The Eurasian Journal of Life Sciences 2025; 1 (1): 43-52

journal homepage: https://www.eajls.com
https://doi.org/10.47093/3033-5493.2025.1.1.43-52

REVIEW

Study of mechanisms and approaches to incretin-based therapy for obesity in children

Timofey V. Chubarov, Igor E. Esaulenko, Valentina A. Peterkova, Olga A. Zhdanova, Weijie Du, Olga G. Sharshova

ORCID number:
Timofey V. Chubarov 0000-0002-1352-7026;
Igor E. Esaulenko 0000-0002-2424-2974;
Valentina A. Peterkova 0000-0002-5507-4627;
Olga A. Zhdanova 0000-0002-3917-0395;
Weijie Du 0000-0003-1197-1462;
Olga G. Sharshova 0000-0003-0412-7853

Correspondence to: Timofey V. Chubarov, Dr. Sci. (Med.), Chief Physician of the Voronezh Children's Clinical Hospital, Head of the Endocrinological Center, Associate Professor of the Department of Propaedeutics of Childhood Diseases and Polyclinic Pediatrics, N. N. Burdenko Voronezh State Medical University.
Address: 16, Health Lane, Voronezh, 394018, Russia.
Email: chubarov25@yandex.ru

Timofey V. Chubarov, Dr. Sci. (Med.), Chief Physician of the Voronezh Children's Clinical Hospital, Head of the Endocrinological Center, Associate Professor of the Department of Propaedeutics of Childhood Diseases and Polyclinic Pediatrics, N. N. Burdenko Voronezh State Medical University, 16, Health Lane, Voronezh, 394018, Russia

Igor E. Esaulenko, Dr. Sci. (Med.), Associate Professor, Rector, N. N. Burdenko Voronezh State Medical University, 10, Studentskaya str., Voronezh, 394036, Russia

Valentina A. Peterkova, Academician of the Russian Academy of Sciences, Professor, Doctor of Medical Sciences, Chief Pediatric Endocrinologist of the Russian Ministry of Health, Head of the Department of Pediatric Endocrinology-Diabetology, Russian National Research Center of Endocrinology of the Russian Ministry of Health, 11, Dmitry Ulyanov str., Moscow, 117292, Russia

Olga A. Zhdanova, Dr. Sci. (Med.), Associate Professor, Professor of the Department of Clinical Pharmacology, N. N. Burdenko Voronezh State Medical University, 10, Studentskaya str., Voronezh, 394036, Russia

Weijie Du, Professor of Department of Pharmacology, Vice Director of the Key Laboratory of Cardiovascular Medicine Research of Ministry of Education, Harbin Medical University, 157 Baojian Rd, Nangang, Harbin, 150088, Heilongjiang, China

Olga G. Sharshova, Deputy Chief Physician on the medical part, Head of the Endocrinology Department, Pediatric Endocrinologist at the Voronezh Children's Clinical Hospital, N. N. Burdenko Voronezh State Medical University, 16, Health Lane, Voronezh, 394018, Russia

Contributors: Timofey V. Chubarov: contributed in study concept, design and manuscript editing. Igor E. Esaulenko: contributed in study concept and design. Valentina A. Peterkova: contributed in manuscript editing. Olga A. Zhdanova: contributed in data analysis, interpretation and manuscript writing. Weijie Du: contributed in manuscript writing. Olga G. Sharshova contributed in data collection and interpretation.
The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Informed consent statement: Not required

Funding: The study was conducted under a clinical trial protocol and funded by compulsory health insurance.

Competing interests: The authors confirm that there is no conflict of interest related to the manuscript.

Ethical approval: Not required.

Data sharing: Not applicable.

Acknowledgments: None.

ABSTRACT

This study highlights data on the increasing role of incretins in interdisciplinary therapy for endocrinopathies, particularly glucagon-like peptide-1 (GLP-1), which affects carbohydrate metabolism, insulin secretion, and other metabolic processes. The mechanisms of secretion, biological activity, and degradation of these peptides are described, along with their role in regulating appetite, gastrointestinal motility, and carbohydrate metabolism. This information allows for a comprehensive understanding of the effects of synthetic GLP-1 analogs. We also explore modern approaches to treating obesity in children and adolescents, including the use of GLP-1 receptor agonists such as liraglutide. It presents the results of a clinical study confirming the effectiveness and safety of liraglutide in reducing body weight and improving metabolic indicators in

Manuscript source: Unsolicited manuscript.

