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Glucagon-Like Peptide-1 Receptor Agonists for Adult Obesity: Where Next?

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Background

- Obesity prevalence continues to rise globally, significantly contributing to chronic diseases, such as type 2 diabetes mellitus (T2DM) and cardiovascular disorders[1]
- Lifestyle-based interventions have shown limited long-term success in managing obesity,[2] necessitating more effective treatment options
- Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) were initially developed to manage T2DM[3] but have demonstrated additional benefits in promoting weight loss and improving cardiovascular health
- As research into anti-obesity medications (AOMs) continues to evolve, systematic literature reviews (SLRs) provide valuable insights into the efficacy and safety of these treatments in the management of obesity
- Understanding the current trends in the usage of GLP-1 RA–containing agents for weight management is essential to guide future research and therapeutic strategies

Objectives

To identify key trends in SLRs of GLP-1 RA–containing agents in adults who are obese or overweight and to explore potential future directions for these agents for obesity treatment

Methods

- A systematic literature search was conducted using National Institute for Health and Care Excellence (NICE)–published search terms for obesity, GLP-1 RAs, and SLRs across Embase, Medline, and Cochrane databases
- SLRs of investigational and approved GLP-1 RA–containing agents published between 1 January 2019 and 19 April 2024 were included; an updated search was also run 14 October 2024
- SLRs focusing solely on GLP-1 RAs for diabetes management or on nonpharmacological interventions (surgical, herbal/supplement-based, or lifestyle interventions) were excluded
- Titles and abstracts were screened by a single reviewer, with a 20% check by a second reviewer for accuracy
- Full-text SLRs that met predefined eligibility criteria were included in the final analysis

Results

- A total of 390 records were identified, with 277 records screened and 162 full-text reports assessed for eligibility
- After exclusions, **76 SLR publications** were included in the final analysis: original search, n=58; updated search, n=18
- Of the 86 excluded full-text reports, the main reasons for exclusion were no GLP-1 RA (n=2), diabetes focus (n=22), economic evaluations (n=1), unavailable publication (n=1), and nonsystematic reviews (n=2) (**Figure 1**)
- The number of SLRs published during the past 5 years increased by 480%, with 5 (7%) published in 2019 and 29 (38%) published in 2024 (**Figure 2**)

SLR characteristics

- The number of included publications in the SLRs ranged from 2 studies (Yokote 2024 and Dutta 2024) to 424 studies (Tsapas 2021)
- Five SLRs (Abdel-Maboud 2021, Tsapas 2021, Shi 2022, Iannone 2023, Shi 2024) included over 100 studies
- The majority of SLRs included meta-analyses (63/76, 84.2%)
- Of the 76 included SLRs, 69 focused solely on randomised controlled trials (RCTs), 1 included only observational studies, and 6 incorporated both RCTs and observational studies

Subgroups

- The most common subpopulations assessed were individuals who were overweight or obese and without diabetes (37%), individuals with type 1 or 2 diabetes (32%), and individuals with metabolic dysfunction-associated fatty liver disease or with postbariatric surgery (both 8%), polycystic ovary syndrome (7%), schizophrenia (4%), and sleep apnoea (2%)
- Subgroups, such as those with Prader-Willi syndrome, chronic kidney disease, and cardiovascular disease, were studied in 1 SLR each (1%) (**Figure 3**)

Interventions assessed

- Semaglutide and liraglutide were the most frequently studied interventions in 51% and 49% of the SLRs, respectively (**Figure 4**)
- Other GLP-1 RAs examined were exenatide (20%) and dulaglutide (17%)
- Less commonly studied agents were orforglipron (7%); mazdutide, efpeglenatide, and albiglutide (4% each); cotadutide (3%); and taspoglutide, danuglipron, and ecnoglutide (1% each)
- Three SLRs (4%) included albiglutide, which was discontinued in 2018 for commercial reasons
- Eight SLRs (11%) included tirzepatide, which targets both glucose-dependent insulinotropic peptide (GIP) and GLP-1 receptors
- Retatrutide, a triple-hormone (GIP, GLP-1, and glucagon) receptor agonist, was assessed in 2 SLRs (3%)

