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Review article / обзорная статья

Practical application of semaglutide: From evidence-based research to expert decisions

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Abstract

The rapid progress in the development of highly effective weekly incretin-based medications offers increasingly broad opportunities for comprehensive management of cardiometabolic disorders in patients with type 2 diabetes and/or obesity. This article aims to summarize existing research that confirms the efficacy and safety of one of the most prescribed medications from the class of glucagon-like peptide-1 receptor agonists – weekly semaglutide. In addition to presenting the main results of randomized clinical trials involving semaglutide, particular emphasis is given to experimental and clinical studies related to the drug's effectiveness in real-world conditions and during during specific clinical scenarios with type 2 diabetes and/or obesity, such as surgical and endoscopic interventions, bariatric surgery, intermittent fasting, and religious dietary restrictions. Based on this evidence base and their own clinical experience, the interdisciplinary author team proposes practical approaches to adjusting hypoglycemic therapy in patients with type 2 diabetes when combined with semaglutide and transitioning to other therapies. Practical recommendations for the use of the drug in patients with obesity during both the active weight-loss phase and the maintenance phase are also provided. Key considerations supporting long-term obesity treatment are presented; however, trial de-escalation therapy schemes are also provided for patients who have successfully modified their lifestyle while achieving target weight outcomes. The reasons and mechanisms of the most frequent adverse events associated with semaglutide use, which represent a potential barrier to its utilization, are examined separately. The most effective strategies for their prevention and correction are outlined, which will enable the realization of the therapeutic potential of weekly semaglutide and thus improve patient outcomes in the long-term control of obesity and type 2 diabetes.

Keywords: type 2 diabetes; obesity, semaglutide, glucagon-like peptide-1 receptor agonist, gastrointestinal adverse events, perioperative period, bariatric surgery, clinical practice

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Практическое применение семаглутида: от доказательных исследований к экспертным решениям

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Резюме

Быстрый прогресс в разработке высокоэффективных еженедельных инкретиновых препаратов представляет все более широкие возможности комплексной коррекции кардиометаболических нарушений у пациентов с сахарным диабетом 2-го типа и/или ожирением. Настоящая статья нацелена на обобщение существующих исследований, подтверждающих эффективность и безопасность одного из самых назначаемых препаратов из класса агонистов рецепторов глюкагоноподобного пептида 1 – еженедельного семаглутида. Помимо изложения основных результатов рандомизированных клинических исследований с семаглутидом, особый акцент сделан на тех экспериментальных и клинических работах, которые касаются эффективности препарата в обычных условиях и в особые периоды жизнедеятельности пациента с сахарным диабетом 2-го типа и/или ожирением, таких как операционные и эндоскопические вмешательства, бариатрическая хирургия, интервальное голодание и религиозные пищевые ограничения. На основании этой доказательной базы и собственного клинического опыта междисциплинарным авторским коллективом предложены практические подходы к коррекции сахароснижающей терапии у больных сахарным диабетом 2-го типа при комбинации с семаглутидом и переключению на другую терапию. Также сформулированы практические рекомендации по применению препарата у пациентов с ожирением в фазе активного снижения массы тела и фазе ее удержания. Представлены ключевые соображения в поддержку длительной терапии ожирения, однако приведены и схемы пробной деэскалации терапии для пациентов, которые в процессе достижения целевых показателей массы тела успешно модифицировали свой образ жизни. Отдельно рассмотрены причины и механизмы развития наиболее распространенных нежелательных явлений, возникающих на фоне применения семаглутида, представляющих собой потенциальный барьер для его использования. Изложены наиболее эффективные меры по их профилактике и коррекции, которые позволят реализовать терапевтический потенциал еженедельного семаглутида и, таким образом, улучшить исходы пациентов в долгосрочном управлении ожирением и сахарным диабетом 2-го типа.

Ключевые слова: сахарный диабет 2-го типа, ожирение, семаглутид, агонист рецепторов глюкагоноподобного пептида 1, нежелательные явления со стороны желудочно-кишечного тракта, периоперационный период, бариатрическая хирургия, клиническая практика

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INTRODUCTION

Obesity and type 2 diabetes mellitus (T2DM) are interdependent chronic diseases that represent a global public health problem [1]. Successful treatment of obesity requires the recognition of its systemic nature, characterized by the complex pathogenesis arising from the combined effects of genetic, metabolic, neuroendocrine, behavioral, sociocultural, and environmental factors. For the time being, obesity is recognized as the most significant risk factor for the development and progression of T2DM in patients of all age groups; therefore, significant weight loss will not only positively impact the course of T2DM but also substantially reduce the number of new cases of dysglycemia [2].

Taking into account the heterogeneous nature of obesity, it is unlikely that a single intervention will effectively address all cases of obesity, and therefore treatment programs must be personalized and multimodal. At the same time, lifestyle modifications involving healthy eating and regular physical activity, which are fundamental components of metabolic health management, frequently demonstrate limited potential in achieving and maintaining target weight parameters. The issue of maintaining achieved results is particularly relevant for many patients and creates conditions for the formation of the "weight variability" phenomenon, which is a significant cardiovascular risk factor, necessitating the minimization of unsuccessful weight correction attempts [3].

