RJNMSR
Review Journal of Neurological & Medical Sciences Review

Volume 3, Issue 2, 2025

Comparison of the GLP-1 Receptor Agonists with other anti-obesity/anti-diabetic medicines: a systematic review

Beenish Khurshid[1*], Sobia Khurshid[2]

[1]*Department of Biochemistry, Faculty of Chemical and Life Sciences, Abdul Wali Khan University, Mardan, Pakistan*
[2]*Senior advanced practitioner, non obstetric ultrasound department, Physiological measurements limited, United Kingdom*
Email: Beenish_khurshid@awkum.edu.pk

Corresponding Author: *Dr. Beenish Khurshid

DOI: https:/doi.org/

Received	Accepted	Published
25 May , 2025	11 June, 2025	25 June, 2025

ABSTRACT

Obesity and type 2 diabetes are increasing and place demands on health systems. Comparative evidence across medicines that influence body weight and glycaemic control is needed. This systematic review compared GLP-1 receptor agonists (GLP-1 RA) with SGLT2 inhibitors, DPP-4 inhibitors, and orlistat in adults with type 2 diabetes or obesity without diabetes. Primary variables were body weight and HbA1c, and safety outcomes were recorded. PRISMA 2020 methods were applied. MEDLINE, Embase, CENTRAL, ClinicalTrials.gov, and WHO ICTRP were searched (2016–2025, English). One reviewer screened, selected, and extracted data. Twenty studies were included. Evidence was synthesised narratively using thematic analysis; no meta-analysis was conducted. GLP-1 RA (semaglutide and liraglutide) and the dual incretin tirzepatide produced the largest reductions in weight and HbA1c. SGLT2 inhibitors produced modest improvements in outcomes. DPP-4 inhibitors were weight-neutral with smaller HbA1c reductions. Orlistat produced small to moderate weight loss with limited glycaemic benefit. Safety signals were observed: gastrointestinal symptoms were frequent with GLP-1 agents and tirzepatide; genitourinary infections were common with SGLT2 inhibitors; orlistat was limited by gastrointestinal intolerance; DPP-4 inhibitors showed a benign profile. Findings support prioritising GLP-1 RA or tirzepatide when substantial weight loss and HbA1c reduction are required, with individualisation by comorbidity and tolerance. Limitations include single-reviewer methods, heterogeneity, English-only searches, and absence of meta-analysis. Future work should test head-to-head trials and assess durability beyond 72 weeks.

Keywords: GLP-1 receptor agonists; tirzepatide; SGLT2 inhibitors; DPP-4 inhibitors; obesity; type 2 diabetes; systematic review.

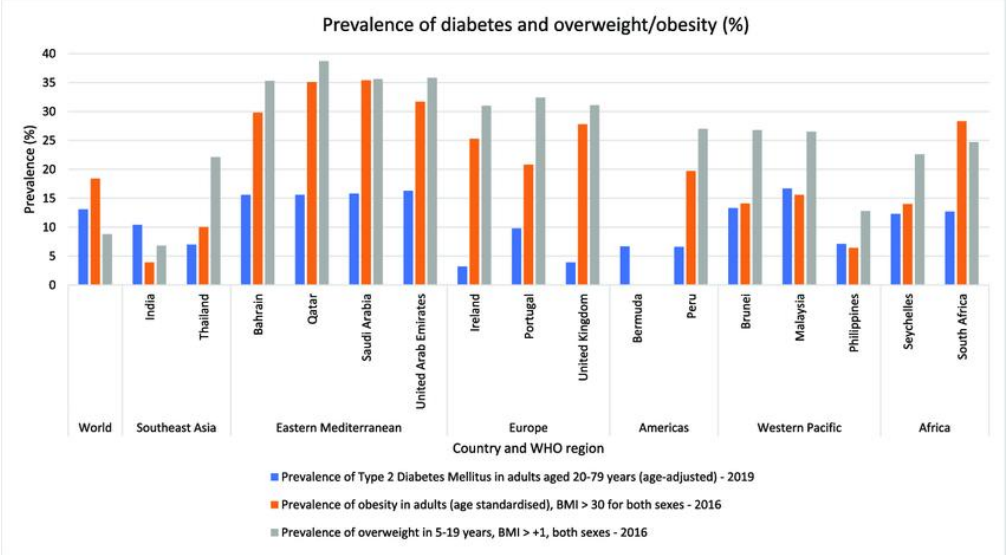
INTRODUCTION

"Type 2 diabetes mellitus" is a chronic metabolic disorder that contributes to substantial illness and premature death worldwide (Dhondge et al., 2024; WHO, 2024a). Globally, more than one billion people are affected by obesity now; over recent decades, its prevalence has more than doubled in adults and increased about fourfold in children (WHO, 2024b). Together, diabetes and obesity raise cardiometabolic risk and place heavy pressure on health systems (Chakraborty et al., 2023; Drozdz et al., 2021; Rao, 2025). Lifestyle modification is essential, but maintaining weight loss is difficult, and weight regain commonly occurs after programs end

(Machado et al., 2022). Therefore, clinical guidelines advise initiating pharmacotherapy and, for selected patients, considering metabolic or bariatric surgery when lifestyle changes alone are not able to achieve clinically meaningful weight loss and sustained glycemic control (American Diabetes Association Professional Practice Committee, 2025).

Figure 1

Prevalence of diabetes and obesity (2016-2019) in 16 Countries (Mulcahy et al., 2022)



The rising prevalence of metabolic syndrome, obesity, and type 2 diabetes has become a major public health challenge worldwide and places a heavy and growing burden on health systems (WHO, 2025). Effective strategies that combine weight reduction, glycaemic control, and structured lifestyle modification improve metabolic risk factors and are core elements of current diabetes care standards (Committee, 2025). Complementary approaches are commonly used, but the quality of evidence for many herbal regimens is variable and often limited by small trials and heterogeneous methods (McBenedict et al., 2024). Recent syntheses suggest that okra (Abelmoschus esculentus) may help improve glycaemic measures in adults with prediabetes or "type 2 diabetes", while more rigorous randomized trials are needed to confirm the size and durability of effect (Bahari et al., 2024). In parallel, modern pharmacotherapy has advanced substantially, with GLP-1 RA demonstrating medically meaningful reductions in weight of body and HbA1c in randomized trials and comparative reviews (Shi et al., 2022; Wilding et al., 2021). These agents have a low intrinsic risk of hypoglycaemia because their glucose-lowering action is glucose-dependent, mainly when not combined with sulfonylureas or insulin (King & Miller, 2023). This review examines pharmacological options for managing body weight and glycaemic control, including "glucagon-like peptide-1 (GLP-1) receptor agonists (such as liraglutide and semaglutide)", "the dual incretin agent tirzepatide", "sodium-glucose cotransporter-2 (SGLT2) inhibitors", "dipeptidyl peptidase-4 (DPP-4) inhibitors", and "orlistat" (Collins & Costello, 2024; Karimi et al., 2025). Among GLP-1 RA,"exenatide", "lixisenatide", "liraglutide", "dulaglutide", and "semaglutide" are widely used and are established treatments for type 2 diabetes, with several also approved or employed for obesity management (Collins & Costello, 2024).

GLP-1 RA is glucose-dependent stimulation of insulin release, slowing of gastric emptying, and appetite inhibition. Evidence from randomized trials shows that they reduce HbA1c and lead to clinically meaningful weight loss (Aldawsari et al., 2023; Popoviciu et al., 2023). Tirzepatide is a co-agonist of

GIP and GLP-1 receptors and produces significant weight loss in obese adults (Jastreboff et al., 2022). SGLT2 inhibitors are oral drugs that lower blood glucose by inhibiting its reabsorption in the kidneys, as well as associated with slight decreases in body weight and blood pressure (Padda et al., 2022; Thomas & Cherney, 2018). DPP-4 inhibitors prolong endogenous incretin action, typically achieve modest HbA1c reductions, and are generally weight-neutral (Saini et al., 2023). Orlistat reduces intestinal fat absorption through gastrointestinal lipase inhibition and commonly causes gastrointestinal adverse effects (Bansal et al., 2024; Katimbwa et al., 2022).

A large body of randomized trials now evaluates anti-obesity and glucose-lowering medicines (Shi et al., 2022), but most compare one active drug with a placebo or a single comparator rather than multiple active agents in the same study, which limits direct comparisons across classes. (Follow-up and dosing also differ across studies: for example, tirzepatide trials often run 72 weeks, whereas semaglutide STEP trials run 68 weeks, and dose-response effects are reported for incretin therapies (Jastreboff et al., 2022; Moiz et al., 2024). Routes of administration vary as well, with once-weekly injectables and newer daily oral regimens, which further complicates interpretation across programs (Knop et al., 2023). Given these variations, clinicians and policymakers benefit from syntheses that compare agents, doses, and routes while weighing durability and tolerability to inform real-world choices and guidelines.

