Advancements and challenges in the management of obesity using pharmacotherapy (Review)

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Abstract. Obesity is a chronic, recurrent and progressive disease that is a major public health issue, contributing to disability, morbidity and mortality worldwide. The global increase in obesity prevalence has been accompanied by an increase in weight-related comorbidity and mortality rates. To address this growing public health issue, the development and use of anti-obesity medications (AOMs) have escalated in recent years. The present review aims to discuss the most recent information on AOMs and the health effects of their regular use. The gastrointestinal (GI)-hypothalamic axis has been revealed to play a key role in the regulation of food intake and energy expenditure, which has led to the development of AOMs to target peptides secreted from the GI tract, including glucagon-like peptide-1 (GLP-1). GLP-1 receptor agonists are among the most widely investigated drugs in the rapidly developing field of hormone-based AOMs. However, most GLP-based drugs cause undesirable side effects. A promising approach to combat cardiometabolic conditions, including diabetes and obesity, is to reduce food consumption while also raising energy expenditure. Notably, novel candidate anti-obesity drugs have been shown to activate neurokinin 2 receptors (NK2Rs) in mice, leading to appetite suppression without the side effects observed with previous generations of treatments. However, additional research is necessary to address the side effects associated with AOMs, particularly those affecting the GI tract, gallbladder and pancreas. Furthermore, the potential of NK2R activation merits investigation in clinical trials, particularly in high-risk patients.

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1. Introduction

Obesity is a chronic lifestyle disease and the fifth leading cause of death globally (1). While obesity is often associated with an inability to adopt healthy habits (1), there are various other factors that can affect fat metabolism and contribute to the development of obesity, including genetic, environmental, pharmacological, behavioral and sociocultural factors (2,3). For example, certain drugs, excessive calorie consumption, low levels of physical activity and endocrinological conditions can all contribute to the development of obesity (4).

Obesity is typically diagnosed by determining the body mass index (BMI), which the World Health Organization defines as a basic weight-for-height indicator used to classify individuals as underweight, normal weight, overweight or obese. BMI (kg/m^2) is calculated by dividing body weight in kilograms by the square of height in meters (5). In adults, a diagnosis of overweight is made when the BMI is 25.0-29.9 kg/m^2, and obesity is diagnosed when the BMI is ≥30 kg/m^2 (6).

Higher BMI values are associated with increased mortality. Specifically, every 5-unit increase in BMI above 25 kg/m^2 has been shown to increase overall mortality by 29%, vascular mortality by 41% and diabetes-related mortality by 21% (6,7). In patients with obesity, a weight loss of 5-15% of body weight is recommended to significantly ameliorate comorbid medical conditions (8).

2. Pathogenesis of obesity

White adipose tissue primarily consists of fat-storing cells known as adipocytes, which store energy from food as triglycerides. In addition to adipocytes, this tissue also contains a variety of immune cells, including lymphocytes, macrophages and fibroblasts (9). Obesity can lead to adipose tissue dysfunction and disrupt the distribution and activity of immune cells, resulting in local and systemic inflammation (10). This inflammation is driven by the activation of inflammatory signaling pathways and the increased expression of inflammatory receptors (9). Insulin resistance and elevated inflammatory markers are associated with visceral fat accumulation in obesity (11). Hyperglycemia, hypertension and dyslipidemia are the hallmarks of metabolic syndrome, which frequently coexists with central obesity (12). It has been demonstrated that individuals with type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD) who are obese and have metabolic syndrome have a high risk of mortality (13).

The homeostatic and hedonic pathways play key roles in the regulation of food and energy intake in humans. When energy stores are low, the homeostatic pathway, which is controlled by the hypothalamus and brain stem, promotes food intake (14). By contrast, the hedonic pathway stimulates food intake during relative energy abundance by engaging the reward or motivational components of the brain, promoting the consumption of appetizing foods even when energy demands are low (15). Overeating has been reported to increase sympathetic nervous system activity, and altered sympathetic nervous system regulation is associated with obesity (16). By contrast, fasting lowers the amount of food consumed and reduces sympathetic nervous system activity (17). Obesity is associated with reduced serotonin signaling in the hypothalamus, which weakens the negative feedback that normally limits food intake and thereby leads to overeating (18). Additionally, it has been suggested that an overindulgence in appetizing foods is associated with a reduction in dopamine signaling (19). Ghrelin, which is also known as the hunger hormone, normally decreases in response to food consumption; however, this regulation is impaired by obesity (20). The reduced activity of anorexigenic hormones such as glucagon-like peptide-1 (GLP-1), peptide tyrosine-tyrosine (PYY) and cholecystokinin has been linked to increased food consumption in patients with obesity (21). Leptin promotes the synthesis of anorexigenic peptides and counterbalances the effects of ghrelin; however, leptin signaling is compromised in overweight individuals, which results in overeating (21). Anti-obesity medications (AOMs) are drugs are recommended by the U.S. National Institutes of Health for individuals with a BMI of ≥30 kg/m^2 who also have comorbidities such as diabetes, hypertension, dyslipidemia or sleep apnea (22). According to the Asia-Pacific Obesity Treatment Guidelines, AOMs should be considered for individuals with a BMI of ≥25 kg/m^2 who also have at least one weight-related comorbidity (23).

3. Obesity and COVID-19

Obesity, among other chronic illnesses, is associated with poor outcomes in diseases such as COVID-19 (24). A study found that when age, sex, hypertension and diabetes are taken into account, obesity is independently associated with inferior outcomes in patients with COVID-19; specifically, compared with patients with a normal BMI, patients with an elevated BMI had a greater risk of death and intubation (25). A key characteristic of the chronic inflammatory state promoted by obesity is the aberrant activation of leukocytes that infiltrate adipocytes and increase the release of proinflammatory cytokines (26). This proinflammatory environment is considered to impair lymphocyte function, thereby increasing the risk of severe COVID-19 in obese individuals (27).

