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# GLP-1RA: New Hope in Obesity Therapy

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## Abstract

Obesity has become a global chronic metabolic disease, posing a serious threat to public health. Glucagon-like peptide-1 (GLP-1) is an important hormone secreted by the L cells of the small intestine during food digestion. It plays a key role in maintaining glucose homeostasis, by promoting insulin synthesis and secretion, inhibiting glucagon release, and reducing hepatic glycogen output. Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are analogs of GLP-1 that can resist degradation by DPP4 enzyme. They exert multiple physiological effects by activating the glucagon-like peptide-1 receptor (GLP-1R) and its downstream signaling pathways, including enhancing insulin secretion, suppressing appetite, and slowing gastric emptying. As a new class of weight management drugs, GLP-1RAs have diverse weight loss mechanisms and significant clinical effects. The new GLP-1RA, which has better weight loss, better safety, and improved dosing methods, significantly improves patient compliance. This article systematically summarizes the mechanism of action, efficacy, and safety of GLP-1 receptor agonists in weight loss treatment, aiming to provide new insights and evidence for clinicians when selecting medications for weight reduction.

## Keywords

Glucagon-Like Peptide-1, Glucagon-Like Peptide-1 Receptor Agonists, Obesity, Clinical Application, Adverse Reactions

## 1. Introduction

Obesity is a chronic, progressive disease, and it is easy to relapse after successful weight loss. The imbalance between energy intake and expenditure is the fundamental cause of obesity [1]. Unhealthy eating habits, such as excessive intake of high-calorie, high-fat, and high-sugar foods, as well as unreasonable dietary structures and reduced levels of physical activity, can all lead to excess energy intake,

thereby causing obesity [2]. Genetic factors also play an important role, and individuals with obese family members are more likely to develop obesity [3]. The global obesity prevalence has been rising continuously over the past few decades, and the latest data show that currently, more than 1 billion people worldwide suffer from obesity, including about 880 million adults and 159 million children and adolescents [4]. Since 1990, the number of adults with obesity worldwide has more than doubled, and the number of children and adolescents (aged 5 to 19) with obesity has increased threefold [5]. The total number of children, adolescents, and adults with obesity worldwide has now exceeded 1 billion [6]. According to the WHO definition, a body mass index (BMI, *i.e.*, weight (kilograms) divided by height (meters) squared) greater than or equal to 25 is considered overweight, and greater than or equal to 30 is considered obese (shown in **Table 1**). In 2022, about 43% of adults worldwide were overweight, and 16% had obesity. In China, the obesity rate is also increasing across all age groups. Among 15.8 million adult subjects, 34.8% were overweight and 14.1% were obese, with the overall proportion of overweight individuals at 34.8% and obese individuals at 14.1% [7].

**Table 1.** Classification of adult body weight based on the WHO BMI.

| BMI (kg/m$^2$) | Classification |
|---|---|
| <18.5 | Underweight |
| 18.5 - 24.9 | Normal Weight |
| 25.0 - 29.9 | Overweight |
| ≥30.0 | Obesity |

Obesity is a high-risk factor for type 2 diabetes, dyslipidemia, hypertension, cardiovascular diseases, kidney diseases, non-alcoholic fatty liver disease, osteoarthritis, and other metabolic diseases [8] [9]. Obesity can also lead to male sexual dysfunction, male infertility [10] [11], female menstrual irregularities, female infertility, hypertensive disorders of pregnancy, gestational diabetes, preterm birth, and stillbirth [12] [13]. At the same time, it is significantly associated with the risk of certain cancers (such as breast cancer, colorectal cancer, endometrial cancer, liver cancer, ovarian cancer, and pancreatic cancer) [14]. It is estimated that high body mass index (BMI) is closely related to the deaths of about 4 million people worldwide, among which cardiovascular diseases account for the majority. Obesity poses a huge threat to public health [15]. This also urgently calls for us to take effective intervention measures to prevent and control the development of overweight, obesity, and their related complications. At present, the main ways to lose weight include exercise [16], diet [17], drug [18] and surgery [19]. Exercise and dietary interventions are the preferred methods for controlling body weight [20]. However, lifestyle adjusting usually only leads to a little weight loss, achieving a weight reduction of 3% - 10%. This weight loss effect is often difficult to maintain in the long term, and the body mass is prone to regain [21]. Most people return their weight after 12 months, and only 2% - 20% of long-term weight loss through

lifestyle modification is successful [22]. So the use of weight-loss drugs is worth considering. The FDA-approved weight-loss drugs include sympathomimetic inhibitors, pancreatic lipase inhibitors, GABAA receptor activators, serotonin 2C receptor agonists, opioid antagonists, dopamine-norepinephrine reuptake inhibitors, and glucagon-like peptide-1 (GLP-1) receptor agonists [23].

## 2. Mechanism of GLP-1RA

Glucagon-like peptide-1 (GLP-1) is an endogenous incretin secreted by the L cells of the small intestine and consists of two bioactive isoforms: GLP-1 (7-37), GLP-1 (7-36). GLP-1 is rapidly degraded by an enzyme called dipe: GLP-1 (9-36), GLP-1 (9-37) [24]. GLP-1 exerts its functions by binding to the glucagon-like peptide-1 receptor (GLP-1R) and is involved in the development and progression of many diseases [25] [26]. The GLP-1R is a transmembrane G protein-coupled receptor family B, discovered in pancreatic B cells, but also distributed in extrapancreatic tissues, including the lung, kidney, central nervous system, enteric nervous system, lymphocytes, blood vessels, and kidneys [27] [28]. The interaction between GLP-1 and GLP-1R exerts multiple physiological functions, including promoting insulin synthesis and secretion, inhibiting the production and release of glucagon by pancreatic islet cells, and reducing hepatic glycogen output, by activating different downstream signaling molecules [29]-[31]. GLP-1R agonists (GLP-1RA) are a group of GLP-1 analogs that are resistant to DPP4 relevant degradation, and exert their effects by activating the GLP-1R and its signaling pathways. They enhance insulin secretion, inhibit glucagon release, slow gastric emptying, reduce appetite and food intake, conduce lower blood glucose and reduce body weight [32]. These make GLP-1RA to be an effective drug for the treatment of type 2 diabetes (T2DM) and other related metabolic diseases. Many studies have shown that the GLP-1/GLP-1R signaling is also involved in the regulation of adipocyte differentiation and lipogenesis [33]. Its influence in adjusting energy balance and body weight has gradually attracted attention [34].