Existing evidence syntheses leave several unresolved issues. Some reviews and trials analyse adults with obesity regardless of diabetes status, while others focus on type 2 diabetes; results are seldom presented in a way that cleanly stratifies both populations for side-by-side judgment. Many trials have limited durations for rare harms, so safety profiles for events such as gallbladder disease, pancreatitis, and retinopathy remain uncertain and require longer observation. Outcome reporting is inconsistent: some trials emphasize mean weight change, whereas others use responder thresholds, which makes cross-study comparison difficult. Moreover, recent regimens like high-dose oral semaglutide and oral small-molecule GLP-1 agonists are post the search window of some of the earlier reviews, and thus previous syntheses may not exhaust them

This systematic review assesses, in adults, the comparative efficacy (changes in body weight and HbA1c) and safety/tolerability of GLP-1 RA versus "SGLT2 inhibitors", "DPP-4 inhibitors", "orlistat", and placebo/usual care, to inform clinical decision-making. The review follows PRISMA 2020 and uses a prospectively registered protocol to ensure transparent, reproducible methods (Page et al., 2021). To meet this aim, the study seeks to answer the following research questions:

. What is the comparative efficacy of GLP-1 RA in relation to other "anti-obesity" and "anti-diabetic drugs" in glycemic control and weight loss results?
. What are the tolerability and safety of GLP-1 RA compared with other therapy forms?
. What is the effect of the patient characteristics (e.g., age, BMI, comorbidities) on the comparative effectiveness and risk profile (GLP-1 RA compared with other therapy forms)?
. Is there any evidence concerning the long-term effects of GLP-1 RA versus the other treatments?

To address these questions, a systematic literature review was the appropriate approach, as it applies transparent and repeatable methods to locate, evaluate, and synthesise evidence on health interventions. This design supports rigorous appraisal and integrates findings across studies to answer the review questions clearly (Yusif & Hafeez-Baig, 2024). A carefully conducted SLR will provide an evidence-based account of comparative efficacy (obesity and diabetes) and safety/tolerability, including longer-term outcomes where available, aligned with contemporary care standards (Committee,

2025). It will also link mechanisms and regimens (e.g., incretin-based therapies, oral vs injectable dosing) to clinical endpoints and harms to inform practice and policy (Moiz et al., 2025). By applying established guidance for study selection, bias assessment, and synthesis, the review will integrate trial and registry evidence as appropriate and deliver decision-ready findings for clinicians and guideline groups.

METHODS

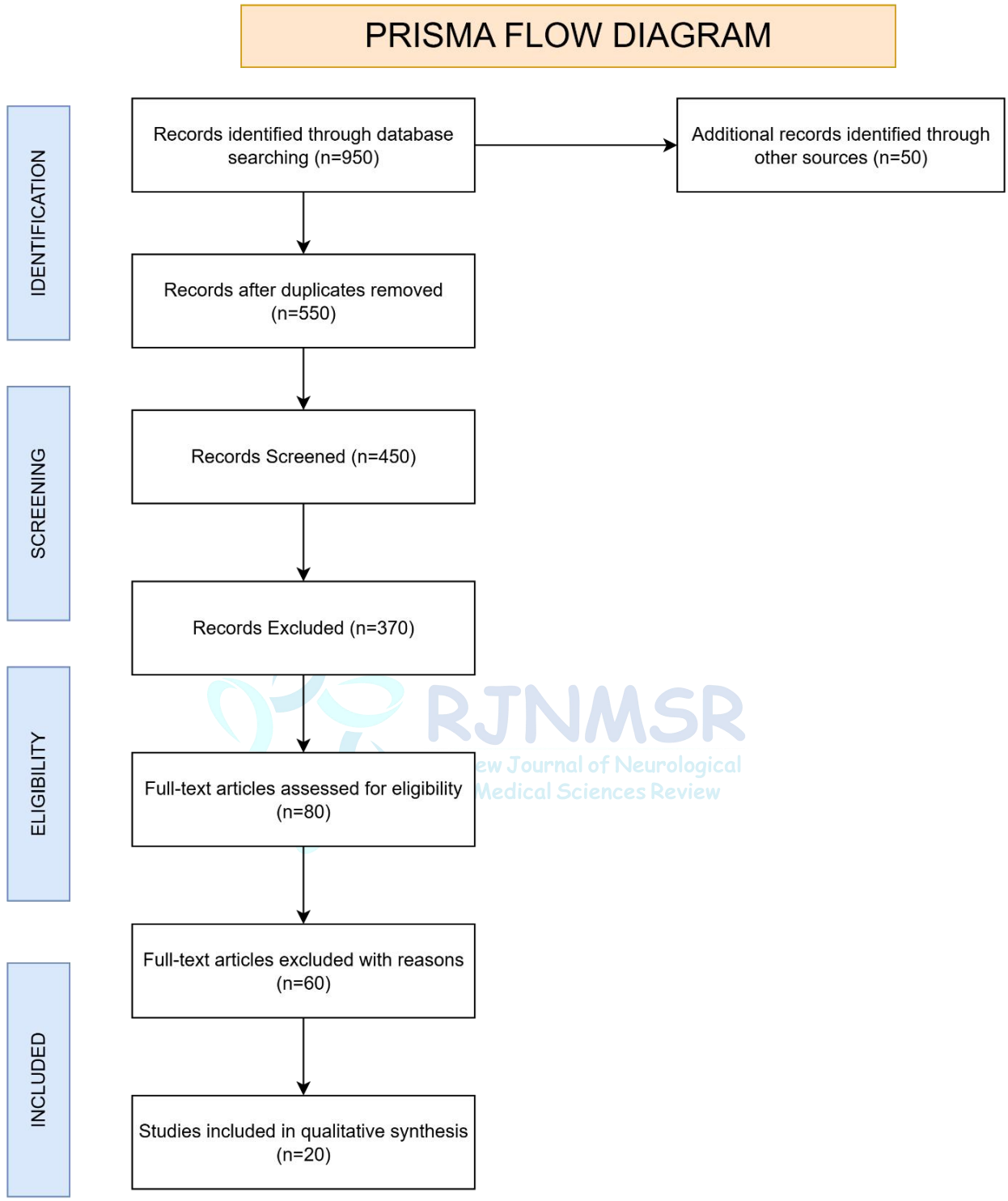
Protocol & Reporting

This review was done and reported as per "PRISMA 2020" to ensure a clear, complete, and transparent presentation of the methods and findings (Page et al., 2021; Sohrabi et al., 2021). The PRISMA checklist is applied in full, and a PRISMA 2020 flow diagram documents records identified, screened, excluded with reasons, and included as an auditable record of study selection (Page et al., 2021). Using "PRISMA 2020" improves the clarity of methods and enables independent appraisal and replication of the review's processes and findings.

Title and abstracts were screened by a single reviewer against predefined PICOS criteria, after which the same reviewer assessed full texts for eligibility for selecting and documenting studies in a systematic review. During full-text assessment, each exclusion was documented in a study-selection log to maintain an auditable record and align with PRISMA 2020 guidance on reporting excluded reports. The overall study flow, including numbers identified, screened, excluded with reasons, and included, was summarised in a PRISMA 2020 flow diagram presented in Figure 2 below:

Figure 2

PRISMA Flow Diagram (self-generated)



Selection Criteria

A priori, definite inclusion and exclusion criteria were created and used uniformly during the screening and full-text evaluation.

Table 1
Inclusion & Exclusion Criteria

Inclusion	Exclusion
Articles published in 2016 or later	Articles published before 2016
Articles in English	Articles in a non-English language.
Articles that discuss the efficacy of "SGLT2 inhibitors/GLP-1 RA *(Liraglutide, Semaglutide, Tirzepatide)* / DPP-4 inhibitors/lipase inhibitor therapies in obesity or type 2 diabetes".	Articles that do not discuss the efficacy of "SGLT2 inhibitors/GLP-1 RA *(Liraglutide, Semaglutide, Tirzepatide)* / DPP-4 inhibitors/lipase inhibitor therapies in obesity or type 2 diabetes".

Based on these inclusion and exclusion criteria, studies were selected and documented in the PRISMA flow diagram, which records numbers identified, screened, excluded with reasons, and included in the review.

Search Strategy

Searches were conducted in MEDLINE (via PubMed), Embase (via Ovid), and the Cochrane Central Register of Controlled Trials (CENTRAL) to capture core biomedical literature and concentrated reports of randomized trials. Trial registries – ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform (ICTRP) – were searched to identify ongoing or unpublished studies and to enhance transparency of the evidence base. Reference lists of included studies and relevant reviews were hand-searched. To keep sources strictly medical, multidisciplinary citation indexes (e.g., Scopus, Web of Science) were not searched; instead, the strategy focused on MEDLINE, Embase, and CENTRAL as key biomedical databases for intervention trials.

A search strategy was done with controlled terms (MeSH in PubMed; Emtree in Embase) and a free-text query of the conditions (obesity, overweight, type 2 diabetes) and interventions (individual GLP-1 RA, liraglutide, semaglutide, dulaglutide; dual incretin tirzepatide; SGLT2 inhibitors empagliflozin, dapagliflozin, canagliflozin; DPP-4 inhibitors sitagliptin, linagli To facilitate reproducibility, Database restriction, Humans, Adults, English, and 2016-2025 publication years had been applied and documented. The search records were kept in a reference manager (EndNote software), and the deduplication and documentation of the entire search process were done as per the PRISMA 2020 guidelines.

Data Extraction

Data were extracted in two stages. Stage one captured bibliographic items (author, year, journal), study design (RCT/phase, blinding), setting/country, sample size, and eligibility. Stage two recorded intervention details (drug class/agent, dose, route, schedule, duration), comparators, and participant characteristics (age, baseline BMI, and HbA1c). Efficacy outcomes included absolute and percentage weight change, HbA1c, and responder thresholds. Units were harmonised where required, and summary tables of drugs, designs, and baseline/after-treatment measures were compiled from the extracted data.

Data Analysis

Data were analysed using manual thematic analysis. The reviewer first familiarised themselves with all included studies and extraction tables, then coded recurring patterns related to efficacy (weight change, HbA1c), safety/tolerability, population

groups (type 2 diabetes vs obesity without diabetes), dosing/route, and follow-up duration. Codes were grouped into potential themes that addressed the research questions. These themes were reviewed against the evidence, clearly named, and organised into a structured narrative. The final write-up presented findings theme-by-theme, with simple summary tables to support the text; no statistical meta-analysis was undertaken.