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) represent a therapeutic breakthrough in managing patient prognosis and their cardiometabolic risks, including powerful glucose-lowering and weight-reducing effects. The "physiological" nature of their mechanism of action is due to their ability to mimic the effects of endogenous GLP-1 by activating widely distributed receptors for this hormone (including in the brain, pancreas, stomach, heart, kidneys, and adipose tissue), resulting in a series of changes in the neurohormonal system that regulate insulin and glucagon secretion, appetite, food intake, metabolism, and energy balance aimed at reducing body weight and fat mass [4]. However, native human GLP-1, produced in response to nutrient intake by enteroendocrine L-cells in the small and large intestine, has a very short half-life, as it is inactivated by the enzyme dipeptidyl peptidase-4 (DPP-4) within 1–2 minutes after entering the bloodstream and is excreted by the kidneys. To confer resistance to enzymatic degradation in the development of GLP-1 RA drugs, structural modifications of the molecules were required through the removal of amino acids or the addition of fatty acid chains [2].

Initially, GLP-1 RAs were developed for the treatment of T2DM, with the first representative of the class,

exenatide, that received regulatory approval for this indication in 2005. By 2015, the American regulatory agency FDA (Food and Drug Administration) approved liraglutide 3.0 mg for the treatment of obesity, and subsequently, in 2021, this indication was approved for semaglutide 2.4 mg with prolonged action (semaglutide was registered for T2DM treatment at a dose of 1.0 mg in 2017) [5]. Semaglutide 2.4 mg – a highly homologous long-acting GLP-1 analogue – demonstrated high efficacy, safety, and an acceptable tolerability profile in the Phase III clinical trials (STEP) among patients with obesity and T2DM or without it as an adjunct to intensive behavioral therapy combined with a low-calorie diet, including an assessment of its long-term clinical application across a broad sample of individuals from diverse racial and ethnic groups [6].

In the STEP 1, 3, 4, and 8 studies, the administration of semaglutide at a dose of 2.4 mg resulted in an average weight loss of 14.9–17.4% by week 68 in individuals with overweight or obesity but without type 2 diabetes mellitus (T2DM); notably, 69–79% of participants achieved ≥10% weight reduction (compared to 12–27% in the placebo group), and 51–64% achieved ≥15% weight loss from baseline (versus 5–13% in the placebo group). In a longer-term study, STEP 5, the use of semaglutide 2.4 mg weekly over 104 weeks led to a mean weight loss of 15.2%, compared to 2.6% in the placebo group. Only in the STEP 2 study (including individuals with overweight or obesity and T2DM) was a weight reduction of 9.6% from baseline observed at week 68, versus 3.4% in the placebo group [7].

Based on the significant weight loss observed in clinical trials, semaglutide 2.4 mg as an adjunct to lifestyle modification has been classified as a "second-generation" anti-obesity medication, capable of inducing weight loss exceeding 10% of baseline in most patients [8]. The accumulated evidence and demonstrated safety and efficacy of semaglutide 2.4 mg have led to the formulation of indications for its use in patients without T2DM: BMI ≥ 30 kg/m² or BMI ≥ 27 kg/m² but < 30 kg/m² with at least one obesity-related comorbidity (prediabetes or T2DM, arterial hypertension, dyslipidemia, obstructive sleep apnea, or cardiovascular disease).

It is important to note that existing studies have demonstrated the beneficial effects of semaglutide on glycemic, cardiometabolic parameters, and quality of life. Clinical trials documented reductions in glycated hemoglobin (HbA1c) and fasting glucose in clinical trials involving patients with and without T2DM, and also decreased the prevalence and incidence of prediabetes and T2DM compared to placebo. The use of semaglutide 2.4 mg was associated with reductions in systolic and diastolic blood pressure, along with improvements in lipid profiles and systemic inflammation markers.

The primary outcomes of weekly semaglutide 1.0 and 2.4 mg studies included the positive impact on cardiovascular and renal outcomes in patients with T2DM (SUSTAIN-6 trial) and in individuals with obesity without T2DM (SELECT trial) [9, 10]. The latter is particularly significant, as it is the first study of an anti-obesity drug to demonstrate a reduction in major adverse cardiovascular events (MACE). Specifically, in over 17,500 individuals with BMI ≥ 27 kg/m² and confirmed cardiovascular disease, semaglutide reduced the incidence of the composite primary endpoint (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) by 20% (OR 0.80; 95% CI 0.72–0.90; p < 0.001) over a median follow-up of 40 months [10].

The adverse effects observed with GLP-1 receptor agonist therapy in clinical trials are predominantly gastrointestinal and generally did not significantly affect treatment adherence. The most common adverse event was nausea (42% vs. 16% in placebo groups), with a tendency for increased frequency with dose escalation, followed by a decrease in occurrence shortly after dose titration. Other gastrointestinal events included diarrhea (26%), vomiting (21%), constipation (22%), abdominal pain (8%), and dyspepsia (10%). Most adverse events (98.1%) were mild or moderate in severity and did not lead to discontinuation of therapy [11].

Given the increased availability of weekly semaglutide for Russian patients, this article will provide practical recommendations for its use (oral semaglutide is not discussed herein) in cohorts of patients with overweight/obesity and/or T2DM, based on existing research findings, international guidelines, and, in their absence, the expert opinion of the authors.

