurmer, T. Putting GLP-1 RAs and Thyroid Cancer in Context: Additional Evidence and Remaining Doubts. Diabetes Care; 2023; 46, pp. 249-251. [DOI: https://dx.doi.org/10.2337/dci22-0052]

35. Chiu, W.Y.; Shih, S.R.; Tseng, C.H. A review on the association between glucagon-like peptide-1 receptor agonists and thyroid cancer. Exp. Diabetes Res.; 2012; 2012, 924168. [DOI: https://dx.doi.org/10.1155/2012/924168] [PubMed: https://www.ncbi.nlm.nih.gov/pubmed/22693487]

36. EMA (European Medicines Agency). Saxenda: EPAR—Product Information. 2022; Available online: https://www.ema.europa.eu/documents/product-information/saxenda-epar-product-information_en.pdf (accessed on 15 June 2023).

37. EMA (European Medicines Agency). Wegovy: EPAR—Product Information. 2023; Available online: https://www.ema.europa.eu/documents/overview/wegovy-epar-medicine-overview_en.pdf (accessed on 15 June 2023).

38. Gallwitz B. Sitagliptin: profile of a novel DPP-4 inhibitor for the treatment of type 2 diabetes (update). Drugs Today (Barc). 2007 Nov;43 (11):801-14. doi: 10.1358/dot.2007.43.11.1157620. PMID: 18174966. https://pubmed.ncbi.nlm.nih.gov/18174966.