4. Classification of AOMs

GLP-1 receptor agonists (GLP1RAs). GLP-1 was identified in the early 1980s as a proglucagon cleavage product generated in intestinal L cells (28). GLP-1 is a key incretin hormone, as it is a gut-derived peptide typically released following the consumption of glucose or a mixed meal and increases the glucose-stimulated release of insulin at physiological plasma concentrations (29). In 2005, a new class of pharmacological agents, known as GLP1RAs, was introduced for the treatment of T2DM (30). These drugs increase insulin secretion and suppress hunger, both of which are critical in the management of T2DM and obesity. In addition, drugs such as tirzepatide, which target both GLP-1 receptors and other receptors involved in energy regulation, have been developed and exhibit potential for use in glycemic management and weight-loss strategies (31). GLP1RAs have been demonstrated to support weight loss, and since GLP-1 maintains its insulinotropic efficacy in individuals with T2DM, GLP-1 may contribute to the pharmacotherapy of this illness (32). In addition, GLP1RAs that are resistant to degradation by dipeptidyl peptidase (DPP)-4 have prolonged activity and target accessible receptors throughout the body (33). Due to their limited absorption and rapid breakdown when taken orally, most GLP1RAs are administered subcutaneously (34). However, several orally administered GLP1Ras are currently in clinical development (35).

GLP1RAs are classified into two categories: Long-acting, including albiglutide, exenatide extended release, dulaglutide and liraglutide, and short acting, including lixisenatide, exenatide immediate release and liraglutide, as summarized in Table I. While the mechanisms by which GLP1RAs lower food intake and aid weight loss have not been fully elucidated, GLP1RAs are known to directly interact with GLP-1 receptors in the circumventricular organs of the hypothalamus, the hindbrain and certain regions of the brain adjacent to ventricles that are considered to promote satiety and weight loss (36). Notably, two GLP1RAs, liraglutide and semaglutide, have been shown to access the area postrema, subfornical organ and median eminence; by contrast, the ability of dulaglutide and albiglutide, which are relatively large molecules, to access to these regions may be limited (37,38). Both mono-agonists

Table I. Features of glucagon-like peptide-1 receptor agonists.

Brand name	Generic name	First approval year, region	Elimination half-life	Recommended dose	Frequency of subcutaneous administration	Expected weight loss, kg	(Refs.)
Adlyxin™	Lixisenatide	2016, USA; 2013, Europe	3 h	Not specified	Once daily	~3	(138,139)
Bydureon	Exenatide ER	2012, USA; 2011, Europe	2 weeks	Not specified	Once weekly	2-3	(140)
Byetta	Exenatide IR	2005, USA; 2006, Europe	2.4 h	Not specified	Twice daily	2-4.4	(141)
Ozempic	Semaglutide	2017, USA; 2018, Europe	1 week	2.4 mg once a week	Once weekly	9.7-15.3	(142,143)
Tanzeum	Albiglutide	2014, USA; 2014, Europe (Eperzan)	5 days	Not specified	Once weekly	~2.21	(144,145)
Trulicity	Dulaglutide	2014, USA; 2014, Europe	4 days	4.5 mg per week	Once weekly	>2.43	(64,146)
Victoza	Liraglutide	2010, USA; 2009, Europe	13 h	3 mg once a day	Once daily	2-3	(147,148)

ER, extended release; IR, immediate release.

targeting GLP-1 alone, and poly-agonists targeting multiple receptors, have been developed as a result of the abundant research and development efforts triggered by the successful outcomes of early GLP-1-based medicines (39). Notably, liraglutide and semaglutide have been evaluated in advanced clinical trials (40) and approved for clinical use. However, despite these advances, efforts to develop safe and efficient therapies for obesity and T2DM are ongoing, as demonstrated by the continuous growth of the pharmacological research pipeline (41) (Table I).

Liraglutide. Liraglutide is a homolog of human GLP-1 that includes a palmitic acid side chain and a lysine-to-arginine substitution at position 34 (42). These modifications slow the rate of degradation by DPP and increase its absorption period (42). Liraglutide has a half-life of 13 h, and a bioavailability of 55% after a daily subcutaneous (s/c) injection (43). As a GLP-1 analog, liraglutide delays the emptying of the stomach, reduces appetite, inhibits glucagon secretion and enhances insulin secretion in a glucose-dependent manner (44). Liraglutide was first approved for the treatment of T2DM in 2010, and subsequently approved by the U.S. Food and Drug Administration (FDA) for the treatment of adult obesity at doses <3.0 mg in 2014, and for the treatment of juvenile obesity in 2020. The effect of liraglutide on obesity in adults was evaluated in five double-blind placebo-controlled clinical studies as part of the Satiety and Clinical Adiposity-Liraglutide Evidence trial (45,46). The results showed a substantial variation in the effect of liraglutide, with the majority of participants not achieving a large (≥10%) weight loss. However, 33.1% of the participants achieved a ≥10% weight loss with liraglutide compared with 10.6% in the placebo group (46). Nevertheless, both liraglutide and semaglutide have been shown to improve glycemic management and support weight loss (47).

Semaglutide. Semaglutide is the most recently approved GLP1RA since these agents first entered the market in 2005 (48). It has a very long half-life, which can reach 183 h and significantly exceeds the half-lives of other GLP1RAs (49). This GLP-1 analog, with a high binding affinity for albumin, was developed to enable weekly s/c GLP1RA administration (50). As a longer-acting GLP1RA, semaglutide ($C_{187}H_{291}N_{45}O_{59}$) shares 94% structural similarity with native GLP-1 (51). Adults and elderly patients with renal, hepatic or cardiovascular conditions can safely use semaglutide (50). Semaglutide is available in two forms: Rybelsus®, comprising once-daily oral tablets, and Ozempic®, which is a once-weekly s/c injection (13). In one study, semaglutide was found to degrade into six distinct metabolites, with the parent molecule accounting for 82.6% of the plasma concentration of the drug (48). The same study also reported that semaglutide was metabolized via β-oxidation of its fatty acid side chain and proteolytic cleavage of its peptide backbone; in addition, plasma metabolite concentrations decreased over time, and only the parent substance was detectable in plasma 28 days after administration. However, the effects of the metabolites on the efficacy of semaglutide and the side-effect profile are unknown (48).