ADJUSTMENT OF ANTIDIABETIC THERAPY IN PATIENTS WITH T2DM INITIATING SEMAGLUTIDE TREATMENT

Combination with oral glucose-lowering agents with low hypoglycemia risk

Semaglutide in patients with T2DM can be combined with metformin and most other oral agents. Exceptions include dipeptidyl peptidase-4 inhibitors (DPP-4 inhibitors), which should not be used concomitantly with semaglutide, as studies have not demonstrated an additive glucose-lowering effect with this combination [12]. No dose adjustments are required when semaglutide is administered with low-risk agents (e.g., metformin, SGLT-2 inhibitors, pioglitazone).

Several studies evaluating the combined use of GLP-1 RAs with SGLT-2 inhibitors in individuals with T2DM have shown improved glycemic control; however, data regarding the additional benefit of this combination for reducing cardiovascular and renal outcomes remain controversial [13]. For instance, in a cardiovascular safety trial of efpeglenatide, some participants were initially on SGLT-2 inhibitors (15% of the total cohort), but the incidence of the primary composite endpoint (MACE) did not differ between those who received SGLT-2 inhibitors and those who did not [14]. In contrast, numerous observational studies suggest additional cardioprotective and nephroprotective benefits of this combination, which

warrants further research [15]. According to the current international and national guidelines, in patients with established cardiovascular disease and/or kidney disease, combined therapy with GLP-1 RAs and SGLT-2 inhibitors may be considered if glycemic targets are not achieved with monotherapy [16, 17].

Combination with insulin or sulfonylureas

Semaglutide may be used concomitantly with insulin or sulfonylureas; however, this significantly increases the risk of hypoglycemia. Proactive reduction of the daily dose of insulin or sulfonylurea may be necessary, depending on the baseline HbA1c level and glycemic profile, which should be assessed immediately prior to initiating semaglutide.

Based on published data and clinical experience, the authors recommend considering the following adjustments at the initiation of semaglutide 0.25 mg:

- For HbA1c < 7%, reduce the basal insulin dose by 20%.
- For HbA1c 7–8%, reduce the basal insulin dose by 10–20%.

(For HbA1c > 8%, maintain the current basal insulin dose; however, if the patient exhibits high glycemic variability and frequent hypoglycemic episodes, reduce the basal insulin dose by 10%).

In a basal-bolus insulin regimen, initiating semaglutide 0.25 mg involves a similar adjustment of the basal insulin dose, with concurrent modification of bolus insulin according to the following algorithm:

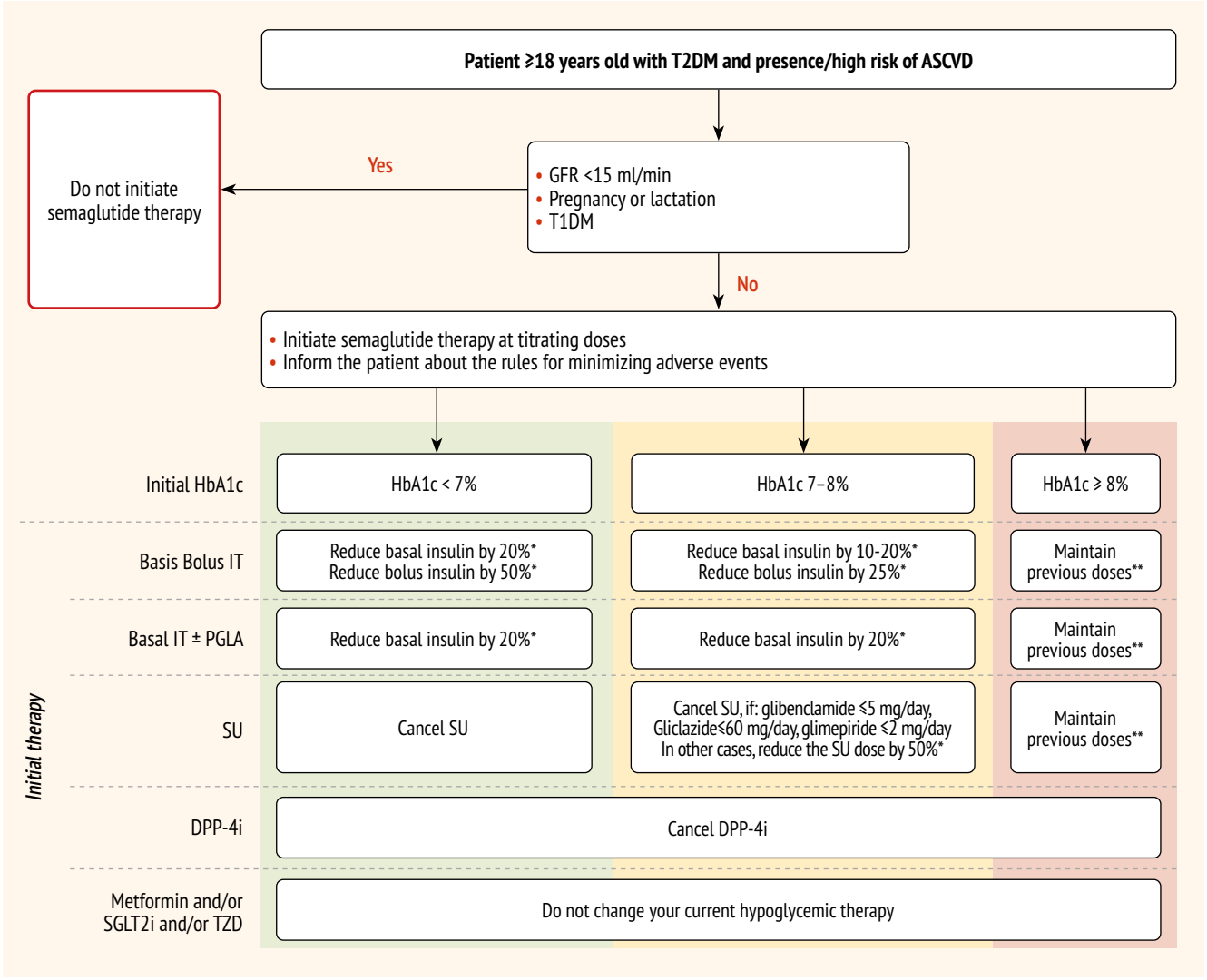
- HbA1c < 7%, reduce bolus insulin by 50%.
- HbA1c 7–8%, reduce bolus insulin by 25%.