GLP-1RA weight loss mechanisms are diverse. For example, anorexigenic effects can be produced by activating GLP-1 receptors in the brain [35], and signaling mediated by GLP-1 receptors at the level of intramuscular neurons, involving nitric oxide and cAMP-dependent mechanisms, inhibiting vagal activity, thereby reducing the phasic contractions of the stomach, delaying gastric emptying, and reducing gastric acid secretion [36]. It is worth mentioning that GLP-1RAs can increase the expression of receptors in neurons related to the ventral tegmental area, nucleus accumbens, and lateral septum, reduce the intake of high-sugar and high-fat foods by regulating brain regions associated with reward and pleasure, thereby controlling body weight [37] [38]. It can also modulate the gut microbiota [39], delay gastric emptying to increase satiety [40], and induce browning of white adipose tissue through a soluble guanylate cyclase-dependent pathway, activate the adenylate cyclase pathway to lose weight [41]. In addition, its weight loss effect may be related to the activation of SIRT1 in adipose tissue [42], SIRT1 is a

deacetylase, and its activation can promote mitochondrial biogenesis and respiration, thereby promoting lipolysis and increasing fat breakdown [43]. In terms of promoting lipid mobilization, it can improve lipid metabolism and hepatic lipid accumulation in mice by promoting reverse cholesterol transport via ABCA1 upregulation mediated by ERK1/2 phosphorylation [44]. Our previous studies have found that GLP-1RAs can reduce body weight by inhibiting lipid synthesis and enhancing fatty acid $\beta$-oxidation through the HIF-2α/PPARα pathway, while also improving hepatic lipid metabolism [45]. In addition to promoting lipid mobilization, GLP-1RA treatment in mice has been shown to significantly reduce the weight of total body fat, brown fat, subcutaneous fat, and visceral fat. The ceramide content in various types of fat tissue was lower than that in the control group, which may inhibit ceramide synthesis, reduce its content, and thereby promote the browning and thermogenesis of adipose tissue. Moreover, GLP-1RA significantly reduced the adipocyte volume in obese mice while maintaining a nearly constant number of adipocytes, resulting in a significant reduction in body fat weight. Additionally, the expression of genes involved in lipogenesis, such as Acly, Accα1, and Fasn, was decreased, while the expression of genes involved in lipolysis, such as Lipe and Pnpla2, was upregulated [46]. These findings indicate that GLP-1RAs not only suppress appetite and delay gastric emptying but also play a positive role in altering food preferences, regulating energy metabolism, and promoting fat breakdown.

## 3. Classification of GLP-1RA

GLP-1RAs can be classified into short-acting and long-acting formulations based on their duration of action (shown in **Table 2**). Short-acting formulations require daily injection, while long-acting formulations have a lower injection frequency,

**Table 2.** The common GLP-1RAs.

| Drug Name | Category | Molecular Structure | Half-life |
|---|---|---|---|
| Exenatide | Short-acting | Exendin-4 | 2.4 h |
| Beinaglutide | Short-acting | Recombinant human GLP-1 | 11 min |
| Lixisenatide | Long-acting | Modified Exendin-4 | 3 h |
| Liraglutide | Long-acting | Recombinant human GLP-1 | 13 h |
| Semaglutide (Injection) | Ultra-long-acting | Recombinant human GLP-1 | 7 days |
| Dulaglutide | Ultra-long-acting | Recombinant human GLP-1 | 4.7 days |
| Exenatide Microspheres | Ultra-long-acting | Exendin-4 | 2.4 h (extended-release) |
| Polyethylene Glycol Loxenatide | Ultra-long-acting | Chemically synthesized GLP-1 | 144 - 155 h |
| Tirzepatide | Ultra-long-acting | Modified GIP/GLP-1 | 116.7 h |
| Masutotide | Ultra-long-acting | Modified GIP/GLP-1 | 174.8 - 1075.7 h |
| Semaglutide (Oral) | Ultra-long-acting | Recombinant human GLP-1 | 7 days |

**Continued**

| Drug Name | Frequency of Administration | Initial Dose | Usual Dose | Route of Administration |
|---|---|---|---|---|
| Exenatide | Bid | 5 μg bid | 5 μg or 10 μg bid | Subcutaneous injection |
| Beinaglutide | Tid | 0.1 mg tid | 0.1 mg or 0.2 mg tid | Subcutaneous injection |
| Lixisenatide | Qd | 10 μg qd | 20 μg qd | Subcutaneous injection |
| Liraglutide | Qd | 0.6 mg qd | 1.2 mg or 1.8 mg qd | Subcutaneous injection |
| Semaglutide (Injection) | Qw | 0.25 mg qw | 0.5 mg or 1 mg qw | Subcutaneous injection |
| Dulaglutide | Qw | 0.75 mg qw | 0.75 mg or 1.5 mg qw | Subcutaneous injection |
| Exenatide Microspheres | Qw | 2 mg qw | 2 mg qw | Subcutaneous injection |
| Polyethylene Glycol Loxenatide | Qw | 0.1 mg qw | 0.1 mg or 0.2 mg qw | Subcutaneous injection |
| Tirzepatide | Qw | 2.5 mg qw | 10 or 15 mg qw | Subcutaneous injection |
| Masutotide | Qw | 2.5 mg qw | 10 mg or 15 mg qw | Subcutaneous injection |
| Semaglutide (Oral) | Qd | 3 mg qd | 7 mg or 14 mg qd | oral |

such as weekly or monthly injections. Currently approved short-acting GLP-1RAs in the domestic market include exenatide, beinaglutide, and liraglutide, while long-acting GLP-1RAs include dulaglutide, semaglutide, polyethylene glycol loxenatide, exenatide microsphere, and dual-target GLP-1R/GIPR drugs such as tirzepatide and masutotide.