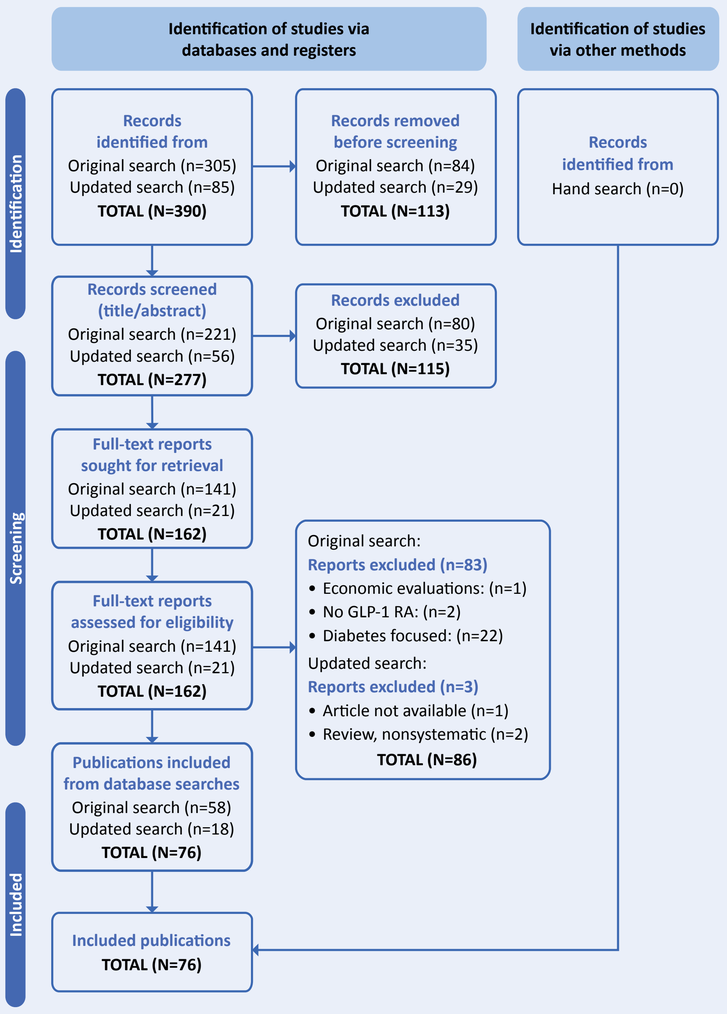
Outcomes

- Weight loss was the most commonly reported outcome in 75/76 SLRs (99%) (**Figure 5**). One SLR reported only cardiovascular outcomes in adults who were overweight or obese, without diabetes
- Waist circumference was evaluated less frequently in 20 SLRs (26%)
- Approximately 40% of included SLRs (30 SLRs) reported adverse events (AEs), noting that GLP-1 RA–containing agents were generally well tolerated, with gastrointestinal-related events being the most commonly reported AEs
- Blood pressure, haemoglobin A1c (HbA1c)/glucose or insulin resistance outcomes, and lipid parameters were similarly reported in 23 SLRs (30%), 22 SLRs (29%), and 18 SLRs (24%), respectively
- Patient-reported outcomes (PROs) and hypoglycaemia were reported in relatively few studies, with only 2 SLRs (3%) focusing on PROs and 12 SLRs (16%) that included hypoglycaemia, reflecting a more limited focus on patient experience and glycaemic events

Drugs in development

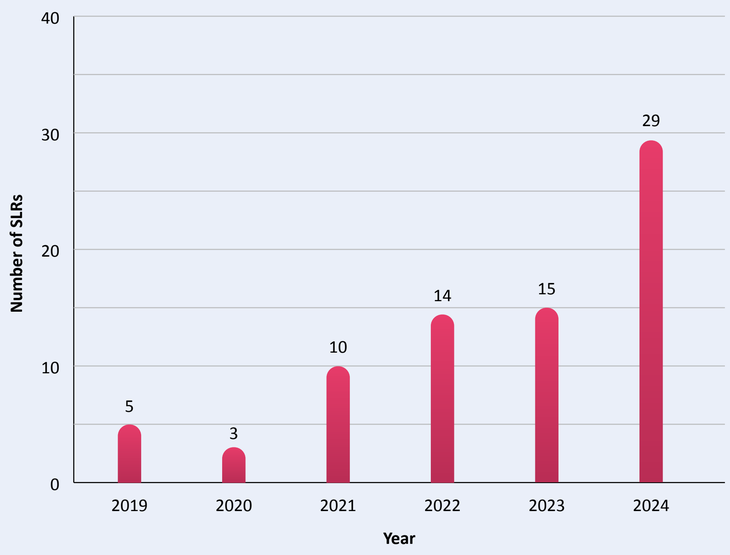
- A targeted search conducted 14 October 2024 for phase 3 trials in adults with obesity or overweight of GLP-1 RA–containing agent that were recruiting, active, or complete as of 2022 or later identified 1 additional agent, survodutide, a dual glucagon/GLP-1 RA, which was not reported in any of the included SLRs