(HbA1c > 8%, no change in insulin doses is required; however, if high glycemic variability and confirmed hypoglycemia are present, reduce bolus insulin by 25%) [18].

Similarly, the sulfonylurea dose should be adjusted or discontinued based on its hypoglycemic potential and HbA1c level (*Fig. 1*).

Comment: Clinical observations indicate that for most patients with poor glycemic control, adding a GLP-1 receptor agonist does not necessitate reducing the daily doses of insulin or sulfonylureas; however, all patients should be informed about

● ***Figure 1.*** Algorithm for adjusting glucose-lowering therapy when prescribing weekly semaglutide
● ***Рисунок 1.*** Алгоритм коррекции сахароснижающей терапии при назначении семаглутида



* – repeat under glycemic control during the next titration step
** – in cases of high glycemic variability, insulin dose correction may be necessary

the risk of hypoglycemia and the appropriate strategy for dose reduction of these medications.

A similar dose-reduction algorithm for insulin or sulfonylureas should be repeated at each step of semaglutide titration depending on glycemic indicators.

Commentary: the authors recommend that, given the insufficient time to accurately assess HbA1c during monthly titration of semaglutide, the estimated method based on daily glycemic profile indicators be used for its evaluation.

"Switching" between GLP-1 receptor agonists and GIP/GLP-1 receptor co-agonists

Currently, there is no consensus regarding indications and recommendations for switching between different GLP-1 receptor agonists and GIP/GLP-1 receptor co-agonists. However, clinical experience shows that such switching may be necessary due to factors such as drug availability, adherence, cost, frequency of adverse events/tolerance, efficacy, and patient preferences [19]. Before switching from one drug to another, it is crucial to analyze the reason for dissatisfaction and only after attempting to address it—based on the drug dose, duration of therapy, and patient experience with side effects—should the "switching" tactic be considered.

Commentary: based on literature and clinical experience, the authors propose the following switching algorithm that considers the tolerability of the initial drug:

A. If well tolerated, switching to another drug at an equivalent dose in terms of glucose-lowering effect is recommended, ensuring a smooth transition while maintaining the desired therapeutic effect (*Table 1*).

B. In cases of gastrointestinal side effects, it is recommended to use all measures to mitigate them, including stepwise dose reduction, which often helps to alleviate adverse reactions. A reduced dose with good tolerability, if the therapeutic effect is insufficient, becomes the basis for choosing an equivalent dose of another agonist. Titration of the new drug at an equivalent dose should involve a slower increase in dose and strict adherence to adverse event prevention measures.

C. In cases of significant gastrointestinal complaints that cannot be alleviated by dose titration of the GLP-1 receptor agonist or GIP/GLP-1 receptor co-agonist tirzepatide, despite implementing all measures to mitigate side effects, complete discontinuation of the medication is recommended. After the symptoms subside, therapy with another GLP-1 receptor agonist or tirzepatide at the lowest dose can be initiated, with consideration for a slower dose escalation while strictly following adverse event prevention protocols [21].

When switching from a once-daily medication (liraglutide) to another GLP-1 receptor agonist, the new drug should be administered the day after stopping the previous medication. When switching from a weekly administered drug, such as dulaglutide, semaglutide, or tirzepatide, it is recommended to start the new medication 7 days after the last dose of the previous one.

DURATION OF SEMAGLUTIDE USE IN PATIENTS WITH OBESITY

Optimal duration of the active weight loss phase

Currently, the longest studied use of weekly semaglutide in patients with obesity without type 2 diabetes is the SELECT trial. Patients receiving semaglutide experienced weight loss sustained through 65 weeks, maintained up to 4 years. After 208 weeks, semaglutide was associated with an average weight reduction of -10.2%, waist circumference -7.7 cm compared to placebo (-1.5%, -1.3 cm, and -1.0%, respectively; $p < 0.0001$ for all comparisons with placebo). Clinically significant weight loss was observed in men and women of all races, with any initial body weight, and from various regions.