Country/territory of origin: Russia, China

Received: 27.03.2025

Accepted: 03.04.2025

Date of publication: 01.07.2025

children with obesity. It is shown that liraglutide not only promotes weight loss but also has cardioprotective effects, improving lipid profiles and reducing blood pressure. The efficacy of liraglutide in children aged 12–18 with obesity was amount to 43.3 - 76.5%. The prevalence of hypertension in obese children decreased from 30.9% to 4.8%, carbohydrate metabolism disorders from 41.1% to 19.4%, dyslipidemia from 20.6% to 9.7%. Liraglutide reduces the risk of major adverse cardiovascular events by 13–22% in patients with type 2 diabetes and high cardiovascular risk. This effect is attributed to moderate blood pressure reduction, improved lipid profiles, enhanced endothelial function, and anti-inflammatory and antioxidant actions. Additionally, the article discusses the prospects for using GLP-1 receptor agonists in cardiology, including their ability to reduce the risk of cardiovascular events in patients with type 2 diabetes and obesity.

Key Words: GLP-1 receptor agonists, liraglutide, obesity, children

Citation: Chubarov TV, Esaulenko IE, Peterkova VA, Zhdanova OA, Du W, Sharshova OG. Study of mechanisms and approaches to incretin-based therapy for obesity in children. *The Eurasian Journal of Life Sciences*. 2025;1(1):43-52. https://doi.org/10.47093/3033-5493.2025.1.1.43-52.

The Role of Incretins in the Body

Incretins are hormones produced by intestinal cells in response to food intake, contributing to 50–70% of postprandial insulin secretion in healthy individuals. This process in referred to as the incretin effect. Glucagon-like peptide (GLP) and gastric inhibitory polypeptide (GIP) (also known as glucose-dependent insulinotropic polypeptide) both belong to the glucagon protein family, sharing significant amino acid homology [1]. GIP is secreted by K-cells in the upper small intestine (duodenum and proximal jejunum) in response to carbohydrate and fat intake. GLP-1, GLP-2, and glicentin (the intestinal form of glucagon) are produced by L-cells, predominantly located in the distal intestine. Additionally, GLP-1 is also expressed in pancreatic alpha cells and neurons in certain brain regions, including hypothalamus, pituitary, reticular nucleus [2]. Despite the distal location of L-cells in the gastrointestinal tract, GLP-1 is released into the bloodstream within minutes after food intake. This indicates an indirect neuroendocrine regulation, rather than direct nutrient stimulation. Experimental studies in animals have confirmed the important role of the parasympathetic nervous system, particularly the vagus nerve, in transmitting neuroendocrine signals through muscarinic receptors [2].

The concentration of GLP-1 and GIP in fasting plasma is extremely low but increases significantly after meals. Both peptides are rapidly degraded by the enzyme dipeptidyl peptidase-4 (DPP-4), which is expressed in capillary endothelial cells. As a result, a large portion of GLP-1 and GIP is inactivated before entering the portal bloodstream, explaining their short half-life. Studies with intravenous administration of GIP and GLP-1 in healthy volunteers and patients with diabetes have shown that the half-life of GIP is 5–7 minutes, while that of intact GLP-1 is 1–2 minutes [3].

GIP receptors are expressed in pancreatic islet cells, the intestine, adipose tissue, the heart, the pituitary, and various brain regions. GLP-1 receptors, in turn, are found in the gastrointestinal tract, the endocrine pancreas (alpha and beta cells), the lungs, kidneys, heart, and various brain regions [4] (Fig. 1).