Semaglutide is used to treat T2DM and obesity (52). For the treatment of T2DM, both a weekly s/c injection (1 mg) and daily oral regimen (<14 mg per day) have been approved. Injectable semaglutide has also been approved for the treatment of obesity, while the oral form has not yet received approval for this condition. The treatment protocol for weekly injectable semaglutide starts with a dose of 0.25 mg, which is increased every 4 weeks until 2.4 mg is reached, which is usually after ~16 weeks. The half-life of semaglutide ranges from 155 to 183 h (53). The use of sodium N-[8-(2-hydroxybenzoyl)amino] caprylate technology has been shown to enhance transcellular

absorption and inhibit the breakdown of orally administered semaglutide in the stomach (54). This technology is incorporated into the oral formulation of semaglutide, which was the first GLP1RA to be approved by the U.S. FDA as a daily oral treatment for T2DM (55). Danuglipron (35), a selective small-molecule GLP1RA, and orforglipron, a non-peptide GLP1RA, are also being developed as oral GLP1RAs for the treatment of obesity and T2DM (56).

Lixisenatide and exenatide. Lixisenatide and exenatide are short-acting GLP1RAs. When injected, they produce brief peaks in plasma drug concentrations, interspersed with intervals of barely detectable concentrations. As a result, the pharmacodynamic profiles of these compounds include 'resting' periods, when GLP-1 receptors are not activated, and periods of several hours when effective medication concentrations are present in the circulation. On the other hand, the sharply delayed gastric emptying caused by the quick rise in plasma levels of these short-acting receptor agonists significantly reduces postprandial glucose excursions after breakfast (for exenatide and lixisenatide) and before dinner (for exenatide) (30).

Albiglutide. Some GLP1RAs have been created by fusing modified GLP-1 or GLP-1 segments to large proteins such as the immunoglobulin (Ig) Fc fragment (dulaglutide and efpeglenatide) or albumin (albiglutide). These compounds decay slowly, with half-lives of ~1 week. After s/c injection, they reach their effective circulation concentrations very quickly, thereby decreasing plasma glucose levels soon after the start of treatment (57). Weekly, biweekly and monthly dosing of albiglutide has been shown to reduce glycated hemoglobin (HbA1c) levels to a similar extent, but weekly treatment causes the least noticeable changes in fasting plasma glucose levels (58). Improvements in fasting blood glucose levels have been noted as early as 2 weeks after the initiation of albiglutide treatment (58). Although evidence suggests that natural GLP-1 can access the central nervous system (CNS) through regions lacking a normal blood-brain barrier (59), the large size of the albiglutide molecule, primarily due to its two human albumin components, suggests that it may not have the same CNS effects as smaller GLP1RAs. Nonetheless, albiglutide treatment has been shown to induce a small reduction in body weight, which may be the result of the medication exerting central effects (60).

Dulaglutide. Dulaglutide consists of two GLP-1 analog peptides, modified with amino acid substitutions that prevent degradation by DPP-4, connected via short peptides to a modified human IgG4-Fc heavy chain, which decreases immunogenicity and cytotoxicity while enhancing the stability of the molecule (61). Due to its high molecular weight of 59.7 kDa, dulaglutide has limited renal clearance. In addition, it has a half-life of ~4 days and a time-to-peak concentration of ~70 h, both of which support its use as a weekly medication and increases patient compliance (62). Large-scale, long-term randomized trials have been conducted, and are ongoing, to evaluate the viability of dulaglutide as a therapeutic agent for the treatment of T2DM (63). It has been demonstrated that weekly doses of 0.05-8.0 mg dulaglutide for 5 weeks can reduce HbA1c levels by 0.2-1.2% (63). However, in a clinical trial, only individuals who received the two highest weekly doses of 5 and 8 mg demonstrated significant mean reductions in body weight of 2.5 and 2.0 kg, respectively (64).

5. Amylin-based AOMs

Amylin, also known as islet amyloid polypeptide, is a peptide hormone co-secreted with insulin that centrally controls satiety pathways and thus regulates food intake (65). It activates certain receptors, such as calcitonin gene-related peptide receptors (66). Amylin has been demonstrated to influence the hedonic pathway, for example, by reducing the activity of neural circuits that mediate the rewarding aspects of food consumption, although it primarily affects energy metabolism by increasing satiety (67). The clinical use of human amylin as an anti-obesity drug is hampered by its tendency to aggregate, which results in pancreatic islet death (68). However, rat-derived amylin analogs, such as pramlintide, have been developed as diabetic treatments that improve glycemic management and provide modest but notable weight loss (65). Pramlintide was approved by the U.S. FDA in 2005 as an adjunct to insulin or oral medications for individuals with T1DM and T2DM (69). However, the effects of pramlintide on body weight and food consumption are not limited to individuals with diabetes. Research has indicated that moderate weight loss can be achieved with pramlintide, regardless of diabetic status (67). In a preclinical trial, pramlintide was found to induce notable weight loss and alleviate leptin resistance when paired with the leptin analog metreleptin (70). As a result of these findings, amylin has become a focal point for research into the management of obesity. Several amylin-based medications have been shown to be safe and effective in humans, such as cagrilintide, which is a long-acting amylin receptor agonist (71). Cagrilintide was designed by making structural modifications to amylin to improve its potency, solubility and duration of action, as well as reducing its propensity to form amyloid fibrils (71). Cagrilintide has been found to significantly reduce body weight in clinical trials (72), particularly when paired with semaglutide (66). Notably, the development of dual-acting amylin and calcitonin receptor agonists is a promising area in obesity pharmacotherapy, as human amylin receptor subtypes include calcitonin receptors complexed with receptor activity-modifying proteins (73).