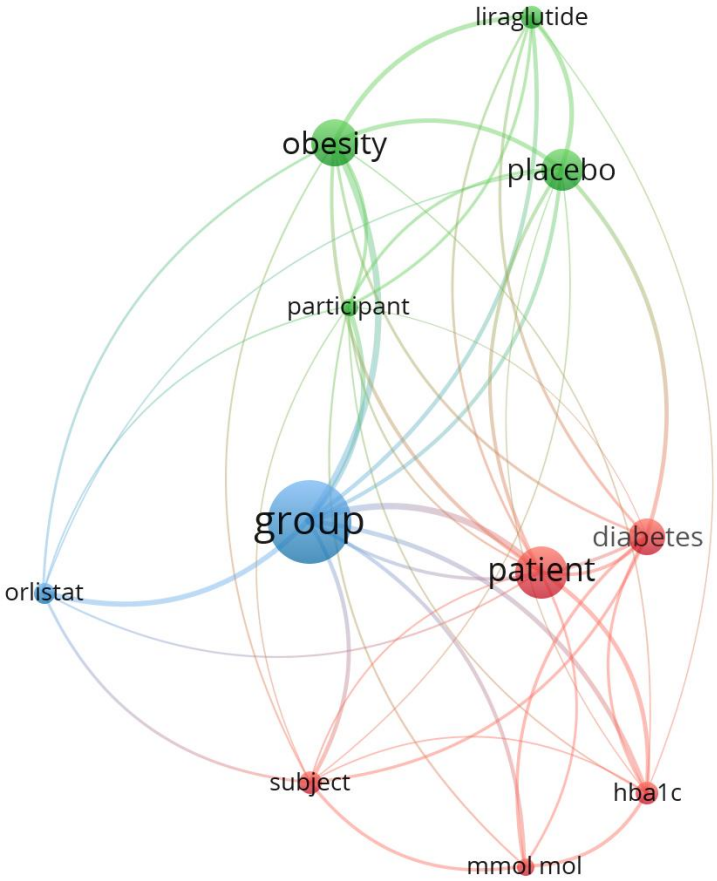
RESULTS

Keyword Co-Occurrence Analysis

The co-occurrence analysis revealed the key terms are group, patient, and obesity as the most associated terms, which illuminate the clinical trial where patient-centred outcomes display the research of obesity management. Close connections to placebo and subject underline the popularity of randomised controlled trials. Pharmacological drugs such as liraglutide and orlistat became dominant terms because they were at the centre of the comparative analysis. HbA1c and mmol/mol are additional clinical indicators that support the argument that glycaemic control is a central outcome in any diabetes-based obesity research. On the whole, the discussion shows that the key themes of the research include obesity, diabetes, and the efficacy of medication in groups of patients.

Figure 3

Title and abstract-based keyword co-occurrence



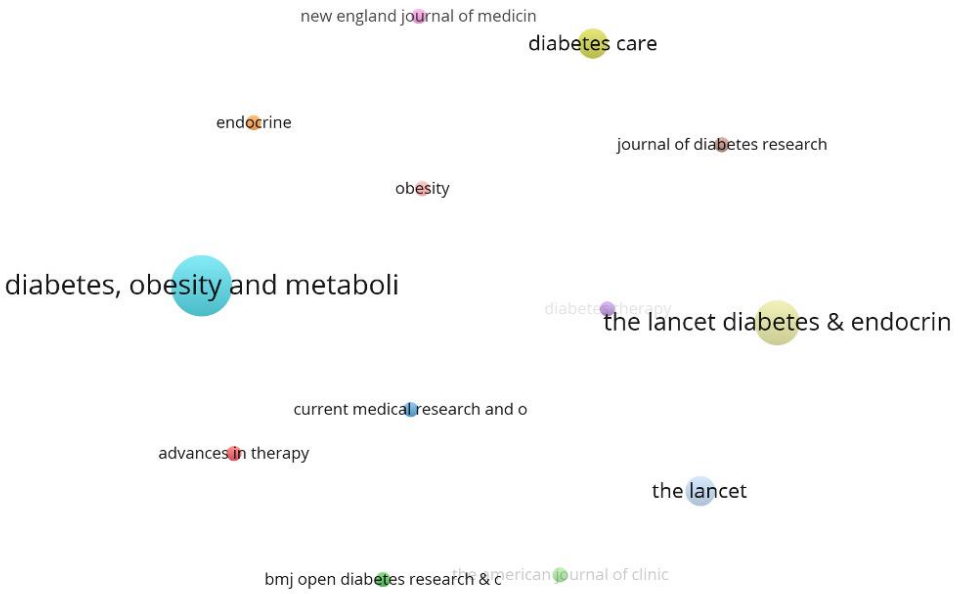
Journal-Wise Trend

The journal-wise tendency notices that most publications were clustered into Diabetes, Obesity and Metabolism (4 articles) and "The Lancet Diabetes and Endocrinology" (3 articles): this shows their role as leading research in the field of obesity and diabetes pharmacotherapy. "The Lancet" published two studies, indicating that diabetes care and "The Lancet" are involved in establishing high-quality clinical evidence. Single articles were in other journals, such as "Advances in Therapy", "BMJ Open Diabetes Research and Care", "Current Medical Research and

Opinion", "Diabetes Therapy", "Endocrine", "Journal of Diabetes Research", "The New England Journal of Medicine", "Obesity", and "The American Journal of Clinical Nutrition". This dissemination indicates that although some specific journals establish a world of discourse, the information is also spread in a variety of medical and nutrition sources, which have extensive clinical and academic coverage.

Figure 4

Journal-wise distribution of articles

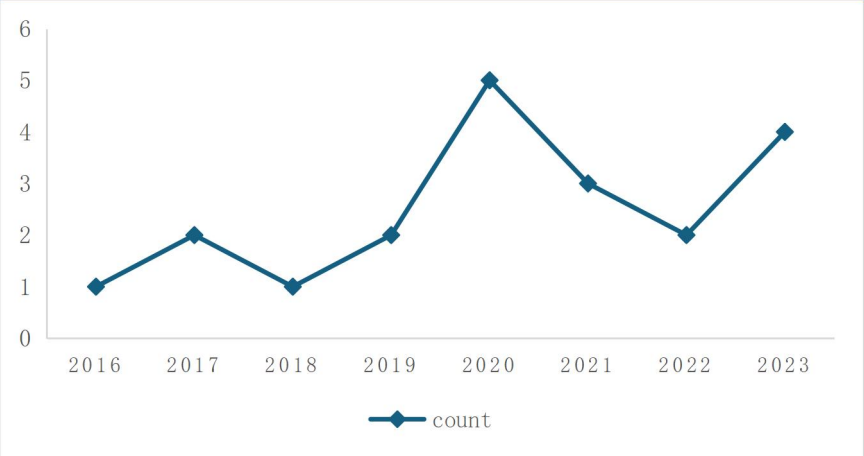


Temporal Trend

The trend of the publication indicates an upward trend in terms of research publications over time, with a sharp increase beginning in the year 2020. The previous contributions were occasional, with one study in 2016, two in 2017, one in 2018, and two in 2019. The highest number of publications happened in 2020, five. Productivity was also stable, with three studies conducted in 2021 and two in 2022 (though slightly lower), and four in 2023. The general picture of the trend supports the greater importance of the studied domain of research, especially over the past four years.

Figure 5

Temporal trends of articles

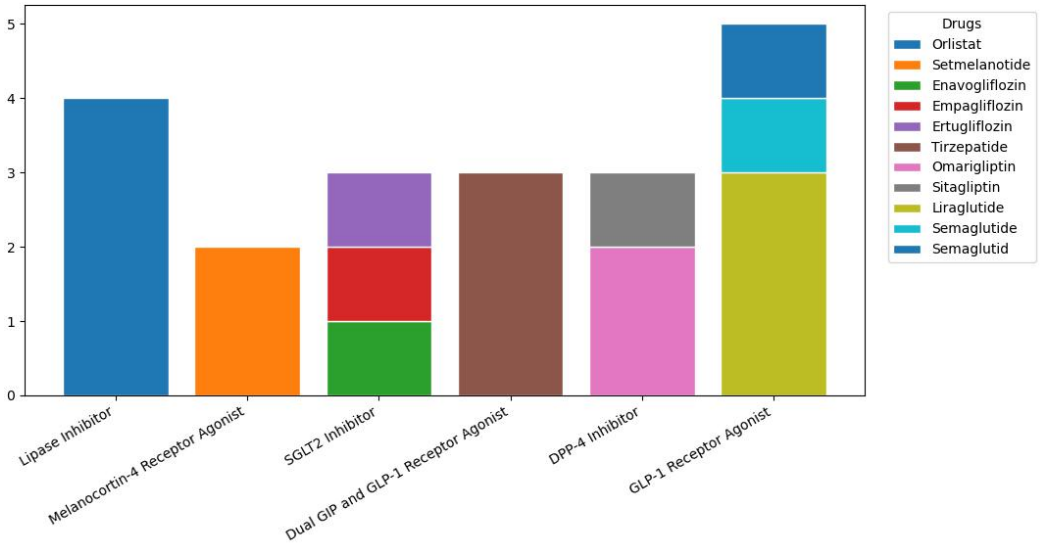


Drugs And Drug Classes

The presented studies reviewed different types of drug classes used to treat obesity and diabetes. Orlistat was regarded as a lipase inhibitor, and it presented itself in four studies, which show its long history in weight management. The two studies tested a melanocortin-4receptor agonist with setmelanotide, which is an obesity medication used infrequently in rare genetic disease obesity practices. SGLT2 inhibitors have been studied in three different agents, enavogliflozin, empagliflozin, and ertugliflozin, which suggests increased attention to this category. Tirzepatide, which is a "GIP" and "GLP-1 receptor agonist", featured in three studies reflecting its recent dominance. Omarigliptin (2) and sitagliptin (1) were examined as "DPP-4 inhibitors", and "GLP-1 receptor agonists", mostly led by liraglutide and semaglutide, appeared most, which indicates the extensive therapeutic significance of them.