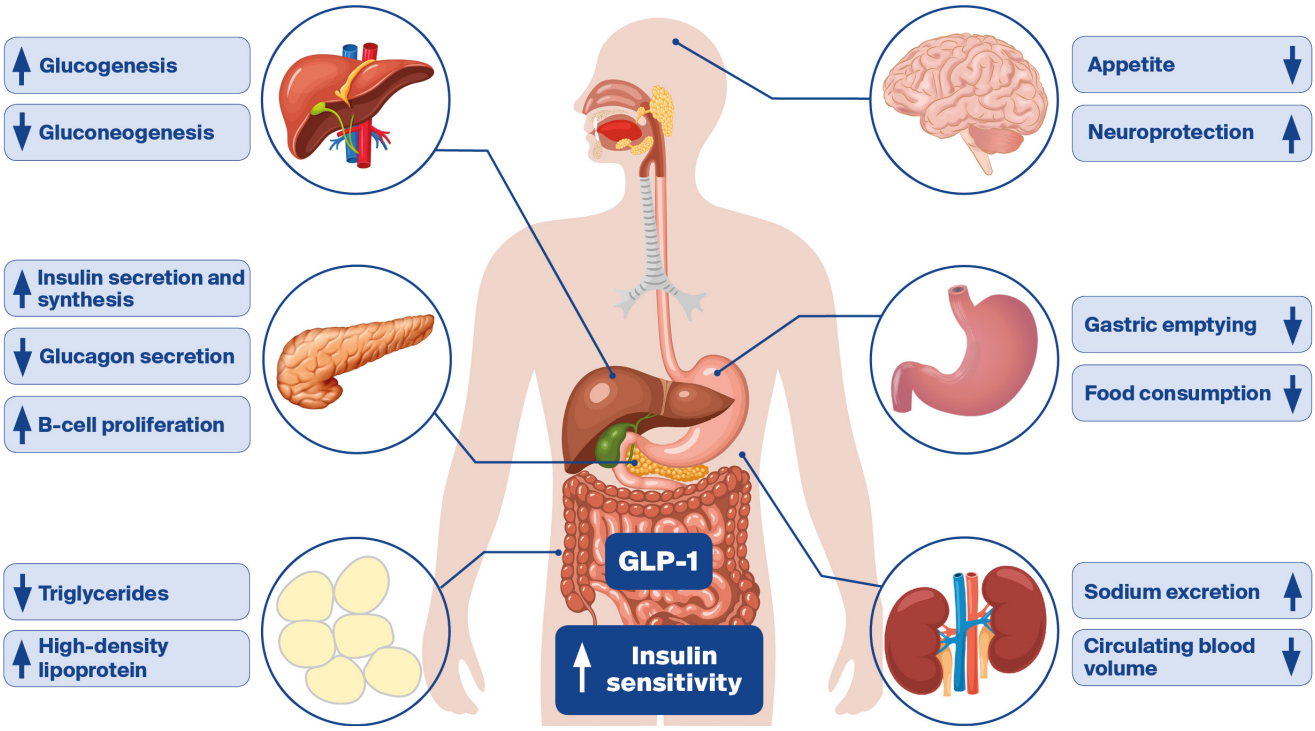

FIG. 1. Metabolic effects of glucagon-like peptide-1 (GLP-1)

A significant portion of secreted GLP-1 is inactivated in the intestine before entering the systemic circulation, suggesting that its biological activity may occur locally or through interaction with afferent sensory nerve fibers transmitting signals to the central nervous system. This interaction modulates the activity of efferent parasympathetic fibers of the vagus nerve, regulating key intestinal functions such as secretory and motor activity, as well as pancreatic secretion [4].

Under physiological conditions, the intake of small amounts of food or easily digestible nutrients primarily stimulates the release of GIP, an incretin secreted in the proximal intestine [5]. Conversely, the digestion of larger volumes of food or complex nutrients activates both GIP and GLP-1. GLP-1 secretion correlates with insulin release throughout the day. Importantly, the action of GLP-1 is strictly glucose-dependent, meaning its effects are directly linked to blood glucose levels. The minimal threshold for glycemia at which GLP-1's effect on insulin secretion ceases is approximately 4.5 glycemia. This indicates that GLP-1's influence on insulin secretion is not associated with a risk of hypoglycemia, as its effect diminishes as glucose levels approach normal. In addition to directly stimulating insulin secretion, GLP-1 promotes insulin gene transcription and all stages of insulin biosynthesis, helping to replenish insulin stores, especially when depleted. GLP-1 is also a potent stimulator of somatostatin secretion, an effect independent of blood glucose levels [5].

GLP-1 inhibits glucagon secretion, likely mediated by increased insulin and somatostatin secretion. Direct effects on alpha cells, which express GLP-1 receptors, also play a role. This inhibition of glucagon secretion is glucose-dependent, ensuring that GLP-1 does not impair the counter-regulatory response to hypoglycemia [6].

GLP-1 slows gastric emptying by inhibiting gastrointestinal motility and secretory functions, likely through neural mechanisms involving the vagovagal reflex pathway [7]. This physiological role of GLP-1 helps regulate intestinal absorption, synchronizing the movement of food with secretory activity. In pathological conditions such as diabetes, delayed gastric emptying can reduce postprandial glucose fluctuations.

One of the key properties of GLP-1 is its ability to reduce food intake by promoting satiety [8]. This effect is mediated by central mechanisms, with GLP-1 acting on brain regions such as the hypothalamus and nucleus tractus solitarius. Peripheral GLP-1 also influences afferent fibers of the parasympathetic nervous system, transmitting signals to the central nervous system to modulate food intake.

Incretin-Based Therapies for Pediatric Obesity

The first line of therapy for constitutional-exogenous obesity involves diet and lifestyle modifications [9]. However, this approach is often ineffective, as it fails to address all the consequences of obesity [10,11]. This is due to low patient engagement, rapid weight gain, having eating disorders, and poor parental compliance. Additionally, obesity-related comorbidities in childhood tend to progress more aggressively than those developing later in life [12]. This situation necessitates the consideration of pharmacotherapy.

The treatment of obesity in children and adolescents aims to achieve two goals: maintaining the BMI SDS (body mass index standard deviation score) in the short term (for 6–12 months) and significantly reducing BMI SDS while controlling and preventing complications in the long term [9]. According to clinical guidelines in Russia, pharmacotherapy (combined with lifestyle changes) is recommended for children aged 12 and older when lifestyle interventions over at least one year have not yielded the desired results [9].