Figure 1. PRISMA diagram



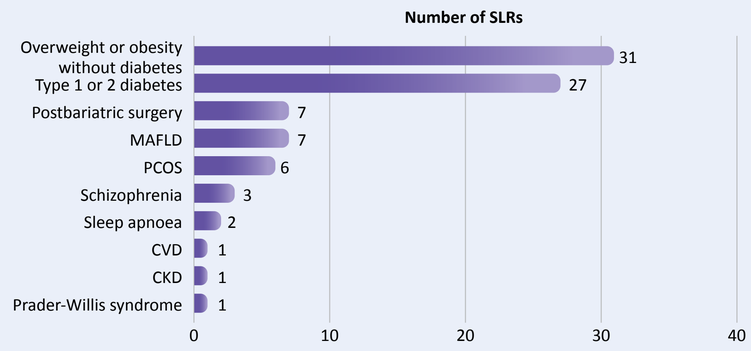
Abbreviation: GLP-1 RA, glucagon-like peptide-1 receptor agonist

Figure 2. Number of SLRs published between 1 January 2019 and 14 October 2024



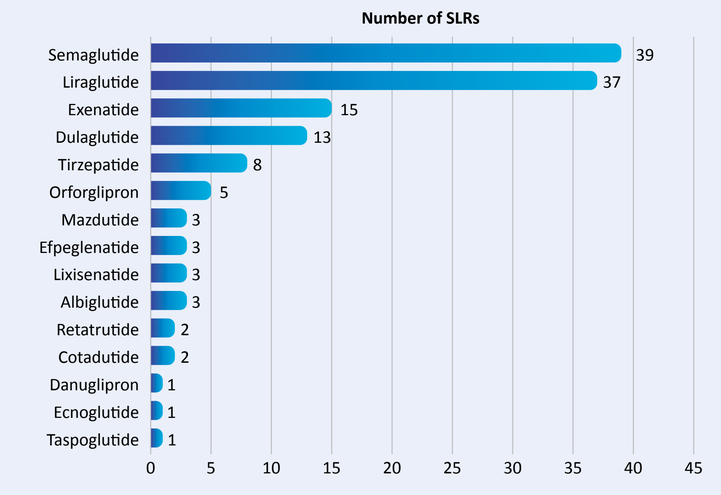
Abbreviation: SLR, systematic literature review

Figure 3. Subgroups assessed in included SLRs (n=76)



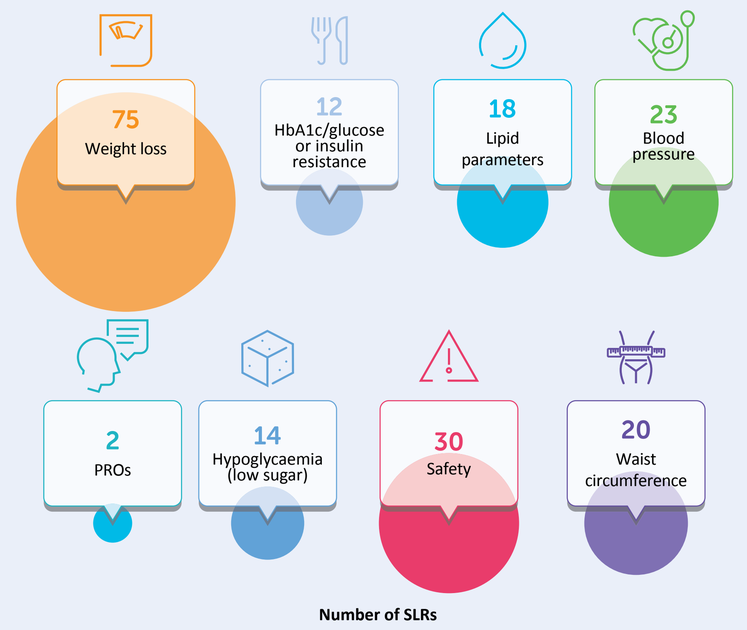
Abbreviations: CKD, chronic kidney disease; CVD, cardiovascular disease; MAFLD, metabolic dysfunction–associated fatty liver disease; PCOS, polycystic ovary syndrome; SLRs, systematic literature reviews