Figure 6

Drugs and drug classes discussed in articles



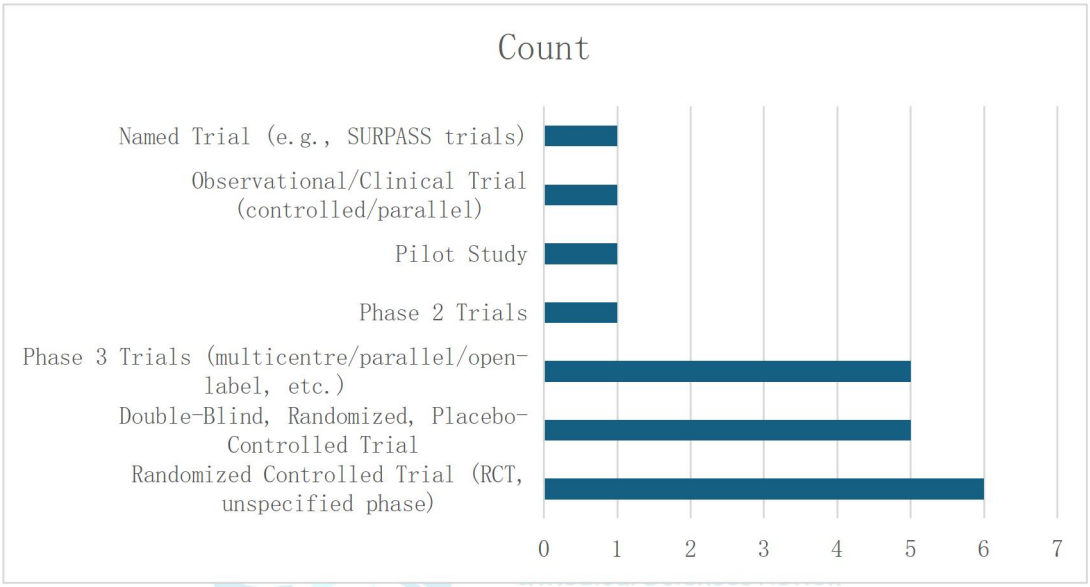
Study Design

The review included a wide spectrum of study design with most of them representative of "randomized controlled trials (RCTs)" which is the gold standard design in determining treatment efficacy and safety. Precisely, six studies were mentioned as RCTs, in which they were not specified by

any phase, and five were done in the form of a "double-blind, randomized", "placebo-controlled trial", which highlights the rigorous approach to methods. Phase 3 trials, which were multicentre, parallel, and open-label trials, in an effort to ensure efficacy and safety in large populations in a real-world setting, were another five. Further, a single Phase 2 trial, one pilot study, one observational clinical study, and one called the SURPASS trial provided distinctive knowledge indicating a discrepancy in evidence quality.

Figure 7

Research design distribution



Patient Characteristics from the Included studies

Tables 2a and 2b below show the characteristics of the patients during trials.

Table 2a

The table shows different characteristics of the patient.

Drug name	Drug class	Duration	Dose	Sample	Age in year/SD Mean
Orlistat	Lipase Inhibitor	24 weeks	60 mg, 3 time a day	100	20–29 years
Orlistat	Lipase Inhibitor	2 months	60 mg, once daily	80	43.6 years
Orlistat	Lipase Inhibitor	24 weeks	120 mg, 3 time a day	40	18- 60 year
Orlistat	Lipase Inhibitor	2 weeks	120 mg, 3 times a day	84	20-60 years
Setmelanotide	Melanocortin-4 Receptor Agonist	14 and 52 weeks	3·0 mg	38	6–15 years
Setmelanotide	Melanocortin-4 Receptor Agonist	12 weeks	3·0 mg, 2 weeks to 12 weeks	10	≥6 year
Enavogliflozin	SGLT2 Inhibitor	24 weeks	0.3 mg	83	59.9 ± 11.5 years

Empagliflozin	SGLT2 Inhibitor	week 12/week 14/week 26	10 mg/25 mg	52	10–17 years
Ertugliflozin	Sglt2 Inhibitor	18 weeks	5 and 15mg doses	618	≥40 years
TZP (Tirzepatide)	GIP, GLP-1 RA	72 weeks and 4-week safety follow-up	10 mg once a week, 15 mg once weekly	312 and 311	54.2 years
TZP (Tirzepatide)	GIP, GLP-1 RA	12 weeks	12 mg -> 4 weeks. 15 mg, -> 2–4 weeks	29	57.4 years
Tirzepatide	GIP, GLP-1 RA	8 weeks up to 72 weeks	weekly dose of 5 mg, 10 mg, and 15 mg	318 and 53	56–58 years
Omarigliptin	DPP-4 Inhibitor.	104 weeks	25 mg, once weekly	400	57.5 ± 8.1 years
Sitagliptin	DPP-4 Inhibitor.	30 weeks	n/a	743	58.3 ± 9.6 years
Omarigliptin	DPP-4 Inhibitor	24 weeks	25 mg, once weekly	642	57.3 years
Liraglutide	GLP-1 RA	56 weeks	3.0 mg	198	55.9 (11.3) years
Liraglutide	GLP-1 RA	24 weeks	0.6 mg per day	143	51:8 ± 11:2 years
Liraglutide	GLP-1 RA	82 weeks	daily dose of 0.6 mg -> 3.0 mg	228	Adolescents
Semaglutide	GLP-1 RA	68-75 week	2·4 mg	404	55 (11) years
Semaglutid	GLP-1 RA	56 weeks	Weekly dose of 1.0 mg	813	56 years (20–82 years)

Table 2b
Body weight and HbA1c at baseline and after being treated with different drugs.

Drug name	**Base line body weight kg or kg/m2**	**Weight reduces kg or kg/m2/ mean/ %**	**Hba1c at baseline mmol/mol or %**	**Hba1c after treated**
Orlistat	80.38	- 2.21 ± 0.23 kg		
Orlistat	35.25 ± 6.04 (29–43) kg/m2	31 ± 5.6* (24–39)		
Orlistat	79.2 ± 12.0 kg	81.2± 10.5		
Orlistat	≤ 39.9 kg/m2	34.8 ± 2.89		
Setmelanotide	≥30 kg/m	−2·4% (4·8%)		
Setmelanotide	30 kg/m²	21·4 + with POMC and 29·6 with LEPR		
Enavogliflozin	20 - 45 kg/m2	25.6 ± 3.1	7.0%-10.0%	7.7 ± 0.6
Empagliflozin	36.04 ± 8.33 kg/m²	35·54 ± 7·17	48–91 mmol/mol	−0·84%, −9·2 mmol/mol
Ertugliflozin	92.5 kg	91.6 kg	8.2%.	18 weeks −0.27% for the 5 mg dose and

				−0.28% for the 15 mg dose
Tirzepatide	36·0 ± 6·4 kg/m²	35·7 ± 6·1	7-10% (53-86 mmol/mol)	<5·7%
Tirzepatide	31.9 kg/m²	31.1 ± 4.21	8.4% (67.8 mmol/mol)	12 mg -> −1.7%, 0.19; 15 mg -> −2.0%, 0.20; 15 mg-> −1.8% , 0.19
Tirzepatide	32 kg/m2	25.4 ± 3.2	8.00%	1.62%, - 1.78%, - 2.05% in 5 mg, 10 mg, 15 mg
Omarigliptin	N/A	N/A	8.0-8.1%	-0.54% (-0.69%, -0.40%)
Sitagliptin	31.1 kg/m²	N/A	8.8 ±0.9%	51.4 mmol/mol (6.85%)
Omarigliptin	32 kg/m²	N/A	≥6.5% to ≤9.0%	−0.47%
Liraglutide	≥30 kg/m2	35.9 (6.5)	≥6.0 ≤10%	-1.10%
Liraglutide	85:5 kg	85:5 ± 14:5	8:85% ± 1:44%	6:78 ± 1:00
Liraglutide	35.3 kg/m2	± 5.1	N/A	N/A
Semaglutide	35·7 (6·3) kg/m2	−9·6%	7–10% (53–86 mmol/mol)	8·1% (0·8)
Semaglutid	95.8 kg	Mean (5.6 kg)	8.3% (67.7 mmol/mol)	6.8% (51.8 mmol/mol

What is the comparative efficacy of GLP-1 RA in relation to other anti-obesity/anti-diabetic drugs in glycaemic control and weight loss results?