Currently, five medications are the United States Food and Drug Administration (FDA) approved for treating obesity in children and adolescents [13]. Prior to 2022, only three drugs were available: orlistat (for adolescents over 12), phentermine (in individuals over 16), and liraglutide (for adolescents over 12). In 2022, the FDA approved the combination drug phentermine/topiramate in a controlled-release form for once-daily use in adolescents over 12 with obesity. However, the efficacy and safety of these drugs do not fully meet desired outcomes. In January 2023, the FDA also approved semaglutide (a GLP-1 receptor agonist) for adolescents over 12 with obesity.

Liraglutide, a GLP-1 receptor agonist, mimics the action of endogenous GLP-1, which is produced in the intestine in response to food intake [14]. Its mechanism of action involves activating GLP-1 receptors in various organs and tissues, including the pancreas, gastrointestinal tract, and central nervous system. In the pancreas, liraglutide stimulates beta cells, enhancing glucose-dependent insulin secretion and improving glycemic control. It also suppresses glucagon release from alpha cells, reducing hepatic glucose production and preventing hyperglycemia. In the gastrointestinal tract, liraglutide delays gastric emptying, prolonging satiety and reducing appetite. In the central nervous system, particularly the hypothalamus, liraglutide acts on satiety centers, reducing hunger and food intake. Additionally, liraglutide exhibits cardioprotective effects by lowering blood pressure and improving lipid profiles through reduced cholesterol and triglyceride levels. Liraglutide has fewer contraindications and better tolerability compared to other weight-loss medications, making it a safer option for pediatric patients [14].

The efficacy and safety of liraglutide has been demonstrated in a large randomized SCALE Teen trial. It involved 251 patients (126 received liraglutide). A body weight loss of ≥5% was achieved in 43.3% in the liraglutide group versus 18.7% in the placebo group [14].

In the study of Vitsebskaya A.V. and Popovich A.V. 10 patients with obesity and gastrointestinal diseases were included. The use of liraglutide for 3 months resulted in a significant decrease in BMI SDS to 2.8 kg/m^2. The severity of obesity decreased by 0.4 kg/m^2 BMI SDS. During liraglutide therapy, there was a statistically insignificant decrease in fasting glucose, glycated hemoglobin, cholesterol, triglycerides and transaminases [15].

The efficacy of liraglutide in children aged 12–18 with obesity was demonstrated in a single-center, observational, single-arm, prospective, uncontrolled study conducted at the Endocrinology Department of the Burdenko Voronezh State Medical University [16]. The study included 68 children with grade II–III obesity and morbid obesity (BMI SDS ≥ 2.5) and a body weight of at least 60 kg. Positive dynamics, defined as a reduction in BMI SDS by 0.25 or more, were observed in 47 children (69.1%). Five patients (7.4%) showed a reduction in BMI SDS of less than 0.25, while 3 children (4.4%) had no change in body weight (BMI SDS change ± 0.05), and 7 patients (10.3%) experienced weight gain (BMI SDS increase > 0.05). During the first month of therapy, 2 patients (2.9%) transitioned from morbid to grade III obesity, 9 children (13.2%) from grade III to grade II, and 3 patients (4.4%) from grade II to grade I. Pairwise comparisons of BMI SDS before treatment and at 1, 4, and 8 months showed statistically significant differences ($p < 0.001$), indicating meaningful changes rather than random fluctuations. Average weight loss was 4.8 kg (4.6%) at 1 month, 8.1 kg (7.7%) at 4 months, 9.7 kg (9.2%) at 8 months, and 6 kg (5.7%) at 12 months. Some patients lost over 20 kg (23–25%) [16].

Adverse effects were reported by 10 patients (14.7%) during dose escalation. Nausea occurred in 8 patients (11.7%), vomiting in 4 (5.9%), abdominal pain in 4 (5.9%), diarrhea in 3 (4.4%), and belching in 1 child (1.5%). One patient (1.5%) with non-alcoholic fatty liver disease developed cholelithiasis after one month of liraglutide therapy. No cases of hypoglycemia were reported.

Liraglutide demonstrated significant efficacy in addressing the primary goals of obesity treatment: positive weight loss dynamics were achieved in 76.5% of patients, and weight stabilization in 4.4% of children. The greatest effect was observed after 8 months of therapy, particularly in children with higher BMI SDS values but not morbid obesity. Weight normalization was accompanied by a reduction in obesity-related complications. The prevalence of hypertension decreased from 30.9% to 4.8% ($p < 0.004$); carbohydrate metabolism disorders from 41.1% to 19.4% ($p = 0.004$); dyslipidemia from 20.6% to 9.7%; and non-alcoholic fatty liver disease from 60.3% to 50% [16].

The use of liraglutide for the treatment of obesity in children in younger age groups is being studied. Thus, when 56 children aged 6-12 years were treated for 56 weeks, the average percentage change in body mass index from baseline was -5.8% among those receiving liraglutide, compared with 1.6% in the placebo group [17].