Figure 4. GLP-1 RAs assessed in included SLRs (n=76)



Abbreviations: GLP-1 RAs, glucagon-like peptide-1 receptor agonists; SLRs, systematic literature reviews

Figure 5. Outcomes reported in included SLRs (n=76)



Abbreviations: HbA1c, haemoglobin A1c; PROs, patient-reported outcomes; SLRs, systematic literature reviews

Conclusions

- GLP-1 RA–containing agents are highly effective treatments for weight loss and for improving metabolic outcomes in adults who are obese or overweight, with nearly all included SLRs reporting significant weight loss effects
- Semaglutide and liraglutide were the most frequently studied interventions
- Newer agents like tirzepatide (a dual GIP/GLP-1 RA) and retatrutide (a triple-hormone [GIP, GLP-1, and glucagon] receptor agonist) are gaining attention, highlighting ongoing innovation in AOMs
- Although weight loss was the primary outcome in most reviews, cardiometabolic outcomes such as blood pressure and lipid profiles were also commonly assessed, while PROs and AEs were evaluated less frequently, highlighting potential areas for further research
- Access to GLP-1 RA–containing agents for weight management has been hindered by drug shortages and payer coverage restrictions; these hurdles will need to be addressed for patients who are overweight or obese to benefit from these innovative medicines