Among the most efficacious in combination with glycaemic control versus weight loss in these 20 articles were GLP-1 RA (liraglutide, semaglutide), and the dual GIP and GLP-1 agonist tirzepatide versus new drug classes (SGLT2, DPP-4, lipase) evaluated. Weight loss: Tirzepatide also observed the biggest and most stable weight reduction proportions of ≥5% (79-83%) and even 31%, ≥ 20% reduction in weight (Frias et al., 2020; Garvey et al., 2023; Min & Bain, 2021). Semaglutide resulted in progressive weight reduction (-9.6 % and 5.6 kg) (Ahmann et al., 2018; Davies et al., 2021). Liraglutide demonstrated great decreases in BMI/weight during clinical trials (Garvey et al., 2020; Kelly et al., 2020; Zhaohu et al., 2022). In comparison, SGLT 2 inhibitors led to small mean weight loss (around 2.5 kg without enavogliflozin; less with empagliflozin/ertugliflozin), which suggested insignificant anti-obesity impacts (Dagogo-Jack et al., 2021; Kwak et al., 2023). Orlistat resulted in small-to-moderate losses in absolute weight (-2.2 kg after one trial) and fat /visceral fat resources (Arzola-Paniagua et al., 2016; Feng et al., 2023; Khedr et al., 2020; Shirai et al., 2019). Inhibitors of DPP4 (sitagliptin, omarigliptin) had insignificant weight effects (Goldenberg et al., 2017; Roussel et al., 2019; Shankar et al., 2017). Setmelanotide resulted in a robust percentage reduction, but solely in uncommon genetic obesity (POMC/ LEPR

deficiency), very high percentage results in those targeted population groups (Clement et al., 2020; Haqq et al., 2022). Glycaemic control: GLP-1 peptide therapies, tirzepatide (reduction -1.6 to -2.1, liraglutide -1.1%), and semaglutide (significant reductions) reduced HbA1c the most (Ahmann et al., 2018; Davies et al., 2021; Garvey et al., 2020; Garvey et al., 2023; Min & Bain, 2021). SGLT2 inhibitors decreased the level of HbA1c by a modest degree (-0.84 to minus 0.99% to empagliflozin, enavogliflozin); the combined DPP-4 ones showed smaller changes in HbA1c (around -0.47 to minus 0.54%). The reported benefit of orlistat was reduction of adiposity, and not direct glycaemic potency (Arzola-Paniagua et al., 2016; Feng et al., 2023; Khedr et al., 2020; Shirai et al., 2019).

Synthesis: GLP-1 RA (and tirzepatide) appear to be better combination agents for weight loss and glycaemic control than SGLT2s, DPP-4s, and orlistat across these 20 studies. Setmelanotide is very effective but restricted to certain types of obesity and an inborn genetic condition. The dose exists within the range of the common clinical regimens (e.g., semaglutide 1.0- 2.4 mg weekly; liraglutide up to 3.0 mg; tirzepatide 5-15 mg weekly).

What are the tolerability and safety of GLP-1 RA compared with other therapy forms?

There were differences in safety and tolerability within drug classes. A significant prevalence of gastrointestinal (GI) adverse effects was also linked to lipase inhibitors (orlistat) with the inevitable accolade of oily spotting, diarrheal, steatorrhea, abdominal discomfort, and constipation (Arzola-Paniagua et al., 2016; Feng et al., 2023; Khedr et al., 2020; Shirai et al., 2019). These side effects were lightly to moderately adverse, with discontinuations occurring frequently in rare instances. Setmelanotide (melanocortin-4 receptor agonist) showed unsatisfying results. Some patients had serious adverse reactions like nausea, changes in the skin, and headaches resulting in withdrawal (Haqq et al., 2022), whereas others had well-tolerated it with only complaints on the issues where the injections were given, along with slight skin disorders (Clement et al., 2020). Notably, there were no reported treatment-related deaths. The SGLT2 inhibitors (enavogliflozin, empagliflozin, ertugliflozin) had somewhat good tolerability. Adverse effects were reported (Kwak et al., 2023), including fractures and musculoskeletal events (modestly in the first case); slight increases were reported in socket infections of the urinary tract, mild hypoglycemia (Dagogo-Jack et al., 2021; Laffel et al., 2023). No reports of serious events like diabetic ketoacidosis or pancreatitis were reported, and this indicates a reasonably satisfactory safety profile, but care is advised on kidney-related AEs. Similar to GLP-1 RA, tirzepatide (dual GIP and GLP-1 agonist) was associated largely with GI have adverse effects, nausea, vomiting, and diarrhoea (Frias et al., 2020; Garvey et al., 2023; Min & Bain, 2021). These were usually dose-related, and slower titration enhanced tolerability. In some instances, discontinuation took place; however, the general safety was also well-favoured and comparable to GLP-1 monotherapy. The least benign safety profiles were found in DPP-4 inhibitors, with sitagliptin and omarigliptin showing no significant safety precautions (Goldenberg et al., 2017; Roussel et al., 2019; Shankar et al., 2017).

The profile of GI-related adverse events (nausea, vomiting, diarrhoea) of GLP-1 RA (liraglutide, semaglutide) was similar, but also involved nasopharyngitis, headache, and a handful of severe events (urinary tract disease, rare psychiatric events), among others (Ahmann et al., 2018; Davies et al., 2021; Garvey et al., 2020; Kelly et al., 2020; Zhaohu et al., 2022). GI events were the most common cause of dropout, whereas overall, it was well-tolerated. GLP-1 RAs and tirzepatide are also effective, but with troubling GI tolerability aspects; orlistat has its issues but is limited by annoying defecation effects; SGLT2 inhibitors show

manageable risks with some issues of infection; and DPP-4 inhibitors are the safest, but least effective.

What is the effect of the patient characteristics (e.g., age, BMI, comorbidities) on the comparative effectiveness and risk profile (GLP-1 RAs compared with other therapy forms)?

The ability of various classes of drugs to perform comparatively in relation to one another was influenced by characteristics among the participants. In the case of lipase inhibitors (orlistat), it was shown that it had greater benefit amongst Asian adults who were obese and who did not respond to lifestyle changes that produced fatty liver diseases, "metabolic-associated fatty liver disease" (MAFLD) (Feng et al., 2023). Orlistat was also mentioned as a crucial supplement to lifestyle changes in cases where diet and exercise had a restricted long-term course effect (Arzola-Paniagua et al., 2016). Setmelanotide (melanocortin-4 receptor agonist) was significantly effective in genetically driven obese cases. Weight and hunger decreases were significant in a patient with "Bardet-Biedl Syndrome" (BBS), "Alstrom Syndrome", and in patients under 18 (Haqq et al., 2022).

There were only slight, non-significant positive changes in cardiovascular parameters in POMC or LEPR-deficient obesity, which could only be attributable to age and genetic background as overall factors (Clement et al., 2020). Results of SGLT2 inhibitors were divided by comorbidity. There was a greater efficacy of ertugliflozin in chronic kidney disease (CKD) stage 3A as compared to 3B, which reflects the severity of the disease on the efficacy of the therapeutic approach (Dagogo-Jack et al., 2021). Tirzepatide ("dual GIP and GLP-1 agonist") proved its recurring effect across all ages, sexes, body mass indices, and glycaemic conditions, but weight loss was minimally reduced in patients with T2D compared to non-diabetic groups. More intense responses were predicted by higher baselines of BMI (Frias et al., 2020; Garvey et al., 2023; Min & Bain, 2021) and HbA1c. Overall, there was a strong effect of genetics, comorbidity patterns, and baseline levels of disease on the outcomes, and still, GLP-1-based treatments have large-scale responses in heterogeneous patient groups (Ahmann et al., 2018).

Is there any evidence concerning the long-term effects of GLP-1 RA versus other treatments?

Anti-obesity and anti-diabetic therapeutic interventions have substantial long-term outcomes, with certain therapeutic classes proving to be sustainable with minimal fluctuations and others exhibiting limited perspectives. Orlistat (lipase inhibitors) can potentially contribute to preventing a further worsening of blood glucose and blood pressure, but the final metabolism has not been directly proven over the long term (Frias et al., 2020). Factors indicating that a pharmacotherapy should be used with lifestyle changes to maintain body weight loss and decrease heart disease risks in the long run include the fact that lifestyle changes by itself is too limited (Arzola-Paniagua et al., 2016). In the case of MC4R, the follow-up literature indicates long-term weight loss and better body composition in a year, especially in rare genetic types of obesity (Clement et al., 2020; Haqq et al., 2022). Empagliflozin (SGLT 2s) has sustained effects on HbA1c for at least 1 year, but after week 26, the effect decreases in paediatric T2D as a result of decreased beta-cell function, casting questions on effectiveness in some groups (Laffel et al., 2023). DPP-4 inhibitors, in turn, demonstrate excellent initiating glycaemic control over up to 104 weeks, and hence their stability over the long term is also confirmed (Shankar et al., 2017). Within the group of GLP-1 RA, evidence is available of persistent response on glycaemic control plus weight loss in a 56-week period with possible long-term effect (Ahmann et al., 2018). On balance, the evidence shows that GLP-1 RA and DPP-4 inhibitors have greater strength in terms of durability, but clinical variability

among classes is observed, and patient-specific considerations are more crucial in terms of long-term results.

DISCUSSION

The results of this systematic review indicate that GLP-1 RA, as well as the dual "GIP/GLP-1 agonist tirzepatide", are always more effective than the other pharmacological alternatives in terms of weight loss outcomes and glycaemic control. In the sampled studies, tirzepatide proved to be the most effective agent with the highest levels of greater than or equal to five percent variations in weight loss alongside substantial percentages of subjects with greater than or equal to 20 percent loss of body weight at its highest point, a response rarely achieved with other treatment options (Frias et al., 2020; Garvey et al., 2023; Min & Bain, 2021). These effects were matched by significant changes in HbA1c, with several studies showing it to be decreasing by over 2% which states that there was a Progressive reduction in hyperglycemia control. Semaglutide and liraglutide showed strong dual efficacy, and semaglutide lowered body weight by approximately 10 per cent in portions of the population, and liraglutide persistently decreased BMI and body weight in a wide range of groups of study populations (Ahmann et al., 2018; Davies et al., 2021; Garvey et al., 2020; Kelly et al., 2020; Zhaohu et al., 2022). In contrast, empagliflozin, enavogliflozin, and ertugliflozin yield milder effects of the order of 2-3 kg weight loss and HbA1c under 1% (Dagogo-Jack et al., 2021; Kwak et al., 2023; Laffel et al., 2023). "DPP-4 inhibitors" added further weight change, negligible reduction of HbA1c (Goldenberg et al., 2017; Roussel et al., 2019; Shankar et al., 2017), and orlistat, despite having an effective effect in some metabolic phenotypes, targeted adiposity effects, not glycaemic control (Arzola-Paniagua et al., 2016; Feng et al., 2023; Khedr et al., 2020; Shirai et al., 2019). The MC4R setmelanotide showed very impressive weight losses, but in limited genetic subgroups only, which shows how limited its overall generalizability (Haqq et al., 2022; Kwak et al., 2023).