## 4. The Weight Loss Effect of GLP-1RA

GLP-1RAs have shown impressive weight loss efficacy in people with type 2 diabetes. Research indicates that lixisenatide can lower BMI [47]. A meta-analysis has validated that lixisenatide treatment results in significant weight and BMI reductions compared to placebo [48] [49]. In a Phase III study, patients treated with various doses of liraglutide (1.2 mg to 3.0 mg) had an average weight loss of 5% - 10% compared to the placebo group [50]. Clinical trials in children aged 6 to 12 years demonstrated that liraglutide treatment combined with lifestyle intervention was more effective in reducing BMI than placebo plus lifestyle intervention [51]. A Japanese prospective case study indicated that daily treatment with 0.9mg of liraglutide for 24 weeks in obese patients with type 2 diabetes reduced body fat and achieved different levels of reduction in visceral and liver fat [52]. In a clinical study, compared with the control group, participants using semaglutide continuously had a weight loss of up to 18.2%, with an average reduction of 17.8 kg. Combining semaglutide with a low-calorie diet and appropriate exercise resulted in a significant and sustained weight loss of 15.2% [53]. Another randomized, double-blind, placebo-controlled study showed that semaglutide not only reduced cardiovascular event risk but also demonstrated sustained weight loss in overweight or obese adults with cardiovascular disease risk. Over the 208-week study period, patients in the treatment group had an average weight loss of 10.2%, a waist circumference reduction of 7.7 cm, and a 6.9% decrease in waist-to-height ratio, which

reflects abdominal fat accumulation [54]. Clinical trials of semaglutide in adolescents with obesity also demonstrated significant weight loss, with an average BMI reduction of 16.1% compared to baseline [55]. Compared with injectable formulations, oral formulations demonstrated similar effects on blood sugar, blood pressure, and lipid regulation. After 68 weeks of treatment with 50 mg of oral semaglutide once daily, the average weight of obese or overweight patients decreased by 15.1% [56]. A Phase III clinical trial in China demonstrated that beinaglutide treatment resulted in an average weight loss of 10.05 kg, with reductions in waist and hip circumference. The weight regain rate 12 weeks after discontinuing beinaglutide treatment was only 0.78% [57]. In a study, dulaglutide treatment for 54 weeks led to significant improvements in glycemic control and weight reduction [58]. The weight loss efficacy of dulaglutide is dose-dependent, with more pronounced effects at the 1.5 mg [59]. Recent research indicates that GLP-1/GCGR dual agonists are more effective for weight loss than GLP-1 agonists alone, with tirzepatide showing superior efficacy in reducing HbA1c and body weight in type 2 diabetes patients [60]. In a 72-week trial, participants receiving 15mg of tirzepatide experienced an average weight loss of 22.5%, or about 24 kg, which confirms that tirzepatide is the most effective weight loss agent reported to date [61].

In addition, 36 randomized clinical trials have shown that obese individuals without diabetes can achieve significant weight loss through GLP-1RA treatment [62]. Research indicates that exenatide is effective for weight loss in both patients with type 2 diabetes and obese individuals without diabete. In a study, non-diabetic obese women experienced an average weight loss of 2.49kg and a significant decrease in waist circumference [63]-[65]. Thus, GLP-1RA can effectively induce weight loss in adults with obesity or overweight, regardless of diabetes status.

## 5. Adverse Effects of GLP-1RA Drugs

GLP-1RA, as a widely used class of antidiabetic drugs, can induce a series of adverse reactions despite their remarkable therapeutic effects. The most frequent gastrointestinal symptoms of GLP-1RA include nausea, vomiting, and diarrhea, with some patients also reporting constipation, indigestion, and abdominal pain, likely due to the drug's effects on gastrointestinal motility and individual variability, Symptoms can be mitigated through improved dietary habits, lifestyle modifications, and changes in administration methods. Initiating treatment with a low dose and titrating up based on patient tolerance can help minimize adverse reactions [66]. There is evidence that GLP-1RA use can significantly increase the risk of cholecystitis, gallstones, and biliary diseases, especially with higher doses and longer treatment durations [67]. In non-diabetic obese patients, the use of GLP-1 RA (liraglutide/semaglutide) has been shown to increase the risk of pancreatitis, intestinal obstruction, and gastroparesis, but not the risk of biliary diseases like cholecystitis, gallstones, and common bile duct stones [68]. Thus, the relationship between GLP-1RA and the risk of cholecystitis or gallstones is still uncertain and needs further research to clarify [69]. Reports have shown that after 28 days of

treatment with GLP-1RA, heart rate may increase slightly, typically by 2 - 4 beats per minute. This effect may be due to the direct action of GLP-1RA on the sino-atrial node or stimulation of the sympathetic nervous system [70]. Injection site reactions, including pain, redness, and hardening, are common local adverse effects of GLP-1RA. These reactions may be associated with injection techniques, drug concentration, and individual variability [71]. To mitigate these reactions, it is recommended to use different injection sites and improve injection techniques [72]. In extremely rare cases, GLP-1RA can cause allergic reactions, such as rashes, itching, and difficulty breathing, and even anaphylaxis. Therefore, patients with a history of allergies should be particularly cautious when using GLP-1RA. In recent years, there have been reports that GLP-1RA may cause neurological symptoms in a very small number of patients, such as tension, anxiety, and insomnia [73]. The specific mechanisms underlying these symptoms are not yet clear.

## 6. Combination of GLP-1RA with Other Drugs

Of course, the combination of GLP-1RA with other drugs or treatment modalities has also shown significant advantages in the treatment of obesity and related metabolic diseases. The combination of dulaglutide and dapagliflozin significantly improves metabolic parameters in overweight and obese type 2 diabetes patients, including reduced body weight, BMI, waist-to-hip ratio, visceral fat area, and visceral fat index [74]. One study compared the cardiorenal effects of an SGLT2 inhibitor (SGLT2i) with GLP-1RA in combination with monotherapy. The results showed significant advantages in lowering blood glucose, reducing body weight, and improving cardiovascular and renal outcomes [75]. Compared with metformin monotherapy, the combination of Semaglutide and metformin significantly improved liver inflammation, fibrosis, and $\beta$ cell function in patients with T2DM and NAFLD [76].

Studies have found that all GLP-1 drugs are beneficial for weight loss. The combination of GLP-1RA with other drugs has shown significant results in weight loss, further enhancing and improving cardiovascular and liver health through multi-mechanism synergies. GLP-1RA, alone or in combination, is associated with relative and absolute weight loss, and the magnitude of weight loss varies between drugs. However, the combination of drugs can achieve better therapeutic effects at lower doses, thereby reducing the side effects of a single drug [77]. Future studies will continue to explore the long-term efficacy and safety of the combination, as well as the prospects for its use in different patient populations.

## 7. Future Perspectives

Weight loss is now recognized as a multifaceted, scientific, and individualized process that encompasses diet, exercise, medical interventions, and psychological support. Current drug development efforts primarily target reducing energy intake and enhancing fat combustion and energy expenditure to induce weight loss [78]-[82].

The application of GLP-1 RA drugs in the field of weight loss is of great clinical

significance, which not only achieves significant weight loss, but also improves the metabolic health of patients, reduces liver inflammation, and expands the scope of clinical application. These strengths position GLP-1RA as a crucial option for treating obesity. The evolution from single-target GLP-1R to dual-target GLP-1R/GCGR, GLP-1R/GIPR, and back to GLP-1R/GCGR, and then to triple-target GLP-1R/GCGR/GIPR and the latest GLP-1R/GCGR/FGF21R has not only raised the bar for new drug development but also provided patients with more diverse and efficient treatment options [83].