6. AOMs that mimic glucose-dependent insulinotropic polypeptide (GIP)

Due to the relatively weak insulinotropic effect observed in patients with T2DM, in addition to the preclinical data on GIP receptor (GIPR) agonism in mice with diet-induced obesity, the use of GIPR agonists (GIPRAs) for the treatment of T2DM and obesity was initially viewed with skepticism (74). However, long-acting GIPRAs have been shown to reduce body weight in obese mice by signaling through the CNS to act on GIPR-expressing neurons and cells in the hindbrain and hypothalamus (75). When acylated GIP was administered centrally to obese mice, they exhibited weight loss and a reduction in food intake. Peripheral injection results in weight loss in both wild-type and GLP1R knockout mice; however,

in CNS GIPR knockout animals, the reduction in body weight was less notable than that in wild-type mice (76). These findings challenge the hypothesis that GIP promotes obesity and support the suggestion that long-acting GIPRAs help to regulate body weight and blood sugar levels.

In addition to promoting weight loss and appetite control, GIPRAs have been shown to provide metabolic benefits beyond those of GLP1RAs by acting through GLP-1 receptor-independent pathways (62). In preclinical models, GIP was shown to counteract the emetic effects of GLP1RAs, whereas in individuals with T2DM, GLP1RAs were found to restore the insulinotropic action of GIP (77). Furthermore, GIPRAs increase the storage capacity of adipocytes, thereby preventing adipocyte lipid spillover and aberrant lipid build-up in other tissues (78). Compounds with dual GLP1RA/GIPRA activity have been developed, and it has been suggested that even when the specific contribution of the GIPRA to weight loss is unclear, it may promote weight loss by modulating GLP-1 signaling (79). To the best of our knowledge, tirzepatide is considered the most effective dual GLP1RA/GIPRA. Tirzepatide has five-fold greater efficacy at the human GIPR receptor compared with that at the GLP-1 receptor (31). In addition, the half-life of tirzepatide is ~117 h (31). The U.S. FDA and the European Medicine Agency approved tirzepatide for the treatment of T2DM based on data from the SURPASS clinical trial (80).

7. Oxyntomodulin and PYY

The L cells of the gastrointestinal (GI) tract produce oxyntomodulin and PYY, with a number of these cells co-secreting both hormones (81). Specifically, PYY and oxyntomodulin are released simultaneously during the postprandial period (82). In addition to acting locally to improve digestion, these hormones act as signalling molecules when their blood levels increase, relaying information about the postprandial shift in energy status to the brain. While oxyntomodulin reduces gastric acid output and retards stomach emptying (83), PYY delays pancreatic and gallbladder secretions, slows stomach emptying and increases ileal absorption (84). Oxyntomodulin is a 37-amino-acid peptide that consists of glucagon (29 amino acids) with an octapeptide C-terminal extension; it is derived from the post-translational processing of proglucagon, which is encoded by the glucagon gene and expressed in the intestine (85). Prohormone convertases 1 and 2 cleave proglucagon to generate various products in a tissue-dependent manner (86). For example, glucagon is the main product in the pancreas and glicentin, and GLP-1 and GLP-2 are produced in the gut and brain. Oxyntomodulin and glicentin are also products of proglucagon processing, and significant levels of oxyntomodulin can be detected in the human distal intestine (87). The tyrosine residues at the C- and N-termini of the 36-amino acid PYY give this peptide its name. PYY belongs to the same family as neuropeptide Y and pancreatic polypeptide, and all of these peptides have a distinctive U-shaped fold in their tertiary structure (88). PYY is most abundant in the rectum, followed by the colon and ileum (89). Certain neurons in the CNS, such as those in the hypothalamus, exhibit PYY immunoreactivity (90). The amount of PYY released from the GI system correlates with calorie intake, with levels peaking 1-2 h after a meal and remaining elevated for up to 6 h (88).

8. Novel approach: AOMs targeting neurokinin 2 receptors (NK2Rs)

A promising strategy for combating cardiometabolic disorders, including obesity and T2DM, is to reduce food intake while boosting energy expenditure (91). However, although current pharmaceutical approaches to accomplish these outcomes have involved a combination of multiple receptor agonists, no safe energy-using solution has yet made it to the clinic (92). Recently, Sass *et al* (93) identified a genetic approach for the discovery of novel candidate anti-obesity drugs by activating NK2Rs in mice. This strategy was able to reduce appetite without the side effects associated with earlier treatments. Mice with diet-induced obesity received s/c injections of neurokinin A (NKA), an NK2R ligand, twice daily for 9 days. These mice exhibited improvements in insulin tolerance, along with decreased food intake, body weight and inguinal and epididymal white adipose tissue. In the study, a longer-acting version of the NK2R ligand was created by covalently attaching a 16-carbon fatty acid conjugate of γ-glutamic acid, which is the same moiety used in the GLP1RA liraglutide, to the Lys2 residue of native NKA. This modification extended the blood retention of the peptide from minutes to hours, likely through albumin binding (93). Targeting energy expenditure is particularly important given the reduction in the average basal metabolic rate over the last 30 years (94). Although agonism of the glucagon receptor has emerged as a promising approach for increasing catabolic metabolism, an elevated heart rate, hepatic glucose production and concerns about lean mass loss, might restrict its application, especially for T2DM (95). Furthermore, most GLP-based drugs cause undesirable side effects such as nausea, stomach motility issues, and disorders of insulin and glucagon release (91).