A good safety and tolerability profile is also available with these agents and which further contextualises their corresponding clinical usefulness. GLP-1 RA, tirzepatide, were also regularly associated with gastrointestinal adverse events, including nausea, vomiting, and diarrhoea, and dose titration strategies in the case of discontinuation were significant (Ahmann et al., 2018; Davies et al., 2021; Frias et al., 2020; Garvey et al., 2020; Garvey et al., 2023; Goldenberg et al., 2017; Kelly et al., 2020; Min & Bain, 2021; Zhaohu et al., 2022). These side effects are common, but mostly temporary, and can be perceived as acceptable in terms of therapeutic usefulness. Intolerability of Orlistat was also problematic because of continued gastrointestinal effects that significantly reversed the rate of adherence despite slight improvements in weight (Arzola-Paniagua et al., 2016; Feng et al., 2023; Khedr et al., 2020; Shirai et al., 2019). SGLT2 inhibitors were generally very well-tolerated; however, with a minor risk of urinary tract and other incidents in some cases, so cautious groups should be observed at this moment (Dagogo-Jack et al., 2021; Kwak et al., 2023; Laffel et al., 2023). Setmelanotide achieved mixed results, and some patients stated that they had experienced withdrawal with this medication through nausea and skin alteration, but others were able to bear through treatment (Clement et al., 2020; Haqq et al., 2022). "DPP-4 inhibitors" were described to have the safest suitability, with no adverse events noted; however, their insufficient particle size contributed to the weakness of efficacy, restraining their clinical importance (Goldenberg et al., 2017; Roussel et al., 2019; Shankar et al., 2017). Therefore, GLP-1-based agents were tolerable, but their ratio of benefits to risks is higher than other agents.

A characteristic that became abundantly decisive in treatment response was patient

traits, which highlights the role of personalised medication. Orlistat seemed to be especially effective in obese/fatty liver metabolic Asian groups, which further supported its ability in those systems in which dietary and lifestyle changes prove insufficient (Arzola-Paniagua et al., 2016; Feng et al., 2023). It is shown by the obvious positive results in the areas of genetically determined obesity, such as "Bardet-Biedl and Alstrom syndromes", or even paediatric cohorts of patients, where genetic profiling is essential in the selection of a suggested work (Clement et al., 2020; Khedr et al., 2020).

On the contrary, SGLT2 inhibitors did not demonstrate homogeneous efficacy according to comorbidity, as ertugliflozin demonstrated stronger efficacy in patients with less severe chronic kidney disease, suggesting that disease stage changes treatment outcomes (Dagogo-Jack et al., 2021). Tirzepatide always achieved high levels of effect in people of different populations, with many higher effects in patients with high baseline BMI and HbA1c levels (Frias et al., 2020; Garvey et al., 2023; Min & Bain, 2021). GLP-1 receptor agonists also showed a wide range of efficacy across populations of various ages and duration of diabetes, yet response magnitude varied, which may indicate that diabetes baseline severity is also a major modifier (Ahmann et al., 2018; Davies et al., 2021; Garvey et al., 2020; Kelly et al., 2020; Zhaohu et al., 2022). Altogether, these results suggest that although GLP-1 therapies are universal, personal conditions like genetic susceptibility, comorbidities, and baseline disease parameters are the crucial determinants of the therapeutic results.

Long-term data give additional information regarding the sustainability of these pharmacotherapies. The trials of liraglutide and semaglutide also indicate that these drugs lead to the maintenance of weight loss and a reduction in the HbA1c after at least 56 or 75 weeks, respectively, suggesting long-term adherence to the treatments (Ahmann et al., 2018; Davies et al., 2021; Garvey et al., 2020; Kelly et al., 2020; Zhaohu et al., 2022). Tirzepatide, also, has been shown to sustain long-term efficacy, but further extension of its long-term reliability requires more years of investigation (Frias et al., 2020; Garvey et al., 2023; Min & Bain, 2021). Although demonstrating short-term effects on adiposity, Orlistat showed less certainty on its long-term effects on metabolic quickly, wherein its benefit was more oriented towards preventing the worsening instead of affecting cardiovascular and glycaemic risk factors (Arzola-Paniagua et al., 2016; Feng et al., 2023; Khedr et al., 2020; Shirai et al., 2019). In the case of setmelanotide, iterative studies of the extension affirmed further weight reduction and enhancements in metabolism after a year in rare inheritable groups (Clement et al., 2020; Haqq et al., 2022). Mixed-duration demonstrations were found with SGLT2 and DPP-4 inhibitors, where empagliflozin maintained its results after 1 year in adult patients, whereas omarigliptin did after 104 weeks in paediatric diabetes, but this means the empagliflozin could be used afterwards, whereas omarigliptin could not due to progressive loss of beta-cells (Laffel et al., 2023), although omarigliptin may continue to be effectively used with long-term administration due to a small overall change in weight (Shankar et al., 2017). Combining these results, GLP-1 RA (and tirzepatide) and DPP-4 inhibitors have the greatest and the smallest long-term benefit, respectively, alongside the modest and lasting glycaemic stability, respectively. All in all, the evidence comparisons in all these 20 studies are indicative of the best use of GLP-1 RA and tirzepatide in combined weight loss and glycaemic control trials, and sufficient tolerability to these drugs in comparison to orlistat and SGLT2s. The efficacy of Setmelanotide underscores the possibility of highly targeted therapy to individual genetic minority groups, and DPP-4 inhibitors are also not the safest, but are not the most potent. Instant distinctiveness of patients and enduring results support the fact that

individual therapy plans must be designed to correspond the therapies to the clinical peculiarities of patients.

IMPLICATIONS

The results of this review have a number of implications for clinical practice and research. To begin with, GLP-1 RA and tirzepatide must be the first-line pharmacotherapies, which are necessary in patients who need to reduce weight considerably and have glycaemic control; they might be consistently effective in various populations (Ahmann et al., 2018; Davies et al., 2021; Frias et al., 2020; Garvey et al., 2020; Garvey et al., 2023; Kelly et al., 2020; Min & Bain, 2021; Zhaohu et al., 2022). However, the remaining limitation is the gastrointestinal tolerability, which needs a better titration process, supplementation, or newer and improved formulations that avoid the adverse reactions. The small yet positive safety profile of SGLT2 inhibitors indicates their utility in patients with a co-occurring cardiovascular or renal risk, the added value of which may be more important than less strong weight loss (Kwak et al., 2023; Laffel et al., 2023). Orlistat should continue to be favoured in resource-limited environments or in populations with limited therapeutic choices, whereas setmelanotide provides an example of how precision medicine has the potential to guide resource-limited conditions of rare genetic obesity (Clement et al., 2020; Haqq et al., 2022). Notably, inconsistency in the response based on baseline BMI, comorbidities, and genetic backgrounds underlines the necessity of being accurate when selecting a patient.

CONCLUSION

This exchange review shows that GLP-1 RA, liraglutide and semaglutide, and the dual "GIP/GLP-1 agonist" tirzepatide have the greatest combination of advantages in the area of weight loss and glycaemic control when compared with other currently existing anti-obesity and anti-diabetic medications. They were shown to be better compared to SGLT2, DPP-4, and orlistat on a variety of randomised trials. Setmelanotide, though very effective, can only be applied in rare genetic situations and thus is not generalizable. Drugs with different classes showed different safety and tolerability, gastrointestinal among GLP-1-based therapies, urinary tract infections in SGLT2-based therapies, and gastrointestinal intolerance limiting clinician use of orlistat. Nevertheless, the GLP-1 RA and tirzepatide still did not experience a better benefit-to-harm ratio, particularly among the groups with excessively high baseline BMI or poorly regulated diabetes. Patient differences or characteristics such as genetics, comorbid conditions, and level of disease contributed to great outcomes, which supported the notion that individual approaches to treatment are important. There is long-term evidence that GLP-1-based treatments have long-term advantageous effects, especially alongside lifestyle change. Taken together, these facts show that the GLP-1 RA and tirzepatide should be considered cornerstones of pharmacotherapy in the treatment of obesity and diabetes, and that research into the topic of precision medicine, as well as long-term effects and means to increase adherence and tolerance, must persist.