In addition, a groundbreaking study by the team of Ana I. Domingos at the University of Oxford has shown that neuropeptide Y (NPY) can regulate thermogenic fat tissue through specific neural pathways, promoting the release of energy as heat, thereby effectively combating obesity without reducing food intake [84]. This discovery paves the way for developing weight loss therapies that do not rely on dietary restrictions. A research team at the University of Bonn has explored the functions of brown fat cells and found that adenosine released from apoptotic brown fat cells can not only increase the basal metabolic rate but also promote thermogenesis in healthy brown fat cells and induce the browning of white fat tissue, thereby combating obesity [85]. Meanwhile, a research team at the University of California, San Diego, has revealed the critical role of glycogen metabolism in the energy balance of fat cells. Their research shows that glycogen metabolism is not only an important process for energy storage and mobilization but also directly affects the thermogenic function of fat tissue [86]. The research team led by Professor Yin Zhinan at Jinan University has focused on the immune molecule IL-27, finding that it can directly act on fat cells to promote their browning and enhance thermogenesis [87]. This mechanism helps to reduce body weight by accelerating lipid combustion. With the development of more novel drugs and the advancement of clinical trials, GLP-1RA are expected to provide more effective treatment options for patients with obesity and metabolic diseases. However, there are also some potential challenges to its application, including drug side effects, treatment costs, and long-term safety issues. Future research needs to optimize drug design further and reduce side effects, while exploring more economical treatment options to improve drug access and patient compliance. In addition, there is a need for enhanced regulation and research on the off-label use and long-term safety of GLP-1RA. We look forward to the discovery of more therapeutic targets related to obesity and the development of safer and more efficient weight loss drugs in the future, bringing more innovation and hope for global obesity and related diseases.

## Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

## References

[1] Romieu, I., Dossus, L., Barquera, S., Blottière, H.M., Franks, P.W., Gunter, M., *et al.*

(2017) Energy Balance and Obesity: What Are the Main Drivers? *Cancer Causes & Control*, **28**, 247-258. https://doi.org/10.1007/s10552-017-0869-z

[2] Al-Jawaldeh, A. and Abbass, M.M.S. (2022) Unhealthy Dietary Habits and Obesity: The Major Risk Factors Beyond Non-Communicable Diseases in the Eastern Mediterranean Region. *Frontiers in Nutrition*, **9**, Article 817808. https://doi.org/10.3389/fnut.2022.817808

[3] Mahmoud, R., Kimonis, V. and Butler, M.G. (2022) Genetics of Obesity in Humans: A Clinical Review. *International Journal of Molecular Sciences*, **23**, 11005. https://doi.org/10.3390/ijms231911005

[4] Phelps, N.H., Singleton, R.K., Zhou, B., Heap, R.A., Mishra, A., Bennett, J.E., *et al.* (2024) Worldwide Trends in Underweight and Obesity from 1990 to 2022: A Pooled Analysis of 3663 Population-Representative Studies with 222 Million Children, Adolescents, and Adults. *The Lancet*, **403**, 1027-1050. https://doi.org/10.1016/s0140-6736(23)02750-2

[5] Zhou, B., Sorić, M., Ahmadi, A., *et al.* (2024) Worldwide Trends in Underweight and Obesity from 1990 to 2022: A Pooled Analysis of 3663 Population-Representative Studies with 222 Million Children, Adolescents, and Adults. *The Lancet* (*British Edition*), **403**, 1027-1050.

[6] Jehan, S., Zizi, F., Pandi-Perumal, S.R., McFarlane, S.I., Jean-Louis, G. and K Myers, A. (2020) Energy Imbalance: Obesity, Associated Comorbidities, Prevention, Management and Public Health Implications. *Advances in Obesity, Weight Management & Control*, **10**, 146-161. https://doi.org/10.15406/aowmc.2020.10.00321

[7] Chen, K., Shen, Z., Gu, W., Lyu, Z., Qi, X., Mu, Y., *et al.* (2023) Prevalence of Obesity and Associated Complications in China: A Cross-Sectional, Real-World Study in 15.8 Million Adults. *Diabetes, Obesity and Metabolism*, **25**, 3390-3399. https://doi.org/10.1111/dom.15238

[8] Piché, M., Tchernof, A. and Després, J. (2020) Obesity Phenotypes, Diabetes, and Cardiovascular Diseases. *Circulation Research*, **126**, 1477-1500. https://doi.org/10.1161/circresaha.120.316101

[9] Chandrasekaran, P. and Weiskirchen, R. (2024) The Role of Obesity in Type 2 Diabetes Mellitus—An Overview. *International Journal of Molecular Sciences*, **25**, Article 1882. https://doi.org/10.3390/ijms25031882

[10] Service, C.A., Puri, D., Al Azzawi, S., Hsieh, T. and Patel, D.P. (2023) The Impact of Obesity and Metabolic Health on Male Fertility: A Systematic Review. *Fertility and Sterility*, **120**, 1098-1111. https://doi.org/10.1016/j.fertnstert.2023.10.017

[11] Qi, R.B., Chen, B., Li, Z.M., *et al.* (2023) Research Progress on the Effects of Obesity on Male Reproductive Health. Chinese *Journal of Endocrinology and Metabolism*, **39**, 1083-1088. https://doi.org/10.3760/cma.j.cn311282-20230511-00219

[12] Broughton, D.E. and Moley, K.H. (2017) Obesity and Female Infertility: Potential Mediators of Obesity's Impact. *Fertility and Sterility*, **107**, 840-847. https://doi.org/10.1016/j.fertnstert.2017.01.017

[13] Davidson, K.W., Barry, M.J., Mangione, C.M., Cabana, M., Caughey, A.B., Davis, E.M., *et al.* (2021) Behavioral Counseling Interventions for Healthy Weight and Weight Gain in Pregnancy: US Preventive Services Task Force Recommendation Statement. *JAMA*, **325**, 2087-2093. https://doi.org/10.1001/jama.2021.6949

[14] Pati, S., Irfan, W., Jameel, A., Ahmed, S. and Shahid, R.K. (2023) Obesity and Cancer: A Current Overview of Epidemiology, Pathogenesis, Outcomes, and Management. *Cancers*, **15**, Article 485. https://doi.org/10.3390/cancers15020485

[15] Zhang, H., Zhou, X., Shapiro, M.D., *et al.* (2024) Global Burden of Metabolic Diseases, 1990-2021. *Metabolism: Clinical and Experimental*, **160**, Article ID: 155999.