Another study, STEP-5, showed a sustained, substantial weight loss over 2 years, with an average reduction of 15.2% after 68 weeks in the semaglutide group compared to 2.6% in the placebo group. Concomitant with weight loss, improvements in cardiometabolic parameters such as HbA1c, blood pressure, and lipid profile were observed, reaching a plateau after 60 weeks of semaglutide therapy. Together, these effects provide a serious potential for clinically meaningful improvement in obesity-related diseases.

Commentary: The duration of semaglutide therapy in patients with obesity should be at least 16–18 months, during

● ***Таблица 1.*** Эквивалентные дозы для некоторых агонистов рецепторов ГПП-1 и коагонистов рецепторов ГИП/ГПП-1 по их влиянию на гликемический контроль [20]

● ***Table 1.*** Equivalent doses of some GLP-1 receptor agonists and GIP/GLP-1 receptor co-agonists based on their effects on glycemic control [20]

Medication	Frequency of administration	Equivalent dose, mg									
Liraglutide	Daily	0,6	1,2	1,8							
Dulaglutide	Weekly		0,75	1,5	3,0*	4,5*					
Semaglutide	Weekly		0,25	0,5		1,0	2,0*				
Tirzepatide	Weekly			2,5		5,0	5,0**	7,5	10	12,5	15

** Not registered in the Russian Federation.*
*** When switching from a higher dose of semaglutide, it is recommended to start tirzepatide at a dose not exceeding 5.0 mg to reduce the risk of hypoglycemia.*

which the maximum weight reduction effect is typically achieved. Shorter treatment programs are less preferred because they may lead to a "yo-yo" effect.

Patients who, after this period on a dose of 2.4 mg semaglutide, have not reached target weight loss but lose ⩾ 0.5% of body weight per week are recommended to continue therapy. If the patient reaches a plateau ("dose-effect") on 2.4 mg semaglutide and, despite optimizing management of adverse effects, does not lose weight within 3 months, it is advisable to switch from a GLP-1 receptor agonist to tirzepatide (Table 1).

In some cases (e.g., clinically significant adverse events after each titration step, persistently high weight loss rate > 1.0% per week, or stage 0 obesity), the authors recommend slower titration than monthly, provided weight loss is at least 0.5% per week; as the weight-reducing effect diminishes (less than 0.5% per week), titration should be resumed according to the prescribing guidelines of semaglutide.

Optimal Approaches to Maintenance/Weight Control Phase

Considering that obesity is a chronic, progressive, and relapsing disease, short-term treatment lasting 3–6 months is not recommended, as it not only fails to provide long-term weight loss benefits but also predisposes to weight regain. The inevitability of weight regain has been demonstrated in the STEP 4 and STEP 1 studies, where patients, after 20 and 68 weeks of semaglutide discontinuation, respectively, regained 50% and 65% of their previous weight loss within the following year of observation [22].

Therefore, for most patients, achieving the target weight reduction during weekly semaglutide therapy, in addition to lifestyle modifications, requires not discontinuing the medication but maintaining long-term pharmacotherapy to sustain the achieved weight loss.

Clinical practice also shows that only a small proportion of individuals, after prolonged use of semaglutide that significantly changed their eating behavior, are capable of controlling their weight through non-pharmacological methods. A key predictor of successful discontinuation of pharmacotherapy in favor of lifestyle modifications alone is the patient's established regular physical activity.

For this cohort, a trial scheme has been tested involving gradual dose reduction of semaglutide with an assessment of the prospects for discontinuing medication support. For example, in the Danish TAILGATE study, after achieving clinically significant weight loss, 353 participants underwent a stepwise reduction of semaglutide dose every two weeks (2.4 mg → 1.7 mg → 1.0 mg → 0.5 mg → 0.25 mg) until complete cessation. Simultaneously, physical activity levels and appetite/food intake were expanded and monitored, supported by digital applications and healthcare professional supervision. After six months off pharmacotherapy, only 21.5% of patients resumed semaglutide due to weight regain [23]. This led to the conclusion that supporting lifestyle modifications with gradual dose reduction of semaglutide is more effective for weight maintenance than abrupt discontinuation, resulting in more successful weight retention over six months in most subjects.

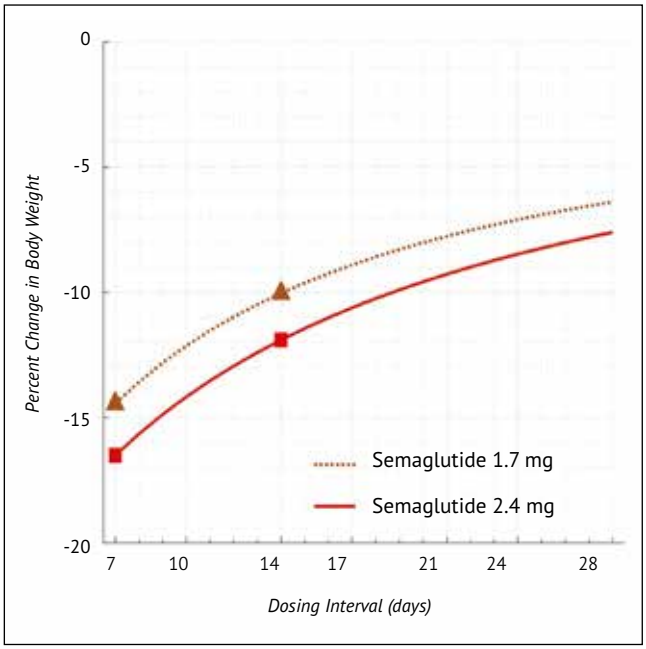
While acknowledging the short-term nature of the non-pharmacological observation period in this study, the practical significance of the "down-titration" strategy of GLP-1 receptor agonists should be noted, as it allows identification of patients capable of maintaining weight loss either on the minimally effective dose of semaglutide or after complete discontinuation.