Cardioprotective Effects of Incretins

Beyond obesity treatment, another promising area is their application in cardiovascular diseases. The cardioprotective effects of GLP-1 receptor agonists (e.g., liraglutide, semaglutide, dulaglutide) are a key focus in modern cardiology and endocrinology. Initially developed for type 2 diabetes, these

drugs have shown significant benefits for the cardiovascular system. Large clinical trials (e.g., LEADER, SUSTAIN-6, REWIND) have demonstrated that GLP-1 agonists reduce the risk of major adverse cardiovascular events, such as myocardial infarction, stroke, and cardiovascular death [18-21]. For example, liraglutide reduces the risk of major adverse cardiovascular events by 13–22% in patients with type 2 diabetes and high cardiovascular risk. This effect is attributed to moderate blood pressure reduction, improved lipid profiles (lower triglycerides and higher high-density lipoproteins (HDL)), enhanced endothelial function, and anti-inflammatory and antioxidant actions [21] (Fig. 2).

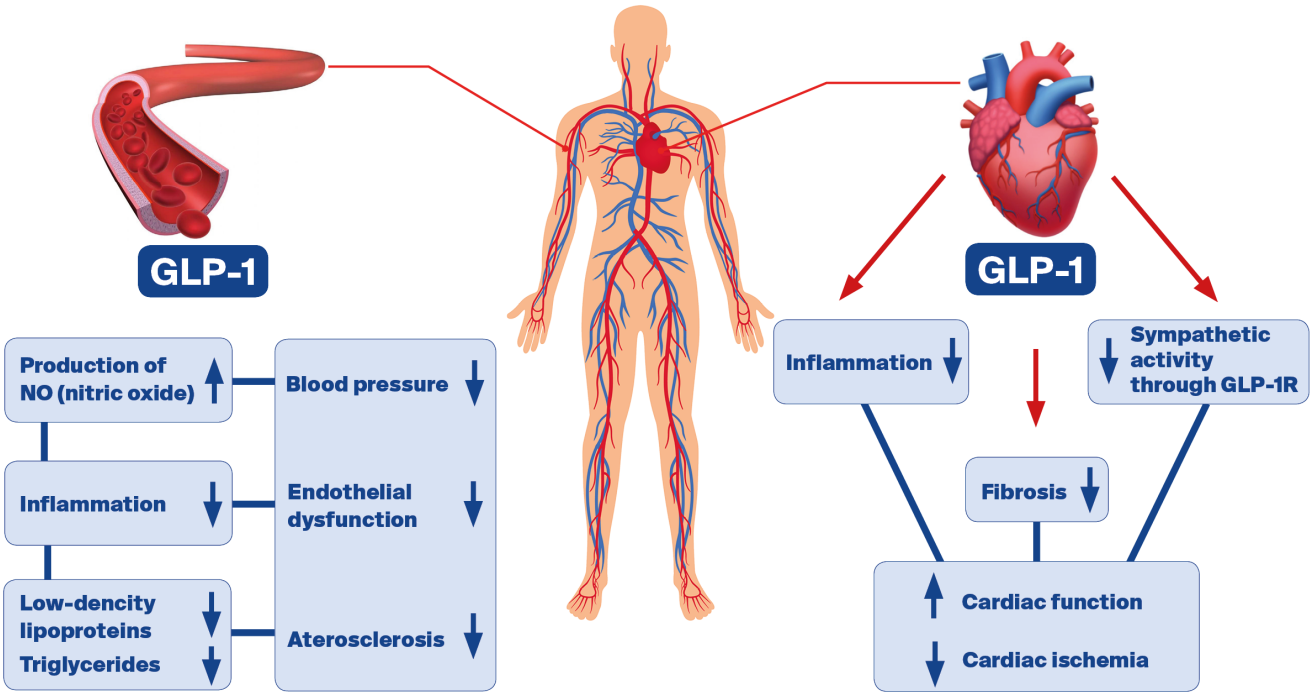

FIG. 2. Cardioprotective effects of incretins on the cardiovascular system

GLP-1 receptor agonists lower blood pressure through multiple mechanisms, including direct and indirect effects on the cardiovascular system. GLP-1 receptors are expressed in vascular smooth muscle cells and cardiomyocytes. Activation of these receptors increases intracellular cyclic adenosine monophosphate (cAMP) levels, activating protein kinase A, which induces smooth muscle relaxation and vasodilation, thereby reducing blood pressure. cAMP also activates endothelial nitric oxide synthase, increasing nitric oxide (NO) production, which further promotes vasodilation. Additionally, GLP-1 reduces pro-inflammatory cytokines by inhibiting the Nuclear factor kappa-light-chain-enhancer of activated B cells signaling pathway, a key regulator of inflammatory gene expression, including cytokine genes such as tumor necrosis factor α, interleukin-6, interleukin-1β [22-25]. It is worth noting that GLP-1 suppresses macrophage activation and their transition into a pro-inflammatory state, thereby contributing to a reduction in pro-inflammatory cytokines [22,23,25,26].