[16] Lopez, P., Taaffe, D.R., Galvão, D.A., Newton, R.U., Nonemacher, E.R., Wendt, V.M., *et al.* (2022) Resistance Training Effectiveness on Body Composition and Body Weight Outcomes in Individuals with Overweight and Obesity across the Lifespan: A Systematic Review and Meta-Analysis. *Obesity Reviews*, **23**, e13428. https://doi.org/10.1111/obr.13428

[17] Cheng, X., Sun, S., Chen, M., Zhou, X., Rao, M., Guo, D., *et al.* (2024) Evaluating the Efficacy of Intermittent Fasting and Exercise Combinations for Weight Loss: A Network Meta-Analysis. *Obesity Reviews*, **25**, e13834. https://doi.org/10.1111/obr.13834

[18] Gudzune, K.A. and Kushner, R.F. (2024) Medications for Obesity: A Review. *JAMA*, **332**, 571-584. https://doi.org/10.1001/jama.2024.10816

[19] Perdomo, C.M., Cohen, R.V., Sumithran, P., Clément, K. and Frühbeck, G. (2023) Contemporary Medical, Device, and Surgical Therapies for Obesity in Adults. *The Lancet*, **401**, 1116-1130. https://doi.org/10.1016/s0140-6736(22)02403-5

[20] Xie, Y., Gu, Y., Li, Z., He, B. and Zhang, L. (2024) Effects of Different Exercises Combined with Different Dietary Interventions on Body Composition: A Systematic Review and Network Meta-analysis. *Nutrients*, **16**, Article 3007. https://doi.org/10.3390/nu16173007

[21] Machado, A.M., Guimarães, N.S., Bocardi, V.B., da Silva, T.P.R., Carmo, A.S.D., Menezes, M.C.D., *et al.* (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

[22] Wing, R.R. and Phelan, S. (2005) Long-Term Weight Loss Maintenance. *The American Journal of Clinical Nutrition*, **82**, 222S-225S. https://doi.org/10.1093/ajcn/82.1.222s

[23] Bessesen, D.H. and Van Gaal, L.F. (2018) Progress and Challenges in Anti-Obesity Pharmacotherapy. *The Lancet Diabetes & Endocrinology*, **6**, 237-248. https://doi.org/10.1016/s2213-8587(17)30236-x

[24] Mahapatra, M.K., Karuppasamy, M. and Sahoo, B.M. (2022) Semaglutide, a Glucagon Like Peptide-1 Receptor Agonist with Cardiovascular Benefits for Management of Type 2 Diabetes. *Reviews in Endocrine and Metabolic Disorders*, **23**, 521-539. https://doi.org/10.1007/s11154-021-09699-1

[25] Li, Q., Gao, H., Guo, Y., Wang, B., Hua, R., Gao, L., *et al.* (2021) GLP-1 and Underlying Beneficial Actions in Alzheimer's Disease, Hypertension, and Nash. *Frontiers in Endocrinology*, **12**, Article 721198. https://doi.org/10.3389/fendo.2021.721198

[26] Nauck, M.A., Quast, D.R., Wefers, J. and Pfeiffer, A.F.H. (2021) The Evolving Story of Incretins (GIP and GLP-1) in Metabolic and Cardiovascular Disease: A Pathophysiological Update. *Diabetes, Obesity and Metabolism*, **23**, 5-29. https://doi.org/10.1111/dom.14496

[27] Hogan, A.E., Tobin, A.M., Ahern, T., Corrigan, M.A., Gaoatswe, G., Jackson, R., *et al.* (2011) Glucagon-like Peptide-1 (GLP-1) and the Regulation of Human Invariant Natural Killer T Cells: Lessons from Obesity, Diabetes and Psoriasis. *Diabetologia*, **54**, 2745-2754. https://doi.org/10.1007/s00125-011-2232-3

[28] Nagae, K., Uchi, H., Morino-Koga, S., Tanaka, Y., Oda, M. and Furue, M. (2018) Glucagon-Like Peptide-1 Analogue Liraglutide Facilitates Wound Healing by Activating PI3K/Akt Pathway in Keratinocytes. *Diabetes Research and Clinical Practice*, **146**, 155-161. https://doi.org/10.1016/j.diabres.2018.10.013

[29] Sandoval, D. (2008) CNS GLP-1 Regulation of Peripheral Glucose Homeostasis. *Physiology & Behavior*, **94**, 670-674. https://doi.org/10.1016/j.physbeh.2008.04.018

[30] Chen, J., Zhao, H., Ma, X., Zhang, Y., Lu, S., Wang, Y., *et al.* (2017) GLP-1/GLP-1R Signaling in Regulation of Adipocyte Differentiation and Lipogenesis. *Cellular Physiology and Biochemistry*, **42**, 1165-1176. https://doi.org/10.1159/000478872

[31] Burmeister, M.A., Brown, J.D., Ayala, J.E., Stoffers, D.A., Sandoval, D.A., Seeley, R.J., *et al.* (2017) The Glucagon-Like Peptide-1 Receptor in the Ventromedial Hypothalamus Reduces Short-Term Food Intake in Male Mice by Regulating Nutrient Sensor Activity. *American Journal of Physiology-Endocrinology and Metabolism*, **313**, E651-E662. https://doi.org/10.1152/ajpendo.00113.2017

[32] Nauck, M. (2016) Incretin Therapies: Highlighting Common Features and Differences in the Modes of Action of Glucagon-Like Peptide-1 Receptor Agonists and Dipeptidyl Peptidase-4 Inhibitors. *Diabetes, Obesity and Metabolism*, **18**, 203-216. https://doi.org/10.1111/dom.12591

[33] Costa, A., Ai, M., Nunn, N., Culotta, I., Hunter, J., Boudjadja, M.B., *et al.* (2022) Anorectic and Aversive Effects of GLP-1 Receptor Agonism Are Mediated by Brainstem Cholecystokinin Neurons, and Modulated by GIP Receptor Activation. *Molecular Metabolism*, **55**, Article ID: 101407. https://doi.org/10.1016/j.molmet.2021.101407

[34] Drucker, D.J. (2022) GLP-1 Physiology Informs the Pharmacotherapy of Obesity. *Molecular Metabolism*, **57**, Article ID: 101351. https://doi.org/10.1016/j.molmet.2021.101351

[35] Fortin, S.M., Lipsky, R.K., Lhamo, R., Chen, J., Kim, E., Borner, T., *et al.* (2020) GABA Neurons in the Nucleus Tractus Solitarius Express GLP-1 Receptors and Mediate Anorectic Effects of Liraglutide in Rats. *Science Translational Medicine*, **12**, eaay8071. https://doi.org/10.1126/scitranslmed.aay8071