REFERENCES

ann, A. J., Capehorn, M., Charpentier, G., Dotta, F., Henkel, E., Lingvay, I., Holst, A. G., Annett, M. P., & Aroda, V. R. (2018). Efficacy and Safety of Once-Weekly Semaglutide Versus Exenatide ER in Subjects With Type 2 Diabetes (SUSTAIN 3): A 56-Week, Open-Label, Randomized Clinical Trial. *Diabetes Care*, *41*(2), 258-266. https://doi.org/10.2337/dc17-0417

*w*sari, M., Almadani, F. A., Almuhammadi, N., Algabsani, S., Alamro, Y., & Aldhwayan, M. (2023). The efficacy of GLP-1 analogues on appetite parameters, gastric emptying, food preference and taste among adults with obesity: systematic review of randomized controlled trials. *Diabetes, Metabolic Syndrome and Obesity*, 575-595.

https://doi.org/https://doi.org/10.2147/DMSO.S387116

American Diabetes Association Professional Practice Committee. (2025). 9. Pharmacologic approaches to glycemic treatment: Standards of Care in Diabetes—2025. *Diabetes Care*, *48*(Supplement_1), S181-S206. https://doi.org/10.2337/dc25-S009

Arzola-Paniagua, M. A., Garcia-Salgado Lopez, E. R., Calvo-Vargas, C. G., & Guevara-Cruz, M. (2016). Efficacy of an orlistat-resveratrol combination for weight loss in subjects with obesity: A randomized controlled trial. *Obesity (Silver Spring)*, *24*(7), 1454-1463. https://doi.org/10.1002/oby.21523

Bahari, H., Shahraki Jazinaki, M., Rahnama, I., Aghakhani, L., Amini, M. R., & Malekahmadi, M. (2024). The cardiometabolic benefits of okra-based treatment in prediabetes and diabetes: A systematic review and meta-analysis of randomized controlled trials. *Frontiers in Nutrition*, *11*, 1454286. https://doi.org/10.3389/fnut.2024.1454286

Bansal, A. B., Patel, P., & Al Khalili, Y. (2024). Orlistat. In *StatPearls [Internet]*. StatPearls Publishing. https://www.ncbi.nlm.nih.gov/books/NBK542202/

Chakraborty, S., Verma, A., Garg, R., Singh, J., & Verma, H. (2023). Cardiometabolic risk factors associated with type 2 diabetes mellitus: a mechanistic insight. *Clinical Medicine Insights: Endocrinology and Diabetes*, *16*, 11795514231220780. https://doi.org/https://doi.org/10.1177/11795514231220780

Clement, K., van den Akker, E., Argente, J., Bahm, A., Chung, W. K., Connors, H., De Waele, K., Farooqi, I. S., Gonneau-Lejeune, J., Gordon, G., Kohlsdorf, K., Poitou, C., Puder, L., Swain, J., Stewart, M., Yuan, G., Wabitsch, M., Kuhnen, P., Setmelanotide, P., & Investigators, L. P. T. (2020). Efficacy and safety of setmelanotide, an MC4R agonist, in individuals with severe obesity due to LEPR or POMC deficiency: single-arm, open-label, multicentre, phase 3 trials. *Lancet Diabetes Endocrinol*, *8*(12), 960-970. https://doi.org/10.1016/S2213-8587(20)30364-8

ns, L., & Costello, R. A. (2024). Glucagon-like peptide-1 receptor agonists. In *StatPearls [internet]*. StatPearls Publishing. https://www.ncbi.nlm.nih.gov/sites/books/NBK551568/

mittee, A. D. A. P. P. (2025). 9. Pharmacologic approaches to glycemic treatment: Standards of Care in Diabetes—2025. *Diabetes Care*, *48*(Supplement_1), S181-S206. https://doi.org/https://doi.org/10.2337/dc25-S009

go-Jack, S., Pratley, R. E., Cherney, D. Z. I., McGuire, D. K., Cosentino, F., Shih, W. J., Liu, J., Frederich, R., Mancuso, J. P., Raji, A., & Gantz, I. (2021). Glycemic efficacy and safety of the SGLT2 inhibitor ertugliflozin in patients with type 2 diabetes and stage 3 chronic kidney disease: an analysis from the VERTIS CV randomized trial. *BMJ Open Diabetes Res Care*, *9*(1). https://doi.org/10.1136/bmjdrc-2021-002484

es, M., Faerch, L., Jeppesen, O. K., Pakseresht, A., Pedersen, S. D., Perreault, L., Rosenstock, J., Shimomura, I., Viljoen, A., Wadden, T. A., Lingvay, I., & Group, S. S. (2021). Semaglutide 2.4 mg once a week in adults with overweight or obesity, and type 2 diabetes (STEP 2): a randomised, double-blind, double-dummy, placebo-controlled, phase 3 trial. *Lancet*, *397*(10278), 971-984. https://doi.org/10.1016/S0140-6736(21)00213-0

ıdge, R. H., Agrawal, S., Patil, R., Kadu, A., & Kothari, M. (2024). A comprehensive review of metabolic syndrome and its role in cardiovascular disease and type 2 diabetes mellitus: mechanisms, risk factors, and management. *Cureus*, *16*(8). https://doi.org/10.7759/cureus.67428

dz, D., Alvarez-Pitti, J., Wójcik, M., Borghi, C., Gabbianelli, R., Mazur, A., Herceg-Čavrak, V., Lopez-Valcarcel, B. G., Brzeziński, M., & Lurbe, E. (2021). Obesity and cardiometabolic risk factors: from childhood

to adulthood. *Nutrients*, *13*(11), 4176. https://doi.org/https://doi.org/10.3390/nu13114176

Feng, X., Lin, Y., Zhuo, S., Dong, Z., Shao, C., Ye, J., & Zhong, B. (2023). Treatment of obesity and metabolic-associated fatty liver disease with a diet or orlistat: A randomized controlled trial. *Am J Clin Nutr*, *117*(4), 691-700. https://doi.org/10.1016/j.ajcnut.2023.02.008

Frias, J. P., Nauck, M. A., Van, J., Benson, C., Bray, R., Cui, X., Milicevic, Z., Urva, S., Haupt, A., & Robins, D. A. (2020). Efficacy and tolerability of tirzepatide, a dual glucose-dependent insulinotropic peptide and glucagon-like peptide-1 receptor agonist in patients with type 2 diabetes: A 12-week, randomized, double-blind, placebo-controlled study to evaluate different dose-escalation regimens. *Diabetes Obes Metab*, *22*(6), 938-946. https://doi.org/10.1111/dom.13979

Garvey, W. T., Birkenfeld, A. L., Dicker, D., Mingrone, G., Pedersen, S. D., Satylganova, A., Skovgaard, D., Sugimoto, D., Jensen, C., & Mosenzon, O. (2020). Efficacy and Safety of Liraglutide 3.0 mg in Individuals With Overweight or Obesity and Type 2 Diabetes Treated With Basal Insulin: The SCALE Insulin Randomized Controlled Trial. *Diabetes Care*, *43*(5), 1085-1093. https://doi.org/10.2337/dc19-1745

Garvey, W. T., Frias, J. P., Jastreboff, A. M., le Roux, C. W., Sattar, N., Aizenberg, D., Mao, H., Zhang, S., Ahmad, N. N., Bunck, M. C., Benabbad, I., Zhang, X. M., & investigators, S.-. (2023). Tirzepatide once weekly for the treatment of obesity in people with type 2 diabetes (SURMOUNT-2): a double-blind, randomised, multicentre, placebo-controlled, phase 3 trial. *Lancet*, *402*(10402), 613-626. https://doi.org/10.1016/S0140-6736(23)01200-X

Goldenberg, R., Gantz, I., Andryuk, P. J., O'Neill, E. A., Kaufman, K. D., Lai, E., Wang, Y. N., Suryawanshi, S., & Engel, S. S. (2017). Randomized clinical trial comparing the efficacy and safety of treatment with the once-weekly dipeptidyl peptidase-4 (DPP-4) inhibitor omarigliptin or the once-daily DPP-4 inhibitor sitagliptin in patients with type 2 diabetes inadequately controlled on metformin monotherapy. *Diabetes Obes Metab*, *19*(3), 394-400. https://doi.org/10.1111/dom.12832

l, A. M., Chung, W. K., Dollfus, H., Haws, R. M., Martos-Moreno, G. A., Poitou, C., Yanovski, J. A., Mittleman, R. S., Yuan, G., Forsythe, E., Clement, K., & Argente, J. (2022). Efficacy and safety of setmelanotide, a melanocortin-4 receptor agonist, in patients with Bardet-Biedl syndrome and Alstrom syndrome: a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial with an open-label period. *Lancet Diabetes Endocrinol*, *10*(12), 859-868. https://doi.org/10.1016/S2213-8587(22)00277-7

boff, A. M., Aronne, L. J., Ahmad, N. N., Wharton, S., Connery, L., Alves, B., Kiyosue, A., Zhang, S., Liu, B., & Bunck, M. C. (2022). Tirzepatide once weekly for the treatment of obesity. *New England Journal of Medicine*, *387*(3), 205-216. https://doi.org/10.1056/NEJMoa2206038

ni, M. A., Gholami Chahkand, M. S., Dadkhah, P. A., Sheikhzadeh, F., Yaghoubi, S., Esmaeilpour Moallem, F., Deyhimi, M. S., Arab Bafrani, M., Shahrokhi, M., & Nasrollahizadeh, A. (2025). Comparative effectiveness of semaglutide versus liraglutide, dulaglutide or tirzepatide: a systematic review and meta-analysis. *Frontiers in Pharmacology*, *16*, 1438318. https://doi.org/https://doi.org/10.3389/fphar.2025.1438318

nbwa, D. A., Oh, J., Jang, C. H., & Lim, J. (2022). Orlistat, a competitive lipase inhibitor used as an antiobesity remedy, enhances inflammatory reactions in the intestine. *Applied Biological Chemistry*, *65*(1), 47. https://doi.org/https://doi.org/10.1186/s13765-022-00712-y

Kelly, A. S., Auerbach, P., Barrientos-Perez, M., Gies, I., Hale, P. M., Marcus, C., Mastrandrea, L. D., Prabhu, N., Arslanian, S., & Investigators, N. N. T. (2020). A Randomized, Controlled Trial of Liraglutide for Adolescents with Obesity. *N Engl J Med*, *382*(22), 2117-2128. https://doi.org/10.1056/NEJMoa1916038