GLP-1 modulates sympathetic nervous system activity, which plays a crucial role in blood pressure regulation. GLP-1 and its agonists can cross the

blood-brain barrier or act on brain regions with higher permeability (e.g., area postrema). In the central nervous system, GLP-1 receptors are expressed in key areas regulating sympathetic activity, such as the hypothalamus, nucleus tractus solitarius, and rostral ventrolateral medulla [24,27,28,29]. Activation of these receptors reduces sympathetic activity, heart rate, and blood pressure [29]. GLP-1 receptors are also expressed in the nephron, where their activation increases sodium and water excretion, reducing blood volume and pressure. GLP-1 receptors are also expressed in various segments of the nephron, including the proximal tubules and collecting ducts. Activation of these receptors increases sodium excretion by suppressing the activity of the Na+/H+ exchanger type 3in the proximal tubules, which reduces sodium reabsorption and enhances its urinary elimination, as well as increases water excretion by decreasing sodium reabsorption (osmotic diuresis) [30]. This leads to a reduction in circulating blood volume and, consequently, a decrease in arterial blood pressure.

GLP-1 positively influences lipid metabolism by increasing HDL levels and reducing triglycerides [31]. It suppresses key lipogenic enzymes, such as acetyl-CoA carboxylase and fatty acid synthase, through adenosine monophosphate activated protein kinase activation. GLP-1 also enhances lipoprotein lipase activity, which breaks down triglycerides in very low-density lipoproteins and chylomicrons. Increased HDL levels result from enhanced apolipoprotein A1 synthesis, the primary structural protein of HDL [32-34].

These mechanisms contribute to GLP-1's beneficial effects on the myocardium. GLP-1 improves energy metabolism in cardiomyocytes, enhances mitochondrial function, reduces ischemia-reperfusion injury, and decreases pro-inflammatory cytokines in the myocardium. It also prevents or reduces myocardial hypertrophy by lowering blood pressure and sympathetic activity, and it inhibits fibrosis by suppressing transforming growth factor-beta activity [35].

GLP-1 receptor agonists do not replace standard cardiovascular therapies (e.g., statins, antihypertensives) but serve as valuable adjuncts. Their multifaceted cardioprotective effects, including blood pressure reduction, improved lipid profiles, and anti-inflammatory and antioxidant actions, make them important additions to standard cardiovascular disease management.

Conclusion

The article presents key directions for the development of incretin-based therapy. The study confirmed the high efficacy of liraglutide in treating obesity in children and adolescents, with significant weight reduction in 76.5% of patients and weight stabilization in 4.4%. The cardioprotective properties of liraglutide were also demonstrated, with improvements in lipid profiles and blood pressure, reducing the risk of cardiovascular complications. These findings align with international studies showing liraglutide's ability to lower cardiovascular risk in patients with obesity and type 2 diabetes. GLP-1 receptor agonists may become an essential component of comprehensive obesity treatment, particularly in patients at high cardiovascular risk. Further research with longer follow-up periods will clarify the long-term effects of liraglutide and its role in preventing obesity-related complications.