9. Mechanisms of action of GLP1RAs

GLP-1 is secreated by specialised enteroendocrine cells, termed L cells, in the GI tract. The secretion of GLP-1 directly stimulates the pancreas to increase insulin secretion and decrease glucagon secretion. It also suppresses stomach motility; delays stomach emptying and decreases hunger by acting on the CNS. However, GLP-1 may also cause nausea (96). Short-acting GLP1RAs have been shown to decrease transpyloric flow and suppress stomach motility (97). These effects result in reduced postprandial insulin secretion, delayed intestinal glucose absorption, nausea induction and appetite suppression. Furthermore, short-acting GLP1RAs appear to directly influence glucagon secretion and the CNS. By contrast, long-acting GLP1RAs have been found to affect the pancreas by directly stimulating insulin secretion and suppressing glucagon secretion through the paracrine production of somatostatin. These compounds also decrease appetite and may cause nausea through their effects on the CNS (98) (Fig. 1).

10. Most commonly used AOMs

Saxenda. Saxenda (liraglutide) is an FDA-approved GLP1RA for chronic weight management in adults. It reduces the rate of stomach emptying, increases satiety and reduces appetite,

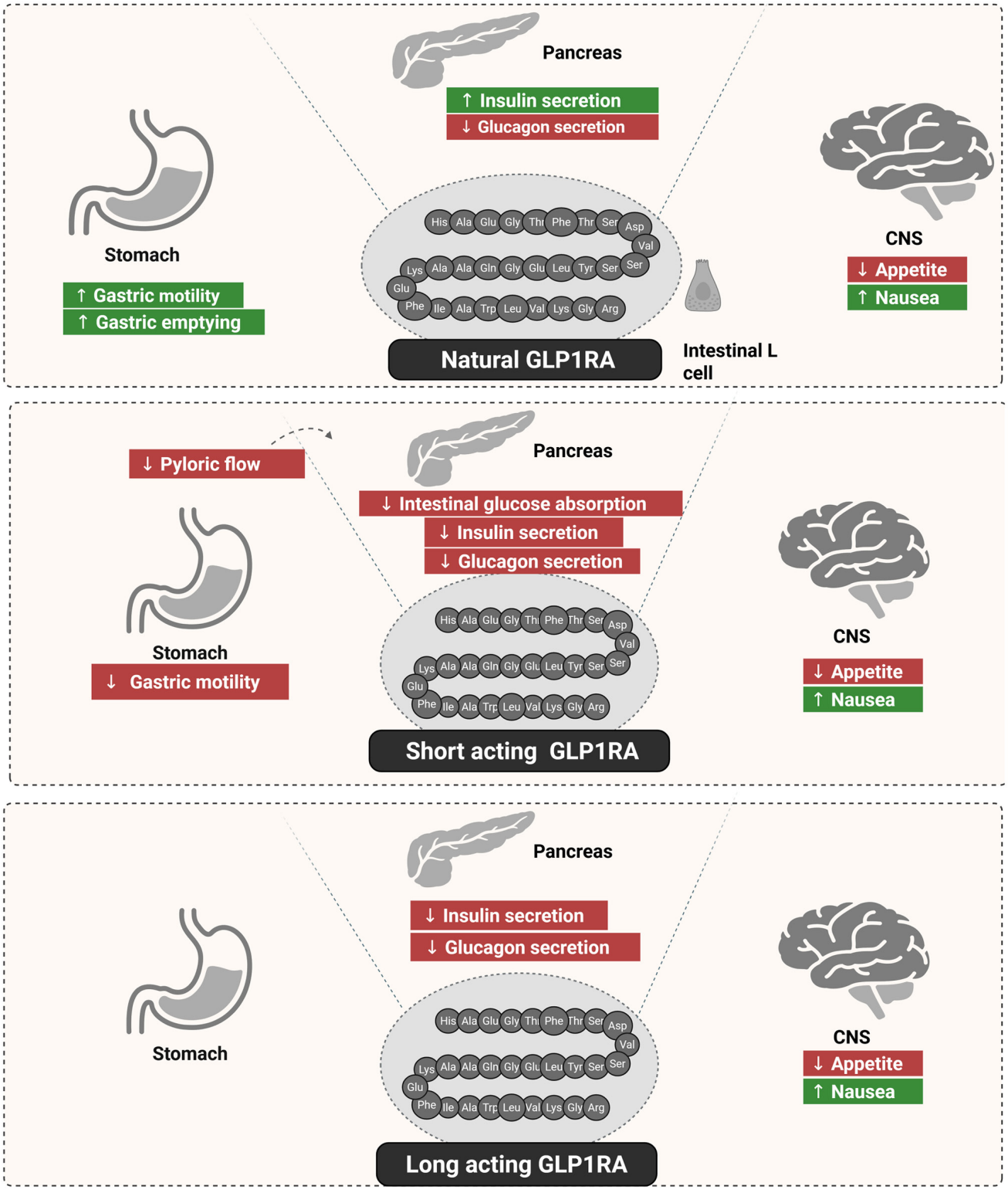

Figure 1. Representation of the mechanisms of action of three different types of GLP1RAs and their impacts on the CNS, gastric motility and pancreas. Natural GLP-1 affects the CNS, resulting in decreased hunger and increased nausea. It also increases gastric motility, leading to faster emptying, and affects the pancreas by increasing insulin secretion and decreasing glucagon release. Short-acting GLP1RAs have a similar effect on the CNS as natural GLP-1, but reduce gastric motility, which in turn reduces pyloric flow and glucose absorption, ultimately diminishing the production of insulin and glucagon by the pancreas. Long-acting GLP1RAs act on the pancreas and CNS to reduce insulin and glucagon production and decrease appetite. GLP-1, glucagon-like peptide-1; GLP1RA, GLP-1A receptor agonist; CNS, central nervous system.

all of which contribute to decreased calorie intake and, consequently, weight loss (46). Clinical research has shown that when is paired with a lower-calorie diet and greater physical activity, Saxenda can lead to a weight loss ranging from 5 to 10% (46). In one randomized controlled trial, after 1 year, individuals who received Saxenda lost an average of 8% more of their body weight than those who received a placebo (99) (Table II).