[36] Halim, M.A., Degerblad, M., Sundbom, M., Karlbom, U., Holst, J.J., Webb, D., *et al.* (2017) Glucagon-Like Peptide-1 Inhibits Prandial Gastrointestinal Motility through Myenteric Neuronal Mechanisms in Humans. *The Journal of Clinical Endocrinology & Metabolism*, **103**, 575-585. https://doi.org/10.1210/jc.2017-02006

[37] Chen, Z., Deng, X., Shi, C., Jing, H., Tian, Y., Zhong, J., *et al.* (2024) GLP-1R-Positive Neurons in the Lateral Septum Mediate the Anorectic and Weight-Lowering Effects of Liraglutide in Mice. *Journal of Clinical Investigation*, **134**, e178239. https://doi.org/10.1172/jci178239

[38] Reiner, D.J., Leon, R.M., McGrath, L.E., Koch-Laskowski, K., Hahn, J.D., Kanoski, S.E., *et al.* (2017) Glucagon-Like Peptide-1 Receptor Signaling in the Lateral Dorsal Tegmental Nucleus Regulates Energy Balance. *Neuropsychopharmacology*, **43**, 627-637. https://doi.org/10.1038/npp.2017.225

[39] Zeng, Y., Wu, Y., Zhang, Q. and Xiao, X. (2024) Crosstalk between Glucagon-Like Peptide 1 and Gut Microbiota in Metabolic Diseases. *mBio*, **15**, e203223. https://doi.org/10.1128/mbio.02032-23

[40] Aldawsari, M., Almadani, F.A., Almuhammadi, N., Algabsani, S., Alamro, Y. and 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*, **16**, 575-595. https://doi.org/10.2147/dmso.s387116

[41] Zhu, E., Yang, Y., Zhang, J., Li, Y., Li, C., Chen, L., *et al.* (2016) Liraglutide Suppresses Obesity and Induces Brown Fat-Like Phenotype via Soluble Guanylyl Cyclase Mediated Pathway *in Vivo* and *in Vitro*. *Oncotarget*, **7**, 81077-81089. https://doi.org/10.18632/oncotarget.13189

[42] Lin, B.S., Xv, H.X., Liang, H., *et al.* (2015) Effect and Mechanism of GLP-1 Receptor Agonists on Adipose Tissue in Obese Mice. *Chinese Journal of Pathophysiology*, **31**, 2021-2026.

[43] Yu, P., Xu, X., Zhang, J., Xia, X., Xu, F., Weng, J., *et al.* (2019) Liraglutide Attenuates Nonalcoholic Fatty Liver Disease through Adjusting Lipid Metabolism via SHP1/AMPK Signaling Pathway. *International Journal of Endocrinology*, **2019**, Article ID: 1567095. https://doi.org/10.1155/2019/1567095

[44] Wu, Y., Shi, X., Ma, C., Zhang, Y., Xu, R. and Li, J. (2019) Liraglutide Improves Lipid Metabolism by Enhancing Cholesterol Efflux Associated with ABCA1 and ERK1/2 Pathway. *Cardiovascular Diabetology*, **18**, Article No. 146. https://doi.org/10.1186/s12933-019-0954-6

[45] Wang, H., Wang, L., Li, Y., Luo, S., Ye, J., Lu, Z., *et al.* (2021) The Hif-2α/pparα Pathway Is Essential for Liraglutide-Alleviated, Lipid-Induced Hepatic Steatosis. *Biomedicine & Pharmacotherapy*, **140**, Article ID: 111778. https://doi.org/10.1016/j.biopha.2021.111778

[46] Zhang, F., Chen, Z., Wu, D., Tian, L., Chen, Q., Ye, Y., *et al.* (2021) Recombinant Human GLP-1 Beinaglutide Regulates Lipid Metabolism of Adipose Tissues in Diet-Induced Obese Mice. *iScience*, **24**, Article ID: 103382. https://doi.org/10.1016/j.isci.2021.103382

[47] Kelly, A.S., Rudser, K.D., Nathan, B.M., Fox, C.K., Metzig, A.M., Coombes, B.J., *et al.* (2013) The Effect of Glucagon-Like Peptide-1 Receptor Agonist Therapy on Body Mass Index in Adolescents with Severe Obesity: A Randomized, Placebo-Controlled, Clinical Trial. *JAMA Pediatrics*, **167**, 355-360. https://doi.org/10.1001/jamapediatrics.2013.1045

[48] Tsapas, A., Karagiannis, T., Kakotrichi, P., Avgerinos, I., Mantsiou, C., Tousinas, G., *et al.* (2021) Comparative Efficacy of Glucose-Lowering Medications on Body Weight and Blood Pressure in Patients with Type 2 Diabetes: A Systematic Review and Network Meta-analysis. *Diabetes, Obesity and Metabolism*, **23**, 2116-2124. https://doi.org/10.1111/dom.14451

[49] Sheng, L., Deng, M., Li, X., Wan, H., Lei, C., Prabahar, K., *et al.* (2024) The Effect of Subcutaneous Lixisenatide on Weight Loss in Patients with Type 2 Diabetes Mellitus: Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Diabetes Research and Clinical Practice*, **210**, Article ID: 111617. https://doi.org/10.1016/j.diabres.2024.111617

[50] Pi-Sunyer, X., Astrup, A., Fujioka, K., Greenway, F., Halpern, A., Krempf, M., *et al.* (2015) A Randomized, Controlled Trial of 3.0 mg of Liraglutide in Weight Management. *New England Journal of Medicine*, **373**, 11-22. https://doi.org/10.1056/nejmoa1411892

[51] Fox, C.K., Barrientos-Pérez, M., Bomberg, E.M., Dcruz, J., Gies, I., Harder-Lauridsen, N.M., *et al.* (2025) Liraglutide for Children 6 to <12 Years of Age with Obesity—A Randomized Trial. *New England Journal of Medicine*, **392**, 555-565. https://doi.org/10.1056/nejmoa2407379

[52] Ishii, S., Nagai, Y., Sada, Y., Fukuda, H., Nakamura, Y., Matsuba, R., *et al.* (2019) Liraglutide Reduces Visceral and Intrahepatic Fat without Significant Loss of Muscle Mass in Obese Patients with Type 2 Diabetes: A Prospective Case Series. *Journal of Clinical Medicine Research*, **11**, 219-224. https://doi.org/10.14740/jocmr3647