References

1. Цыганкова ОВ, Веретюк ВВ, Аметов АС. Инкретины сегодня: множественные эффекты и терапевтический потенциал. *Сахарный диабет*. / Tsygankova OV, Veretyuk VV, Ametov AS. Incretins today: multiple effects and therapeutic potential. *Diabetes Mellitus.* 2019;22(1):70-78. https://doi.org/10.14341/dm9841. (In Russ.).
2. Демидова ТЮ, Лобанова КГ, Ойноткинова ОШ. Кишечная микробиота как эндокринный орган. *Ожирение и метаболизм*. / Demidova TY, Lobanova KG, Oynotkinova OS. Gut microbiota is an endocrine organ. *Obesity and Metabolism.* 2020;17(3):299-306. https://doi.org/10.14341/omet12457. (In Russ.).
3. Gautier J, Fetita S, Sobngwi E, Salaün-Martin C. Biological actions of the incretins GIP and GLP-1 and therapeutic perspectives in patients with type 2 diabetes. *Diabetes & Metabolism.* 2005;31(3):233-242. https://doi.org/10.1016/s1262-3636(07)70190-8.
4. Drucker DJ. MiniReview: The Glucagon-Like Peptides. *Endocrinology.* 2001;142(2):521-527. https://doi.org/10.1210/endo.142.2.7983.
5. Zhang X, Young RL, Bound M, et al. Comparative effects of proximal and distal small intestinal glucose exposure on glycemia, incretin hormone secretion, and the incretin effect in health and type 2 diabetes. *Diabetes Care.* 2019;42(4):520-528. https://doi.org/10.2337/dc18-2156.
6. Ким ЕИ, Ершова ЕВ, Мазурина НВ, Комшилова КА. Постбариатрические гипогликемии: взгляд эндокринолога. *Ожирение и метаболизм*. / Kim EI, Ershova EV, Mazurina NV, Komshilova KA. A view at postbariatric hypoglycemia by endocrinologist. *Obesity and Metabolism*. 2022;18(4):471-483. https://doi.org/10.14341/omet12785. (In Russ.).
7. Nauck MA, Kemmeries G, Holst JJ, Meier JJ. Rapid tachyphylaxis of the glucagon-like peptide 1-induced deceleration of gastric emptying in humans. *Diabetes.* 2011;60(5):1561-1565. https://doi.org/10.2337/db10-0474.
8. Holst JJ. The physiology of glucagon-like peptide 1. *Physiol Rev.* 2007;87(4):1409-1439. https://doi.org/10.1152/physrev.00034.2006.
9. Петеркова ВА, Безлепкина ОБ, Болотова НВ, и соавт. Клинические рекомендации «Ожирение у детей». *Проблемы эндокринологии.* / Peterkova VA, Bezlepkina OB, Bolotova NV, et al. Clinical guidelines «Obesity in children». *Problems of Endocrinology.* 2021;67(5):67-83. https://doi.org/10.14341/probl12802. (In Russ.).
10. Johnson VR, Washington TB, Chhabria S, et al. Food as medicine for obesity treatment and management. *Clin Ther.* 2022;44(5):671–681. https://doi.org/ 10.1016/J.CLINTHERA.2022.05.001.
11. Nicolucci A, Maffeis C. The adolescent with obesity: what perspectives for treatment? *Ital J Pediatr.* 2022;48(1). https://doi.org/10.1186/S13052-022-01205-W.
12. Smith JD, Fu E, Kobayashi MA. Prevention and Management of Childhood Obesity and Its Psychological and Health Comorbidities. *Annu Rev Clin Psychol*. 2020 May 7;16:351-378. https://doi.org/10.1146/annurev-clinpsy-100219-060201.
13. Kim A, Nguyen J, Babaei M, Kim A, Geller DH, Vidmar AP. A Narrative review: Phentermine and topiramate for the Treatment of Pediatric Obesity. *Adolescent Health Medicine and Therapeutics.* 2023;Volume 14:125-140. https://doi.org/10.2147/ahmt.s383454.
14. Kelly AS, Auerbach P, Barrientos-Perez M, Gies I, Hale PM, Marcus C, Mastrandrea LD, Prabhu N, Arslanian S; NN8022-4180 Trial Investigators. A Randomized, Controlled Trial of Liraglutide for Adolescents with Obesity. *N Engl J Med.* 2020 May 28;382(22):2117-2128. https://doi.org/10.1056/NEJMoa1916038.
15. Витебская АВ, Попович АВ. Опыт применения лираглутида у подростков с простым ожирением и сопутствующими заболеваниями желудочно-кишечного тракта. *Ожирение и метаболизм.* / Vitebskaya AV, Popovich AV. Liraglutide in adolescents with simple obesity and gastrointestinal comorbidities: treatment experience. *Obesity and metabolism.* 2023;20(2):124-130. https://doi.org/10.14341/omet12922. (In Russ.).
16. Шаршова ОГ, Чубаров ТВ, Петеркова ВА, Жданова ОА, Артющенко АИ. Эффективность и безопасность применения лираглутида в терапии детского ожирения. *Вестник Российской академии медицинских наук.* /

Sharshova OG, Chubarov TV, Peterkova VA, Zhdanova OA, Artyushchenko AI. Effectiveness and safety of liraglutide in the treatment of childhood obesity. *Annals of the Russian Academy of Medical Sciences.* 2024;79(6):515-522. https://doi.org/10.15690/vramn18011. (In Russ.).