Another alternative dosing scheme for semaglutide aimed at maintaining weight loss involves reducing the frequency of administration. This approach is based on mathematical modeling of semaglutide's "effect-response" efficacy, derived from the STEP 1–3 studies, which predicts the trajectory of weight loss over one year [24].

According to this model, the interval between injections of 2.4 mg semaglutide every 7 days (S7) is expected to sustain a weight reduction of approximately 17%, consistent with existing clinical data on semaglutide in obese patients. Prolonging the dosing period to 14 days (S14) predicts a lesser weight loss of about 12% from baseline. Despite halving the drug concentration over time by reducing injection frequency from S7 to S14, the model forecasts that patients retain about 72% of the initial weight loss. Similarly, semaglutide 1.7 mg administered with a 14-day interval (S14) preserves approximately 69% of weight loss compared to the same dose given weekly (S7). Furthermore, the model predicts that further reducing injection frequency from weekly to monthly (S28) could maintain nearly 50% of the initial weight loss (*Fig. 2*).

● ***Figure 2.*** Percentage change in body weight according to the dosing interval (the time between injections) of semaglutide [24]

● ***Рисунок 2.*** Процентное изменение массы тела в зависимости от интервала дозирования (времени между инъекциями) семаглутида [24]



According to this model, an acceptable level of efficacy could support a scenario of less frequent administration of higher doses of semaglutide, which, however, demands verification through further analysis of research data. Thus, the optimal GLP-1 receptor agonist therapy scheme and the selection of an "effectively sufficient" dose for weight maintenance remain to be determined by future studies, and may be tailored based on individual patient characteristics.

Commentary: For the vast majority of patients who achieve clinically significant weight loss, indefinite long-term therapy with semaglutide in addition to lifestyle modifications is recommended to maintain the result. The authors consider that, in motivated patients with regular adequate physical activity, it may be appropriate to consider a trial reduction of semaglutide dose either: a) gradual "down-titration" with a step every two weeks, or b) decreasing the frequency of administration until complete discontinuation. In case of failure and weight regain, it is necessary to revert to the minimally effective dose for long-term therapy, avoiding future attempts to discontinue GLP-1 receptor agonists. The criterion for effectiveness should be a level of appetite suppression achieved with the medication that allows the patient to manage eating behavior without a noticeable reduction in quality of life.

VARIABILITY OF RESPONSE TO SEMAGLUTIDE IN INDIVIDUALS WITH OBESITY AND/OR TYPE 2 DIABETES

Research from the STEP program reported significant variability in response to semaglutide: 32–39.6% of patients were super-responders, achieving weight loss of more than 20%; 10.2–16.7% were non-responders, demonstrating less than 5% weight reduction from baseline; and responders, observed in 51% of cases, experienced weight loss of more than 5% but less than 20% [25].

Analysis of study results identified two predictors of lower weight loss with semaglutide: presence of type 2 diabetes and male sex. Specifically, the average weight reduction in obese individuals without diabetes was 14.9% of baseline, compared to 9.6% in those with diabetes. Men experienced an average weight loss of 8–9.3% relative to baseline, whereas women lost 14–16.2% [26].

This variability in weight reduction highlights the need for further research into prognostic factors such as demographic characteristics (sex, ethnicity, age), metabolic parameters (initial BMI, glycated hemoglobin, fasting glucose, insulin resistance markers, lipid profile), eating behaviors (hunger, satiety, episodes of hyperphagia, food cravings), and others.

Commentary: Patients classified as non-responders to semaglutide therapy—those who, over 3–6 months, demonstrate less than 5% weight loss from baseline—are advised to switch to a GIP/GLP-1 receptor co-agonist tirzepatide (Table 1), or, in cases of morbid obesity, to consider bariatric surgery as a more appropriate intervention.

THERAPY WITH SEMAGLUTIDE DURING SPECIFIC PERIODS

Use of Semaglutide During Planned Surgical or Endoscopic Procedures

There are concerns that perioperative use of GLP-1 receptor agonists may be associated with an increased risk of bronchopulmonary aspiration due to delayed gastric emptying. Indeed, activation of GLP-1 receptors reduces gastric emptying by inhibiting gastric motility while simultaneously increasing pyloric tone and augmenting postprandial gastric volume, a process likely mediated via the vagus nerve [27].