[53] Rubino, D.M., Greenway, F.L., Khalid, U., O'Neil, P.M., Rosenstock, J., Sørrig, R., *et al.* (2022) Effect of Weekly Subcutaneous Semaglutide vs Daily Liraglutide on Body Weight in Adults with Overweight or Obesity without Diabetes: The STE P 8

Randomized Clinical Trial. *JAMA*, **327**, 138-150. https://doi.org/10.1001/jama.2021.23619

[54] Ryan, D.H., Lingvay, I., Deanfield, J., Kahn, S.E., Barros, E., Burguera, B., *et al.* (2024) Long-term Weight Loss Effects of Semaglutide in Obesity without Diabetes in the SELECT Trial. *Nature Medicine*, **30**, 2049-2057. https://doi.org/10.1038/s41591-024-02996-7

[55] Weghuber, D., Barrett, T., Barrientos-Pérez, M., Gies, I., Hesse, D., Jeppesen, O.K., *et al.* (2022) Once-Weekly Semaglutide in Adolescents with Obesity. *New England Journal of Medicine*, **387**, 2245-2257. https://doi.org/10.1056/nejmoa2208601

[56] Knop, F.K., Aroda, V.R., do Vale, R.D., Holst-Hansen, T., Laursen, P.N., Rosenstock, J., *et al.* (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**, 705-719. https://doi.org/10.1016/s0140-6736(23)01185-6

[57] Chen, K., Chen, L., Shan, Z., Wang, G., Qu, S., Qin, G., *et al.* (2023) Beinaglutide for Weight Management in Chinese Individuals with Overweight or Obesity: A Phase 3 Randomized Controlled Clinical Study. *Diabetes, Obesity and Metabolism*, **26**, 690-698. https://doi.org/10.1111/dom.15360

[58] Li, Y., Gong, X., Găman, M., Hernández-Wolters, B., Velu, P. and Li, Y. (2023) The Effect of Subcutaneous Dulaglutide on Weight Loss in Patients with Type 2 Diabetes Mellitus: Systematic Review and Meta-Analysis of Randomized Controlled Trials. *European Journal of Clinical Investigation*, **54**, e14125. https://doi.org/10.1111/eci.14125

[59] Pratley, R.E., Aroda, V.R., Lingvay, I., Lüdemann, J., Andreassen, C., Navarria, A., *et al.* (2018) Semaglutide versus Dulaglutide Once Weekly in Patients with Type 2 Diabetes (SUSTAIN 7): A Randomised, Open-Label, Phase 3B Trial. *The Lancet Diabetes & Endocrinology*, **6**, 275-286. https://doi.org/10.1016/s2213-8587(18)30024-x

[60] Karagiannis, T., Malandris, K., Avgerinos, I., Stamati, A., Kakotrichi, P., Liakos, A., *et al.* (2024) Subcutaneously Administered Tirzepatide vs Semaglutide for Adults with Type 2 Diabetes: A Systematic Review and Network Meta-Analysis of Randomised Controlled Trials. *Diabetologia*, **67**, 1206-1222. https://doi.org/10.1007/s00125-024-06144-1

[61] Zhao, L., Cheng, Z., Lu, Y., Liu, M., Chen, H., Zhang, M., *et al.* (2024) Tirzepatide for Weight Reduction in Chinese Adults with Obesity: The S URMOUNT-CN Randomized Clinical Trial. *JAMA*, **332**, 551-560. https://doi.org/10.1001/jama.2024.9217

[62] Iqbal, J., Wu, H., Hu, N., Zhou, Y., Li, L., Xiao, F., *et al.* (2022) Effect of Glucagon-Like Peptide-1 Receptor Agonists on Body Weight in Adults with Obesity without Diabetes Mellitus—A Systematic Review and Meta-Analysis of Randomized Control Trials. *Obesity Reviews*, **23**, e13435. https://doi.org/10.1111/obr.13435

[63] Dushay, J., Gao, C., Gopalakrishnan, G.S., Crawley, M., Mitten, E.K., Wilker, E., *et al.* (2011) Short-Term Exenatide Treatment Leads to Significant Weight Loss in a Subset of Obese Women without Diabetes. *Diabetes Care*, **35**, 4-11. https://doi.org/10.2337/dc11-0931

[64] Wang, X., Zhao, X., Gu, Y., Zhu, X., Yin, T., Tang, Z., *et al.* (2020) Effects of Exenatide and Humalog Mix25 on Fat Distribution, Insulin Sensitivity, and $\beta$-Cell Function in Normal BMI Patients with Type 2 Diabetes and Visceral Adiposity. *Journal of Diabetes Research*, **2020**, Article ID: 9783859. https://doi.org/10.1155/2020/9783859

[65] Shao, Q., Yu, Y.N., Huang, Y.H., *et al.* (2022) Predictors of Exenatide in Reducing Body Weight in Patients with Type 2 Diabetes Mellitus. *Chinese Clinical Pharmacology*

*and Therapeutics*, **27**, 287-294. https://doi.org/10.12092/j.issn.1009-2501.2022.03.007

[66] Gorgojo-Martínez, J.J., Mezquita-Raya, P., Carretero-Gómez, J., Castro, A., Cebrián-Cuenca, A., de Torres-Sánchez, A., *et al.* (2022) Clinical Recommendations to Manage Gastrointestinal Adverse Events in Patients Treated with GLP-1 Receptor Agonists: A Multidisciplinary Expert Consensus. *Journal of Clinical Medicine*, **12**, Article 145. https://doi.org/10.3390/jcm12010145

[67] He, L., Wang, J., Ping, F., Yang, N., Huang, J., Li, Y., *et al.* (2022) Association of Glucagon-Like Peptide-1 Receptor Agonist Use with Risk of Gallbladder and Biliary Diseases: A Systematic Review and Meta-Analysis of Randomized Clinical Trials. *JAMA Internal Medicine*, **182**, 513-519. https://doi.org/10.1001/jamainternmed.2022.0338

[68] Sodhi, M., Rezaeianzadeh, R., Kezouh, A. and Etminan, M. (2023) Risk of Gastrointestinal Adverse Events Associated with Glucagon-Like Peptide-1 Receptor Agonists for Weight Loss. *JAMA*, **330**, 1795-1797. https://doi.org/10.1001/jama.2023.19574

[69] Saxena, A.R., Gorman, D.N., Esquejo, R.M., Bergman, A., Chidsey, K., Buckeridge, C., *et al.* (2021) Danuglipron (PF-06882961) in Type 2 Diabetes: A Randomized, Placebo-Controlled, Multiple Ascending-Dose Phase 1 Trial. *Nature Medicine*, **27**, 1079-1087. https://doi.org/10.1038/s41591-021-01391-w