List of included SLRs

Ali MM et al. *BMC Endocr Disord.* 2022;22(1):113. **Ding C** et al. *Acta Diabetol.* 2022;59(4):519-533. **Blazina I** et al. *Syst Rev.* 2019;8(1):295. **Dutta D** et al. *Obes Surg.* 2024;34(5):1653-1664. **Ferdinand KC** et al. *Cardiovasc Diabetol.* 2023;22(1):49. **Ghosal S** et al. *Sci Rep.* 2021;11(1):22063. **Gomes DA** et al. *Cardiovasc Drugs Ther.* 2024;Jan 12. **Guo M** et al. *Endocrine.* 2020;67(2):294-304. **Farrash S** et al. *Int J Pharm Res Allied Sci.* 2023;12(4):95-103. **He L** et al. *JAMA Intern Med.* 2022;182(5):513-519. **Ida S** et al. *Curr Diabetes Rev.* 2021;17(3):293-303. **Kramer CK** et al. *J Clin Endocrinol Metab.* 2024;109(8):e1634-e1641. **Abdel-Maboud M** et al. *PLoS One.* 2021;16(7):e0254412. **Lingvay I** et al. *J Clin Endocrinol Metab.* 2022;107(5):1461-1469. **Long Y** et al. *Ir J Med Sci.* 2023;192(6):2809-2814. **Cai W** et al. *Front Public Health.* 2024;12:1277113. **Dai D** et al. *Medicine (Baltimore).* 2019;98(36): e17081. **Li H** et al. *Biomed Pharmacother.* 2024;171:116150. **Nalisa DL** et al. *Front Endocrinol (Lausanne).* 2024;15:1309118. **Panunzi S** et al. *Diabetes Obes Metab.* 2021;23(4):980-990. Karakasis P et al. *Metabolism.* 2023;149:155710. **Lin Q** et al. *Expert Rev Clin Pharmacol.* 2022;15(12):1461-1469. **Ma H** et al. *BMJ Open.* 2023;13(3):e061807. **Ma R** et al. *Medicine (Baltimore).* 2021;100(23):e26295. **Moon S** et al. *Endocrinol Metab (Seoul).* 2021;36(3):647-660. **Rohani P** et al. *Front Endocrinol (Lausanne).* 2023;14:1230206. **Sarma S** et al. *Obesity (Silver Spring).* 2022;30(11):2111-2121. **Siskind D** et al. *Diabetes Obes Metab.* 2019;21(2):293-302. **Tandon S** et al. *Diabetes Obes Metab.* 2021;23(2):350-362. **Tian D** et al. *Minerva Med.* 2022;113(3):542-550. **Imam A** et al. *J Endocr Soc.* 2023;7(12):bvad129. **Tsapas A** et al. *Diabetes Obes Metab.* 2021;23(9):2116-2124. **Uneda K** et al. *Sci Rep.* 2021;11(1):10166. **Ng NBH** et al. *Clin Endocrinol (Oxf).* 2022;96(2):144-154. **Pan CS** et al. *Front Endocrinol (Lausanne).* 2020;11:70. **Shi Q** et al. *Lancet.* 2022;399(10321):259-269. **Pratama KG** et al. *Obes Surg.* 2024;34(5):1653-1664. **Singh AK** et al. *Expert Rev Clin Pharmacol.* 2020;13(1):53-64. **Zeng Q** et al. *Front Endocrinol (Lausanne).* 2023; 14:1214334. **Vosoughi K** et al. *EClinicalMedicine.* 2021;42:101213. **Macfarlane M** et al. *medRxiv* 2024;01.12.24301166. **Zhang R** et al. *Front Endocrinol (Lausanne).* 2023;14:1132004. **Zhong P** et al. *Endocrine.* 2022;75(3):718-724. **Zhu K** et al. *World J Gastroenterol.* 2023;29(37):5327-5338. **Dorneles G** et al. *Exp Clin Endocrinol Diabetes.* 2024;132(6):316-327. **Gao X** et al. *Front Pharmacol.* 2022; 13:935823. **Guo X** et al. *Horm Metab Res.* 2022;54(7):458-471. **Iannone A** et al. *Diabetes Obes Metab.* 2023;25(9):2535-2544. **Iqbal J** et al. *Obes Rev.* 2022;23(6):e13435. **Leite AR** et al. *Diabetes Obes Metab.* 2022;24(8):1676-1680. **Shridharani SM** et al. *Aesthet Surg J.* 2023;44(1):68-79. **Wharton S** et al. *J Drug Assess.* 2019;8(1):184-191. **Qin W** et al. *Diabetes Obes Metab.* 2024;26(3):911-923. **Ruan B** et al. *Am J Clin Nutr.* 2023;118(3):614-626. **Wang W** et al. *Diabetes Metab Res Rev.* 2023;39(7):e3680. **Yeh TL** et al. *PLoS One.* 2023;18(1):e0278685. **Zhang P** et al. *Afr Health Sci.* 2019;19(3):2591-2599. **Li Y** et al. *Eur J Clin Invest.* 2024;54(4):e14125. **Kramer CK** et al. *J Clin Endocrinol Metab.* 2024;109(8):e1634-e1641. **Dutta D** et al. *Obes Surg.* 2024;34(5):1653-1664. **Xie W** et al. *J Diabetes Complications.* 2024;38(1):107124. **de Moraes FCA** et al. *Obes Surg.* 2024;34(8):2844-2853. **Alsanea S** et al. *Endocr Pract.* 2024;30(8):737-745. **Hegde NC** et al. *Gen Hosp Psychiatry.* 2024;90:12-21. **Shi Q** et al. *Lancet.* 2024;403(10434):e21-e31. **Xie Z** et al. *Metabolism.* 2024;Sep 19:161:156038. **de Athayde de Hollanda Morais BA** et al. *J Diabetes Complications.* 2024;38(10):108834. **de Oliveira Almeida G** et al. *Am J Cardiovasc Drugs.* 2024;24(4):509-521. **Yokote K** et al *Adv Ther.* 2024;41(9):3452-3470. **Kelkar R** et al. *Front Cardiovasc Med.* 2024;11:1453297. **Dutta D** et al. *touchREV Endocrinol.* 2024;20(2). **Qin W** et al. *Endocrine.* 2024;86(1):70-84. **Li J** et al. *Am J Transl Res.* 2024;16(8):3545-3556. **Kokkorakis M** et al. *Pharmacol Rev.* 2024;Sep 20:PHARMREV-AR-2023-001045. **Moiz A** et al. *Am J Cardiol.* 2024;222:121-130. **Zhang MQ** et al. *Biomed Environ Sci.* 2024;37(6):607-616.

References

1. World Obesity Federation. World Obesity Atlas 2024. Accessed 14 October 2024. https://www.worldobesity.org/news/world-obesity-atlas-2024
2. Wilding JPH, et al. *N Engl J Med*. 2021;384(11):989-1002. doi: 10.1056/NEJMoa203218
3. NICE Clinical Knowledge Summaries. Diabetes type 2: GLP-1 receptor agonists. Accessed 14 October 2024. https://cks.nice.org.uk/topics/diabetes-type-2/prescribing-information/glp-1-receptor-agonists/
4. Eperzan: Withdrawal of the marketing authorisation in the European Union. News release. European Medicines Agency; 29 October 2018. https://shorturl.at/FZOKl

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