Table II. Comparison of the three commonly used AOMs: Saxenda, Mounjaro and Ozempic.

	General information					Pharmacokinetics			Side effects		
AOM	Primary use	Mechanism	Approval by U.S. FDA	Injection frequency	Half-life	Onset of action	Bioavailability, %	Average body weight loss, %	Common	Severe	(Refs.)
Liraglutide (Saxenda®)	Weight management	GLP-1R agonist	December 2014	Weekly	13 h	C_{max} reached within 9-14 h	55	5-10	Nausea, vomiting, diarrhea	Pancreatitis, thyroid tumors	(46,149)
Tirzepatide (Mounjaro™)	T2DM and weight management	Dual GIPR/ GLP-1R agonist	May 2022 for T2DM: November 2032 for obesity	Weekly	5 days	C_{max} observed in 1-2 days	80	≤22.5	Nausea, vomiting, diarrhea	Pancreatitis	(150,151)
Semaglutide (Ozempic)	T2DM and weight management	GLP-1R agonist	2017 for T2DM; later expanded for weight management	Weekly	7 days	C_{max} reached within 1-3 days	89	10-15	Nausea, vomiting, diarrhea, constipation	Pancreatitis, thyroid tumors	(152,153)

C_{max}, maximum plasma concentration; GLP-1R, glucagon-like peptide-1 receptor; T2DM, type 2 diabetes mellitus; GIPR, glucose-dependent insulinotropic polypeptide agonist.

Mounjaro. Mounjaro (tirzepatide) is a dual GIPRA/GLP1RA. Due to its dual actions, Mounjaro not only reduces appetite but also enhances insulin sensitivity and glucose regulation. It has been suggested that its use may lead to superior weight loss and glucose-lowering effects compared with those achieved with single-hormone treatments, such as those targeting the GLP-1R alone (100). A study found that patients receiving high doses of Mounjaro experienced a weight loss of up to 22.5% of their initial body weight over 72 weeks, along with significant improvements in blood HbA1c levels, a marker of long-term blood glucose control. The efficacy achieved was comparable to that of bariatric surgery (101) (Table II).

Ozempic. Ozempic (semaglutide) is another GLP1RA that stimulates insulin release, suppresses hunger and slows stomach emptying. Ozempic, which was first licensed for the treatment of T2DM, has also been demonstrated to induce significant weight-loss effects, prompting the creation of a higher-dose version (Wegovy) exclusively for the induction of weight loss (50). Studies have shown that Ozempic can lead to a 10-15% reduction in body weight, particularly at higher doses (102,103). In a randomized clinical trial, participants who received Ozempic lost significantly more weight than those in the placebo group (103). Ozempic has also been found to improve HbA1c levels and other markers of metabolic health, making it highly effective for both diabetes management and weight loss (104) (Table II).

11. Efficacy and safety of AOMs in children

At present, to the best of our knowledge, no drugs have been authorized for the treatment of non-monogenic, non-syndromic obesity in children <12 years of age. Liraglutide has been demonstrated to help obese adults and adolescents lose weight, but its efficiency and safety in children have not been established (105). In one study, liraglutide treatment for 56 weeks combined with lifestyle modifications led to a higher reduction in BMI among obese children aged 6 to <12 years than was achieved with placebo plus lifestyle modifications (105). However, another study raised uncertainty about the efficacy of anti-obesity drugs in children and teenagers (106). In a comprehensive weight management clinic, however, semaglutide has shown promise as a safe and effective weight loss aid for patients aged 10-18 years (107).

12. Effects of selected approved AOMs on physiological systems and conditions

Effects on joints. Osteoarthritis (OA) is a degenerative joint disease closely associated with obesity, as excess body weight increases the mechanical stress on joints and exacerbates systemic inflammation. Given that obesity is a modifiable risk factor for OA, the use of AOMs to promote weight has been observed to improve joint health by reducing both load and inflammation (108). Studies have shown that a 5-10% weight loss achieved using AOMs such as Saxenda and Ozempic significantly reduces joint load and alleviates OA symptoms, particularly in weight-bearing joints such as the knees (109). Load reduction has been associated with improvements in pain, function and quality of life in patients with OA (110). As previously reviewed, a number of studies have investigated how AOM-induced weight loss affects bone density, and have indicated that rapid weight reduction may raise the risk of fractures by decreasing bone density, which a potentially serious side effect for obese patients with OA (111). However, GLP1RA use may reduce systemic inflammation. Specifically, the use of Saxenda has been linked to reductions in the level of C-reactive protein, an inflammatory marker associated with OA progression (46).

Effects on the digestive system. GLP1RAs and dual-action GIPRA/GLP1RA compounds primarily act on the digestive system by slowing gastric emptying and enhancing satiety, leading to reduced calorie intake (112). However, side effects impacting the GI tract, gallbladder and pancreas have been reported. Regarding GI side effects, a notable proportion of patients experience nausea, vomiting, diarrhoea and constipation when taking GLP1RAs such as semaglutide and liraglutide. However, these effects are dose-dependent and typically diminish over time (113). Clinical trial data indicate that Mounjaro is associated with a higher incidence of nausea than other AOMs, likely due to its dual mechanism of action (114). The rapid weight loss induced by AOMs has also been linked to an increased risk of gallstone formation. Specifically, a study has shown that GLP1RAs, including Ozempic, can reduce gallbladder motility, potentially leading to cholelithiasis (103). Although definitive evidence is lacking, a study has indicated that the risk of pancreatitis may be elevated among patients who use GLP1RAs, particularly those with a history of pancreatic disorders (115). However, further research is required to confirm existing findings.

Effects on the CNS. AOMs such as Saxenda and Ozempic act on appetite regulation centers in the hypothalamus by mimicking GLP-1, thereby reducing hunger and increasing satiety. These actions contribute to lower calorie intake and facilitate weight loss (50). A preliminary study has suggested that GLP1RAs may have positive effects on mood and could provide benefits to patients with mood disorders, such as depression (116). However, these effects are likely secondary to weight loss and overall health improvements, and further investigation in this area is warranted (117).