A prospective study of individuals who started semaglutide (19 out of 20 without type 2 diabetes, mean BMI 26.9 kg/m^2), evaluated via ultrasound after overnight fasting, demonstrated that 70% of participants on weekly semaglutide retained a solid gastric content consistent with digested food after at least 10 hours of fasting [28]. Similarly, a prospective assessment of residual gastric content before planned surgery was conducted in participants who, on average, received weekly semaglutide, dulaglutide, or tirzepatide for 5 days prior to evaluation (mean BMI 33.9 kg/m^2), following fasting periods of 2 to 8 hours. Ultrasound revealed residual gastric content in 30% of individuals on GLP-1 receptor agonists without diabetes and in 47% of those with diabetes, compared to 19% in the control group. Other studies using capsule endoscopy, sonography, scintigraphy, and other methods have also documented delayed gastric emptying in patients on GLP-1 receptor agonist therapy [27].

A retrospective analysis of patients with diabetes and/or obesity who underwent esophagogastroduodenoscopy showed a higher percentage with residual gastric content in those on semaglutide versus controls (6.7% vs. 5.1%), with gastrointestinal symptoms such as nausea/vomiting, dyspepsia, and bloating more frequently reported–likely reflecting recent dose escalation or limited clinical experience with these agents [29]. This is supported by tirzepatide studies, which demonstrated a greater delay in gastric emptying at initiation or dose escalation, with the effect diminishing after 23 days, indicating tachyphylaxis, i.e., a reduction in response to prolonged exposure [30].

Therefore, the presence of gastrointestinal complaints following recent dose titration of GLP-1 receptor agonists can indirectly suggest a period of more pronounced impact on gastric emptying. The resolution of gastrointestinal symptoms, which typically occurs after 12–20 weeks of semaglutide therapy, appears to reflect the development of tachyphylaxis and improved gastric emptying [31].

Analysis of bowel preparation adequacy for diagnostic colonoscopy indicated that participants on GLP-1 receptor agonists for diabetes or obesity had higher rates of inadequate bowel prep, resulting in increased need for repeat colonoscopy [32].

These data prompted professional associations in anesthesiology, gastroenterology, and surgery to develop guidelines for pre- and perioperative management of patients on GLP-1 receptor agonists, which often contain conflicting recommendations. The most common advice for patients with obesity without diabetes is to discontinue weekly GLP-1 receptor agonists 7 days before planned surgery, whereas for patients with diabetes, it is suggested to continue the medication while following a liquid diet 24 hours before the procedure [33].

However, there is currently no evidence that discontinuing weekly GLP-1 therapy one week prior to surgery minimizes gastroparesis, especially considering the drug's half-life. For example, if a patient on 1.0 mg weekly semaglutide interrupts the medication, plasma concentrations will remain similar to those in a person continuing 0.5 mg weekly during the following week [34]. These findings, along with recent studies showing residual gastric content despite a 21-day discontinuation of semaglutide, suggest that the standard 7-day cessation period is insufficient to reduce the risk of bronchopulmonary aspiration [35].

Conversely, it is also important to consider the risk of perioperative hyperglycemia in patients with diabetes, which may occur due to loss of glycemic control upon discontinuing semaglutide. Such hyperglycemia increases the probability of prolonged hospitalization, surgical wound infections, acute kidney injury, and adverse cardiovascular events [36]. Additionally, obese patients without diabetes are at increased risk of stress hyperglycemia during the perioperative period, which is associated with even worse outcomes than in patients with diabetes [37].

It is important to note that GLP-1 receptor agonists have been used in millions of patients worldwide over the past 20 years, but only a few reports describe significant perioperative bronchopulmonary aspiration cases. This suggests that proper clinical assessment, anesthetic risk evaluation, consideration of the procedure's nature, and chosen anesthetic techniques generally balance out the challenges posed by GLP-1-induced delayed gastric emptying and perioperative preparation.

Commentary: Based on the above, the authors maintain that discontinuing semaglutide before elective surgery or endoscopy is not advisable, as current evidence is insufficient to demonstrate the benefits and improved safety of preoperative cessation in patients with diabetes and/or obesity.

Elective surgical or endoscopic procedures should be performed after completing dose titration and resolution of nausea/vomiting, dyspepsia, or constipation; however, these symptoms should not be considered mandatory signs of gastric content retention.

Patients should receive only liquid nutrition for 24 hours prior to surgery or endoscopy, followed by the standard 8-hour fasting period.

For assessment of residual gastric content before the procedure, transabdominal ultrasound is recommended. If residual content is detected, measures such as prokinetic agents (e.g., metoclopramide), gastric drainage via nasogastric tube, or rapid sequence induction protocols should be considered to reduce aspiration risk.

Use of semaglutide before and after bariatric surgery

Recurrent weight regain after bariatric procedures is a common phenomenon, with a prevalence reaching up to 67% among operated patients at five years post-surgery. The rate varies depending on the type of surgery, institution, length of follow-up, and other factors [38]. The application of GLP-1 receptor agonists appears to be a promising approach for treating patients who regain weight after initial successful treatment—commonly referred to as "regainers"—who have demonstrated weight gain following bariatric procedures. The efficacy of weekly semaglutide in managing obesity relapse after surgery, along with a favorable safety profile, has been confirmed in several retrospective studies, showing an average weight loss of 9.8–11.4% (approximately two-thirds of the weight gained postoperatively) over six months of therapy, with only a small proportion (3%) discontinuing treatment due to gastrointestinal adverse events typically associated with GI complaints [39–41].