[70] Monami, M., Dicembrini, I., Nardini, C., Fiordelli, I. and Mannucci, E. (2014) Glucagon-Like Peptide-1 Receptor Agonists and Pancreatitis: A Meta-Analysis of Randomized Clinical Trials. *Diabetes Research and Clinical Practice*, **103**, 269-275. https://doi.org/10.1016/j.diabres.2014.01.010

[71] Filippatos, T.D., Panagiotopoulou, T.V. and Elisaf, M.S. (2014) Adverse Effects of GLP-1 Receptor Agonists. *The Review of Diabetic Studies*, **11**, 202-230. https://doi.org/10.1900/rds.2014.11.202

[72] Anthony, M.S., Aroda, V.R., Parlett, L.E., Djebarri, L., Berreghis, S., Calingaert, B., *et al.* (2024) Risk of Anaphylaxis among New Users of GLP-1 Receptor Agonists: A Cohort Study. *Diabetes Care*, **47**, 712-719. https://doi.org/10.2337/dc23-1911

[73] Chen, W., Cai, P., Zou, W. and Fu, Z. (2024) Psychiatric Adverse Events Associated with GLP-1 Receptor Agonists: A Real-World Pharmacovigilance Study Based on the FDA Adverse Event Reporting System Database. *Frontiers in Endocrinology*, **15**, Article 1330936. https://doi.org/10.3389/fendo.2024.1330936

[74] Liang, J., Liu, Q., Chen, Y., *et al.* (2022) Effect of Glucotide Combined with Metformin and Dapagliflozin on Glucose and Lipid Metabolism in Patients with Newly Diagnosed Type 2 Diabetes Mellitus. *Internal Medicine*, **17**, 495-498.

[75] Zhang, M., Lin, C., Cai, X., Jiao, R., Bai, S., Li, Z., *et al.* (2024) One or Two? Comparison of the Cardiorenal Effects between Combination Therapy and Monotherapy with SGLT2i or GLP1RA. *Diabetes, Obesity and Metabolism*, **27**, 806-815. https://doi.org/10.1111/dom.16078

[76] Ren, R., Pei, Y., Kong, L. and Shi, Y. (2025) The Effect of Semaglutide Combined with Metformin on Liver Inflammation and Pancreatic Beta-Cell Function in Patients with Type 2 Diabetes and Non-Alcoholic Fatty Liver Disease. *Journal of Diabetes and its Complications*, **39**, Article ID: 108932. https://doi.org/10.1016/j.jdiacomp.2024.108932

[77] Moiz, A., Filion, K.B., Toutounchi, H., Tsoukas, M.A., Yu, O.H.Y., Peters, T.M., *et al.* (2025) Efficacy and Safety of Glucagon-Like Peptide-1 Receptor Agonists for Weight Loss among Adults without Diabetes: A Systematic Review of Randomized Controlled Trials. *Annals of Internal Medicine*, **178**, 199-217. https://doi.org/10.7326/annals-24-01590

[78] Wilding, J.P.H., Batterham, R.L., Calanna, S., Davies, M., Van Gaal, L.F., Lingvay, I., *et al.* (2021) Once-Weekly Semaglutide in Adults with Overweight or Obesity. *New England Journal of Medicine*, **384**, 989-1002. https://doi.org/10.1056/nejmoa2032183

[79] Garvey, W.T., Batterham, R.L., Bhatta, M., Buscemi, S., Christensen, L.N., Frias, J.P., *et al.* (2022) Two-Year Effects of Semaglutide in Adults with Overweight or Obesity: The STEP 5 Trial. *Nature Medicine*, **28**, 2083-2091. https://doi.org/10.1038/s41591-022-02026-4

[80] Wadden, T.A., Bailey, T.S., Billings, L.K., Davies, M., Frias, J.P., Koroleva, A., *et al.* (2021) Effect of Subcutaneous Semaglutide vs Placebo as an Adjunct to Intensive Behavioral Therapy on Body Weight in Adults with Overweight or Obesity: The STEP 3 Randomized Clinical Trial. *JAMA*, **325**, 1403-1413. https://doi.org/10.1001/jama.2021.1831

[81] Davies, M., Færch, L., Jeppesen, O.K., Pakseresht, A., Pedersen, S.D., Perreault, L., *et al.* (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. *The Lancet*, **397**, 971-984. https://doi.org/10.1016/s0140-6736(21)00213-0

[82] Rubino, D., Abrahamsson, N., Davies, M., Hesse, D., Greenway, F.L., Jensen, C., *et al.* (2021) Effect of Continued Weekly Subcutaneous Semaglutide vs Placebo on Weight Loss Maintenance in Adults with Overweight or Obesity: The STEP 4 Randomized Clinical Trial. *JAMA*, **325**, 1414-1425. https://doi.org/10.1001/jama.2021.3224

[83] Alfaris, N., Waldrop, S., Johnson, V., Boaventura, B., Kendrick, K. and Stanford, F.C. (2024) GLP-1 Single, Dual, and Triple Receptor Agonists for Treating Type 2 Diabetes and Obesity: A Narrative Review. *eClinicalMedicine*, **75**, Article ID: 102782. https://doi.org/10.1016/j.eclinm.2024.102782

[84] Zhu, Y., Yao, L., Gallo-Ferraz, A.L., Bombassaro, B., Simões, M.R., Abe, I., *et al.* (2024) Sympathetic Neuropeptide Y Protects from Obesity by Sustaining Thermogenic Fat. *Nature*, **634**, 243-250. https://doi.org/10.1038/s41586-024-07863-6

[85] Pfeifer, A., Mikhael, M. and Niemann, B. (2024) Inosine: Novel Activator of Brown Adipose Tissue and Energy Homeostasis. *Trends in Cell Biology*, **34**, 72-82. https://doi.org/10.1016/j.tcb.2023.04.007

[86] Keinan, O., Valentine, J.M., Xiao, H., Mahata, S.K., Reilly, S.M., Abu-Odeh, M., *et al.* (2021) Glycogen Metabolism Links Glucose Homeostasis to Thermogenesis in Adipocytes. *Nature*, **599**, 296-301. https://doi.org/10.1038/s41586-021-04019-8

[87] Wang, Q., Li, D., Cao, G., Shi, Q., Zhu, J., Zhang, M., *et al.* (2021) IL-27 Signalling Promotes Adipocyte Thermogenesis and Energy Expenditure. *Nature*, **600**, 314-318. https://doi.org/10.1038/s41586-021-04127-5