Effects on the cardiovascular system. GLP1RAs have been demonstrated to lower the risk of cardiovascular events in individuals with T2DM and obesity. Specifically, the LEADER and SUSTAIN-6 trials (116) found that liraglutide and semaglutide were associated with reductions in major adverse cardiovascular events, such as heart attack and stroke. The findings suggest that AOMs may confer cardiovascular protection by lowering blood pressure, improving lipid profiles and reducing systemic inflammation (118). In addition, small reductions in both systolic and diastolic blood pressure have been associated with AOM-induced weight loss. However, some patients receiving GLP1RAs have exhibited an increase in resting heart rate (101), and more research is necessary to determine the therapeutic importance of this result.

Other effects. It is well established that GLP1RAs increase insulin sensitivity and reduce blood glucose levels, making them particularly effective for use in the management of T2DM. It is also notable that the improved glucose regulation achieved with GLP1RAs also mitigates diabetes-related complications such as neuropathy and nephropathy (115). The weight loss associated with AOMs typically involves a preferential loss of visceral fat, which is strongly associated with the risk of metabolic disorders and CVDs. As a result, AOMs are considered to improve metabolic health and lower systemic inflammation by decreasing visceral adiposity (110).

13. Advantages of AOMs beyond weight loss

Exenatide was the first GLP1RA to receive approved, which occurred in 2005 in the USA, followed by liraglutide in 2010 and lixisenatide in 2016. Another GLP1RA, albiglutide, was approved in 2014 in Europe, but was taken off the market due to economic considerations (119). In its latest recommendations for the management of chronic coronary syndrome, the European Society of Cardiology suggested as a class 1, level A recommendation that GLP1RAs can be used to treat T2DM patients with CVD (120). Similarly, the American Diabetes Association recommends the use of GLP1RAs to treat individuals who are at high risk for CVD (121). This recommendation also includes the use of sodium-glucose transport protein 2 inhibitors to treat patients with heart failure or chronic renal disease (119). Regarding substances of abuse other than food, the effects of GLP1RAs on alcohol consumption in laboratory animals, such as male rats, mice and non-human primates have been investigated (122,123). In addition, it has been observed that systemic exenatide injection inhibits cocaine-conditioned location preference in mice (124,125). Exenatide or liraglutide administration has also been shown to lessen the psychomotor stimulant effects of amphetamine in rats and mice, as evidenced by changes in locomotor activity (126). Furthermore, in several tests, liraglutide attenuated the harmful effects of amphetamine on cognitive function in rats (127).

14. Obesity in the Kingdom of Saudi Arabia (KSA)

A nationwide survey conducted between 1995 and 2000 indicated that 35.6% of the Saudi population were obese (128). Additionally, a subsequent systematic review of obese and overweight adults in Middle Eastern countries from 2000 to 2020 indicated that the prevalence of obesity in the KSA was 24.95%, (129), and 31.80% of individuals in the KSA were overweight (130). According to the World Atlas, 35.4% of the population of the KSA is obese, making it the 14th most obese nation in the world (131). In addition, a national study performed in 2013 found that the overall prevalence of obesity in the KSA was 28.7%, with 33.5% of women and 24.1% of men being obese (132). Furthermore, a Survey of Health Information in the KSA (131) reported that childhood obesity was increasing in the KSA and affected 6-10% of preschool- and school-aged children. Therefore, both adult and childhood obesity are major national public health issues (131). Data reported in 2024 indicate that 20% of adults and 39% of adolescents are obese, with T2DM (60.7%), hypertension (67.6%) and hypercholesterolemia (51.3%) being the most commonly reported obesity-related conditions. Additionally, an association between obesity and obesity-related comorbidities was established, indicating an increased risk of comorbidity as BMI rises, and the cost of treating and managing obesity in the KSA was estimated to be $6.4 billion (133).

15. Obesity challenges: Saudi Vision 2030

Obesity is a major issue in the KSA. Previous research has shown an increase in overweight and obesity rates in the KSA, which are major risk factors for other disorders, including diabetes, obstructive sleep apnoea, hyperlipidaemia and OA (134). The direct healthcare costs of managing overweight- and obesity-related conditions was estimated to be $3.8 billion in 2019, accounting for 4.3% of the total healthcare spending in the KSA (135). In addition, the medical cost of reduced productivity while at work (presenteeism) or absent from work (absenteeism) due to weight-related health issues was estimated to be $15.5 billion in 2019, representing 0.9% of the gross domestic product. Therefore, these findings indicate that obesity and excess weight pose a significant financial burden in the KSA (135).

The KSA aims to reduce the prevalence of obesity by 3% and diabetes by 10% by 2030. To help consumers make improved choices, measures such as mandatory calorie labeling on menus in all food service facilities have been implemented. In addition, as part of a strategy to manage obesity, the implementation of a 50% tax on sugar-sweetened beverages and a 100% levy on energy drinks introduced in 2017 has resulted in the sales of carbonated drinks dropping by 35%. A number of mandatory and optional measures have also been implemented to encourage businesses to reduce the sugar, fat and salt content of their food and beverage products (136). Furthermore several school-based policies have been established with the aim of preventing obesity. For example, a wide range of products are banned from canteens, including sweets, chips, soft drinks and fried food (137). Priority is now also being given to child-focused interventions and the promotion of physical activity in all schools. In 2017, the KSA first permitted physical education in girls' schools and launched ‘Rashaqa’, a promising program implemented in boys' and girls' schools as part of broader efforts to address obesity by improving dietary habits and promoting physical activity (136,137) (Fig. 2).