Khedr, N. F., Ebeid, A. M., & Khalil, R. M. (2020). New insights into weight management by orlistat in comparison with cinnamon as a natural lipase inhibitor. *Endocrine*, *67*(1), 109-116. https://doi.org/10.1007/s12020-019-02127-0

King, A., & Miller, E. M. (2023). Glucagon-like peptide 1 receptor agonists have the potential to revolutionize the attainment of target A1C levels in type 2 diabetes—so why is their uptake so low? *Clinical Diabetes*, *41*(2), 226-238. https://doi.org/10.2337/cd22-0027

Knop, F. K., Aroda, V. R., do Vale, R. D., Holst-Hansen, T., Laursen, P. N., Rosenstock, J., Rubino, D. M., & Garvey, W. T. (2023). Oral semaglutide 50 mg taken once per day in adults with overweight or obesity (OASIS 1): a randomised, double-blind, placebo-controlled, phase 3 trial. *The Lancet*, *402*(10403), 705-719. https://doi.org/10.1016/S0140-6736(23)01185-6

Kwak, S. H., Han, K. A., Kim, K. S., Yu, J. M., Kim, E., Won, J. C., Kang, J. G., Chung, C. H., Oh, S., Choi, S. H., Won, K. C., Kim, S. G., Cho, S. A., Cho, B. Y., & Park, K. S. (2023). Efficacy and safety of enavogliflozin, a novel SGLT2 inhibitor, in Korean people with type 2 diabetes: A 24-week, multicentre, randomized, double-blind, placebo-controlled, phase III trial. *Diabetes Obes Metab*, *25*(7), 1865-1873. https://doi.org/10.1111/dom.15046

Laffel, L. M., Danne, T., Klingensmith, G. J., Tamborlane, W. V., Willi, S., Zeitler, P., Neubacher, D., Marquard, J., & Group, D. S. (2023). Efficacy and safety of the SGLT2 inhibitor empagliflozin versus placebo and the DPP-4 inhibitor linagliptin versus placebo in young people with type 2 diabetes (DINAMO): a multicentre, randomised, double-blind, parallel group, phase 3 trial. *Lancet Diabetes Endocrinol*, *11*(3), 169-181. https://doi.org/10.1016/S2213-8587(22)00387-4

ıado, A. M., Guimarães, N. S., Bocardi, V. B., da Silva, T. P. R., do Carmo, A. S., de Menezes, M. C., & Duarte, C. K. (2022). Understanding weight regain after a nutritional weight loss intervention: systematic review and meta-analysis. *Clinical nutrition ESPEN*, *49*, 138-153. https://doi.org/10.1016/j.clnesp.2022.03.020

ɛnedict, B., Orfao, A. L., Goh, K. S., Yau, R. C. C., Alphonse, B., Lima, J. M., Ahmed, H. A., Ienaco, G. P., de Souza, E. C., & Pessôa, B. L. (2024). The role of alternative medicine in managing type 2 diabetes: A comprehensive review. *Cureus*, *16*(6). https://doi.org/10.7759/cureus.61965

T., & Bain, S. C. (2021). The Role of Tirzepatide, Dual GIP and GLP-1 Receptor Agonist, in the Management of Type 2 Diabetes: The SURPASS Clinical Trials. *Diabetes Ther*, *12*(1), 143-157. https://doi.org/10.1007/s13300-020-00981-0

, A., Filion, K. B., Tsoukas, M. A., Yu, O. H., Peters, T. M., & Eisenberg, M. J. (2025). The expanding role of GLP-1 receptor agonists: a narrative review of current evidence and future directions. *Eclinicalmedicine*, *86*. https://www.thelancet.com/pdfs/journals/eclinm/PIIS2589-5370(25)00295-0.pdf

, A., Levett, J. Y., Filion, K. B., Peri, K., Reynier, P., & Eisenberg, M. J. (2024). Long-term efficacy and safety of once-weekly semaglutide for weight loss in patients without diabetes: a systematic review and meta-analysis of randomized controlled trials. *The American Journal of Cardiology*, *222*, 121-130. https://doi.org/https://doi.org/10.1016/j.amjcard.2024.04.041

ahy, G., Boelsen-Robinson, T., Hart, A. C., Pesantes, M. A., Sameeha, M. J., Phulkerd, S., Alsukait, R. F., & Thow, A. M. (2022). A comparative policy analysis of the adoption and implementation of sugar-sweetened beverage taxes (2016–19) in 16 countries.

Health policy and planning, *37*(5), 543-564. https://doi.org/10.1093/heapol/czac004

Padda, I. S., Mahtani, A. U., & Parmar, M. (2022). Sodium-glucose transport protein 2 (SGLT2) inhibitors. https://europepmc.org/article/nbk/nbk576405

Page, M. J., McKenzie, J. E., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., Shamseer, L., Tetzlaff, J. M., Akl, E. A., & Brennan, S. E. (2021). The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *Bmj*, *372*. https://doi.org/https://doi.org/10.1136/bmj.n71

Popoviciu, M.-S., Păduraru, L., Yahya, G., Metwally, K., & Cavalu, S. (2023). Emerging role of GLP-1 agonists in obesity: a comprehensive review of randomised controlled trials. *International Journal of Molecular Sciences*, *24*(13), 10449. https://doi.org/https://doi.org/10.3390/ijms241310449

Rao, G. H. (2025). Cardiometabolic diseases: Risk factors and novel approaches for the management of risks. In *Cardiometabolic Diseases* (pp. 3-26). Elsevier. https://doi.org/10.23880/oajc-16000199

Roussel, R., Duran-Garcia, S., Zhang, Y., Shah, S., Darmiento, C., Shankar, R. R., Golm, G. T., Lam, R. L. H., O'Neill, E. A., Gantz, I., Kaufman, K. D., & Engel, S. S. (2019). Double-blind, randomized clinical trial comparing the efficacy and safety of continuing or discontinuing the dipeptidyl peptidase-4 inhibitor sitagliptin when initiating insulin glargine therapy in patients with type 2 diabetes: The CompoSIT-I Study. *Diabetes Obes Metab*, *21*(4), 781-790. https://doi.org/10.1111/dom.13574

Saini, K., Sharma, S., & Khan, Y. (2023). DPP-4 inhibitors for treating T2DM-hype or hope? an analysis based on the current literature. *Frontiers in molecular biosciences*, *10*, 1130625. https://doi.org/10.3389/fmolb.2023.1130625

Shankar, R. R., Inzucchi, S. E., Scarabello, V., Gantz, I., Kaufman, K. D., Lai, E., Ceesay, P., Suryawanshi, S., & Engel, S. S. (2017). A randomized clinical trial evaluating the efficacy and safety of the once-weekly dipeptidyl peptidase-4 inhibitor omarigliptin in patients with type 2 diabetes inadequately controlled on metformin monotherapy. *Curr Med Res Opin*, *33*(10), 1853-1860. https://doi.org/10.1080/03007995.2017.1335637

Q., Wang, Y., Hao, Q., Vandvik, P. O., Guyatt, G., Li, J., Chen, Z., Xu, S., Shen, Y., & Ge, L. (2022). Retracted: Pharmacotherapy for adults with overweight and obesity: a systematic review and network meta-analysis of randomised controlled trials. *The Lancet*, *399*(10321), 259-269. https://doi.org/10.1016/S0140-6736(24)00351-9

i, K., Fujita, T., Tanaka, M., Fujii, Y., Shimomasuda, M., Sakai, S., & Samukawa, Y. (2019). Efficacy and Safety of Lipase Inhibitor Orlistat in Japanese with Excessive Visceral Fat Accumulation: 24-Week, Double-Blind, Randomized, Placebo-Controlled Study. *Adv Ther*, *36*(1), 86-100. https://doi.org/10.1007/s12325-018-0835-5

abi, C., Franchi, T., Mathew, G., Kerwan, A., Nicola, M., Griffin, M., Agha, M., & Agha, R. (2021). PRISMA 2020 statement: What's new and the importance of reporting guidelines. In (Vol. 88, pp. 105918): Elsevier.

nas, M. C., & Cherney, D. Z. (2018). The actions of SGLT2 inhibitors on metabolism, renal function and blood pressure. *Diabetologia*, *61*(10), 2098-2107. https://doi.org/https://doi.org/10.1007/s00125-018-4669-0

D. (2024a). *Diabetes*. https://www.who.int/news-room/fact-sheets/detail/diabetes

D. (2024b). *One in eight people are now living with obesity*. https://www.who.int/news/item/01-03-2024-one-in-eight-people-are-now-living-with-obesity

D. (2025). *Obesity and overweight*. https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight

Wilding, J. P., Batterham, R. L., Calanna, S., Davies, M., Van Gaal, L. F., Lingvay, I., McGowan, B. M., Rosenstock, J., Tran, M. T., & Wadden, T. A. (2021). Once-weekly semaglutide in adults with overweight or obesity. *New England Journal of Medicine*, *384*(11), 989-1002. https://doi.org/10.1056/NEJMoa2032183

Yusif, S., & Hafeez-Baig, A. (2024). Evidence-based Information Systems (IS) research: the case of systematic literature review (SLR). *Authorea Preprints*. https://doi.org/10.22541/au.170668933.33258272/v1

Zhaohu, H., Xiao, H., Hailin, S., & Feng, H. (2022). Efficacy and Safety of Dapagliflozin versus Liraglutide in Patients with Overweight or Obesity and Type 2 Diabetes Mellitus: A Randomised Controlled Clinical Trial in Tianjin, China. *J Diabetes Res*, *2022*, 4126995. https://doi.org/10.1155/2022/4126995