17. Fox CK, Barrientos-Pérez M, Bomberg EM, Dcruz J, Gies I, Harder-Lauridsen NM, Jalaludin MY, Sahu K, Weimers P, Zueger T, Arslanian S; SCALE Kids Trial Group. Liraglutide for Children 6 to <12 Years of Age with Obesity - A Randomized Trial. *N Engl J Med.* 2025;392(6):555-565. https://doi.org/10.1056/NEJMoa2407379.
18. Li Y, Rosenblit PD. Glucagon-Like Peptide-1 Receptor Agonists and Cardiovascular Risk Reduction in Type 2 Diabetes Mellitus: Is It a Class Effect? *Curr Cardiol Rep.* 2018 Sep 26;20(11):113. https://doi.org/10.1007/s11886-018-1051-2.
19. Gerstein HC, Colhoun HM, Dagenais GR, et al.; REWIND Trial Investigators. Design and baseline characteristics of participants in the Researching cardiovascular Events with a Weekly INcretin in Diabetes (REWIND) trial on the cardiovascular effects of dulaglutide. *Diabetes Obes Metab.* 2018 Jan;20(1):42-49. https://doi.org/10.1111/dom.13028.
20. Fisher M, Petrie MC, Ambery PD, et al. Cardiovascular safety of albiglutide in the Harmony programme: a meta-analysis. *Lancet Diabetes Endocrinol.* 2015 Sep;3(9):697-703. https://doi.org/10.1016/S2213-8587(15)00233-8.
21. Marso SP, Daniels GH, Brown-Frandsen K, et al.; LEADER Steering Committee; LEADER Trial Investigators. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med.* 2016 Jul 28;375(4):311-22. https://doi.org/10.1056/NEJMoa1603827.
22. Helmstädter J, Keppeler K, Aust F, et al. GLP-1 analog liraglutide improves vascular function in polymicrobial sepsis by reduction of oxidative stress and inflammation. *Antioxidants*. 2021;10(8):1175. https://doi.org/10.3390/antiox10081175.
23. Mehdi SF, Pusapati S, Anwar MS, et al. Glucagon-like peptide-1: a multi-faceted anti-inflammatory agent. *Frontiers in Immunology.* 2023;14. https://doi.org/10.3389/fimmu.2023.1148209.
24. Bendotti G, Montefusco L, Lunati ME, et al. The anti-inflammatory and immunological properties of GLP-1 Receptor Agonists. *Pharmacological Research.* 2022;182:106320. https://doi.org/10.1016/j.phrs.2022.106320.
25. Халимов ЮШ, Агафонов ПВ, Кузьмич ВГ, Салухов ВВ. Агонисты рецепторов глюкогоноподобного пептида 1 типа и новые возможности первичной профилактики сердечно-сосудистых осложнений у больных сахарным диабетом 2 типа. *Доктор. Ру* / Khalimov YuSh, Agafonov PV, Kuzmich VG, Salukhov VV. Glucagon-like Peptide-1 Receptor Agonists and New Opportunities in Primary Prevention of Cardiovascular Complications in Patients with Type 2 Diabetes Mellitus. *Doctor Ru*. 2021;20(2):21-29. https://doi.org/10.31550/1727-2378-2021-20-2-21-29 (In Russ.).
26. Lu C, Xie T, Guo X, et al. Glucagon-like peptide-1 receptor agonist exendin-4 mitigates lipopolysaccharide-induced inflammatory responses in RAW264.7 macrophages. *International Immunopharmacology.* 2019;77:105969. https://doi.org/10.1016/j.intimp.2019.105969.
27. Diz-Chaves Y, Herrera-Pérez S, González-Matías LC, Mallo F. Effects of Glucagon-like peptide 1 (GLP-1) analogs in the hippocampus. *Vitamins and Hormones.* January 2022:457-478. https://doi.org/10.1016/bs.vh.2021.12.005.
28. Manavi MA. Neuroprotective effects of glucagon-like peptide-1 (GLP-1) analogues in epilepsy and associated comorbidities. *Neuropeptides.* 2022;94:102250. https://doi.org/10.1016/j.npep.2022.102250.
29. Cheng D, Yang S, Zhao X, Wang G. The role of Glucagon-Like Peptide-1 Receptor Agonists (GLP-1 RA) in Diabetes-Related Neurodegenerative Diseases. *Drug Design Development and Therapy.* 2022;Volume 16:665-684. https://doi.org/10.2147/dddt.s348055.
30. Shamkhalova MS, Sklyanik IA, Shestakova MV. Nephroprotective potential of glucagon-like peptide-1 receptor agonists. *Diabetes Mellitus.* 2020;23(1):56-64. https://doi.org/10.14341/dm12379.
31. Chen J, Zhao H, Ma X, et al. GLP-1/GLP-1R signaling in regulation of adipocyte differentiation and lipogenesis. *Cellular Physiology and Biochemistry.* 2017;42(3):1165-1176. https://doi.org/10.1159/000478872.

32. Balteau M, Van Steenbergen A, Timmermans AD, et al. AMPK activation by glucagon-like peptide-1 prevents NADPH oxidase activation induced by hyperglycemia in adult cardiomyocytes. *AJP Heart and Circulatory Physiology.* 2014;307(8):H1120-H1133. https://doi.org/10.1152/ajpheart.00210.2014.
33. Veprik A, Denwood G, Liu D, et al. Acetyl-CoA-carboxylase 1 (ACC1) plays a critical role in glucagon secretion. *Communications Biology.* 2022;5(1). https://doi.org/10.1038/s42003-022-03170-w.
34. Bu T, Sun Z, Pan Y, Deng X, Yuan G. Glucagon-Like peptide-1: new regulator in lipid metabolism. *Diabetes & Metabolism Journal.* 2024;48(3):354-372. https://doi.org/10.4093/dmj.2023.0277.
35. Gaspari T, Brdar M, Lee HW, et al. Molecular and cellular mechanisms of glucagon-like peptide-1 receptor agonist-mediated attenuation of cardiac fibrosis. *Diabetes and Vascular Disease Research*. 2015;13(1):56-68. https://doi.org/10.1177/1479164115605000.