16. Conclusions and future perspectives

The rising incidence of obesity, a global health concern associated with numerous complications, necessitates creative solutions. The history of pharmacological obesity treatment is long and encompasses notable setbacks. Large-scale, long-term clinical trials in diverse individuals with obesity are costly to conduct and challenging to justify given previous failures. As part of Saudi Vision 2030, a number of measures are being used to lessen the negative effects of obesity on diet and health. The most commonly used AOMs include compounds targeting GLP-1 and amylin, with emerging compounds under investigation targeting GIP, oxyntomodulin and PYY. Promising new strategies in development include stable PYY analogs, improved amylin

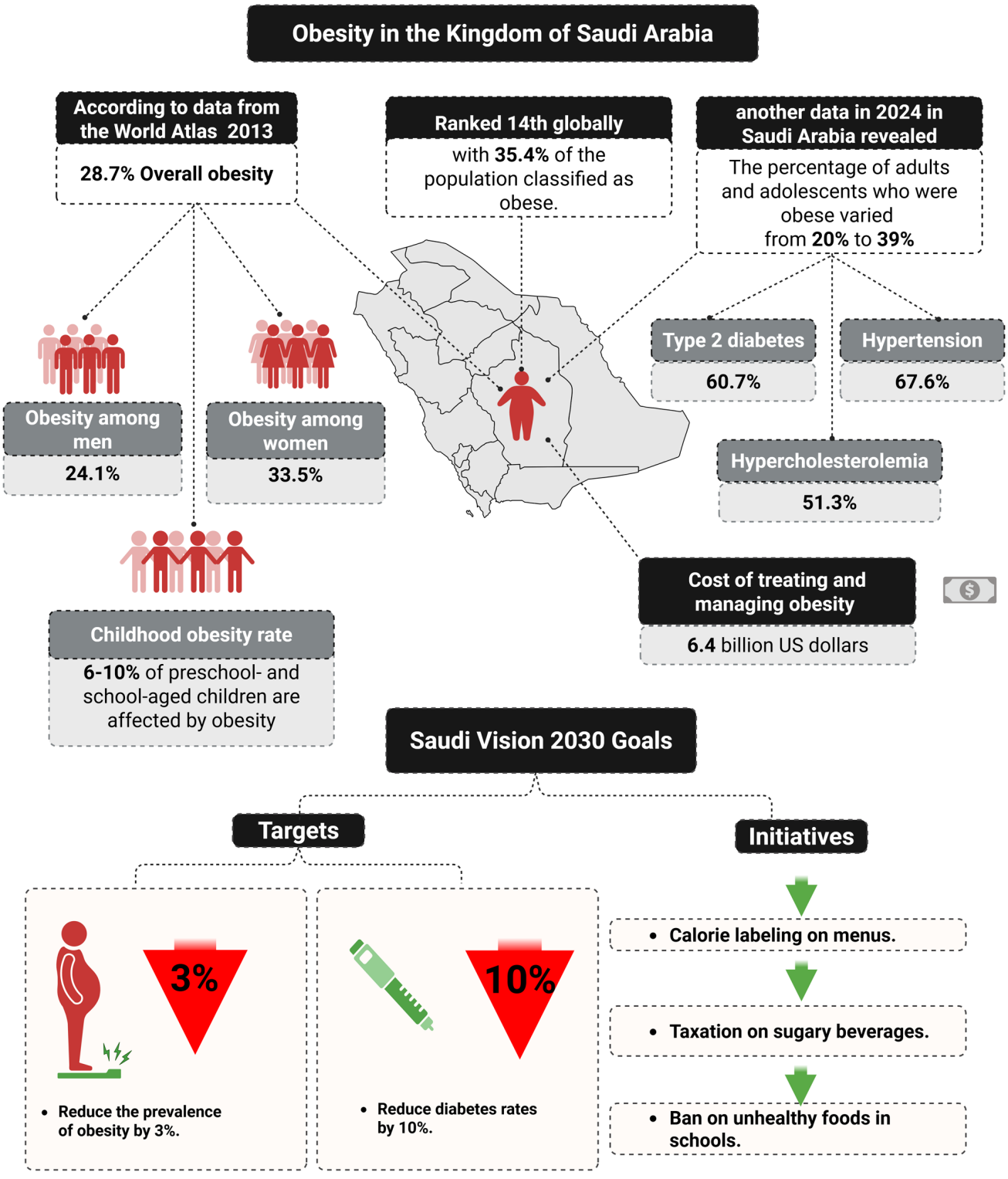

Figure 2. Obesity in the Kingdom of Saudi Arabia and Saudi Vision 2030. This infographic underscores the high prevalence of obesity and overweight in both adults and children, and highlights substantial public health issues. Saudi Vision 2030 is a program that seeks to mitigate these difficulties by targeting a 3% reduction in obesity rates and a 10% reduction in diabetes rates by measures including calorie labeling on menus, taxes on sugary drinks, and the prohibition of unhealthy foods in educational institutions.

analogs and NK2R-targeting agents, which may offer more precise and efficient treatments for the treatment of obesity, particularly in individuals with T2DM. Saxenda, Mounjaro and Ozempic have exhibited significant effects on weight loss and T2DM. Childhood obesity is also a global public health concern; however, only a limited number of AOMs are currently approved to manage this condition under medical supervision. In addition, AOMs have been observed to have positive benefits on cardiovascular risk factors and joint health. Preclinical research suggests that the activation of GPL-1Rs may reduce alcohol and cocaine abuse. Finally, ongoing clinical research aims to ascertain whether certain

AOMs could be as effective as bariatric surgery. In conclusion, ongoing advances in pharmacological development may help to address current challenges and achieve superior outcomes in the treatment of obesity.

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Authors' contributions

AA and SSA were responsible for conception and design. AA, SSA and EHE performed data collection and/or processing, and searched the literature. SSA, EHE, AA, SMA and OD wrote and proofread the review. All authors read and approved the final version of the manuscript. Data authentication was not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

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Competing interests

The authors declare that they have no competing interests.

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