Another promising approach involves the use of GLP-1 receptor agonists in patients who have not achieved the target weight reduction after bariatric surgery. Some observational studies have indicated a correlation between successful weight loss post-surgery and higher endogenous GLP-1 levels [42]. Therefore, insufficient surgical effect can potentially be corrected by adding long-acting weekly GLP-1 receptor agonists, which not only elevate baseline GLP-1 levels—enhancing its beneficial effects—but also attenuate "metabolic adaptation". This adaptation involves a decrease in energy expenditure during weight loss, which hampers further weight reduction. Semaglutide has been shown to mitigate this "barrier" to more effective weight loss, as demonstrated in experimental models [43].

In addition to weight reduction in regainers, GLP-1 receptor agonists may reduce the severity of post-bariatric hypoglycemia (developing 2–3 hours after meals and more precisely characterized as postprandial hyperinsulinemic hypoglycemia). Postprandial hyperinsulinemic hypoglycemia develops in the long-term postoperative period and is a serious complication requiring management. Continuous glucose monitoring shows that post-bariatric hypoglycemia occurs in approximately 55% of patients after sleeve gastrectomy and up to 75% after gastric bypass. A recent systematic review indicated that GLP-1 receptor agonists can potentially decrease the frequency of postprandial hypoglycemic episodes and improve glycemic stability, despite elevated levels of GLP-1, insulin, and C-peptide observed in hypoglycemic individuals due to rapid transit of food into the small intestine [44]. The mechanisms underlying the paradoxical reduction in hypoglycemia frequency after GLP-1 receptor stimulation are not fully understood

but may involve decreased postprandial GLP-1 variability, preventing insulin secretion peaks, and slowing gastric transit, thereby reducing postprandial glycemic excursions and limiting insulin needs [45].

An important, yet still understudied, area is the use of GLP-1 receptor agonists as preoperative (neoadjuvant) pharmacotherapy before bariatric surgery, which could potentially improve surgical outcomes and reduce complication risks, especially in patients with "superobesity" (BMI > 50 kg/m^2) [46].

Commentary: Based on current literature and clinical experience, the authors recommend considering a 3–6 month course of semaglutide in patients with BMI > 50 kg/m^2 prior to bariatric surgery to reduce body weight, liver size, and operative risks.

Postoperative use of weekly semaglutide is safe and justified not only in patients with weight regain but also in those who have not achieved the targeted weight loss. In cases of long-term post-surgical postprandial hyperinsulinemic hypoglycemia, a trial of semaglutide may be considered.

Use of Semaglutide During Intermittent Fasting, Religious Fasts, and Ramadan

In patients with type 2 diabetes, intermittent fasting and dietary restrictions during Christian fasting periods and the holy month of Ramadan can pose challenges in maintaining glycemic control. However, published studies have shown that using GLP-1 receptor agonists during Ramadan is safe and effective, with good glycemic control and weight loss. For example, exenatide was associated with a very low incidence of hypoglycemia (0.08%), and liraglutide was linked to fewer symptomatic hypoglycemic episodes compared to sulfonylureas ($p = 0.0009$) [47]. This is attributable to their glucose-dependent insulin and glucagon regulation, which minimizes hypoglycemia risk when used alone but increases the risk when combined with other hypoglycemic agents.

Therefore, semaglutide can be considered a suitable choice for patients with T2D undergoing dietary restrictions, aiming to replace therapies that carry a higher hypoglycemia risk. It is recommended to initiate weekly semaglutide 4–8 weeks before fasting begins, with close monitoring of gastrointestinal side effects, dehydration, and titration to ensure tolerability [48].

ADVERSE EVENTS RELATED TO GLP-1 RECEPTOR AGONISTS

Adverse events (AEs) associated with GLP-1 receptor agonists are actively studied regarding their frequency, conditions of occurrence, preventive measures, and correction strategies. Currently, accumulating evidence allows for the objective documentation of AEs—more common in clinical trials than in placebo groups—through dedicated studies, meta-analyses, and observational programs. At present, AEs can be classified as either questionable or genuinely occurring (*Fig. 3*).

Gastrointestinal Adverse Events

Nausea, vomiting, diarrhea, and constipation are the most common adverse events associated with GLP-1 receptor agonists. However, it is important to exclude infectious diseases or underlying gastrointestinal conditions when these symptoms develop (*Table 2*). Typically, these adverse events occur during dose escalation and tend to subside over time. Nonetheless, in some cases, gastrointestinal complaints are the primary reason for temporary or permanent discontinuation of therapy, which occurs in approximately 1.6–6% of patients initiating GLP-1 receptor agonist treatment. Severe and persistent gastrointestinal adverse events may limit fluid intake and potentially lead to dehydration and acute kidney injury [11].

Mechanism: The effect is dose-dependent and is thought to be related to activation of GLP-1 receptors in the central amygdala, which triggers aversive reactions to the medication, as well as in brain centers that regulate intestinal motility and delay gastric emptying.

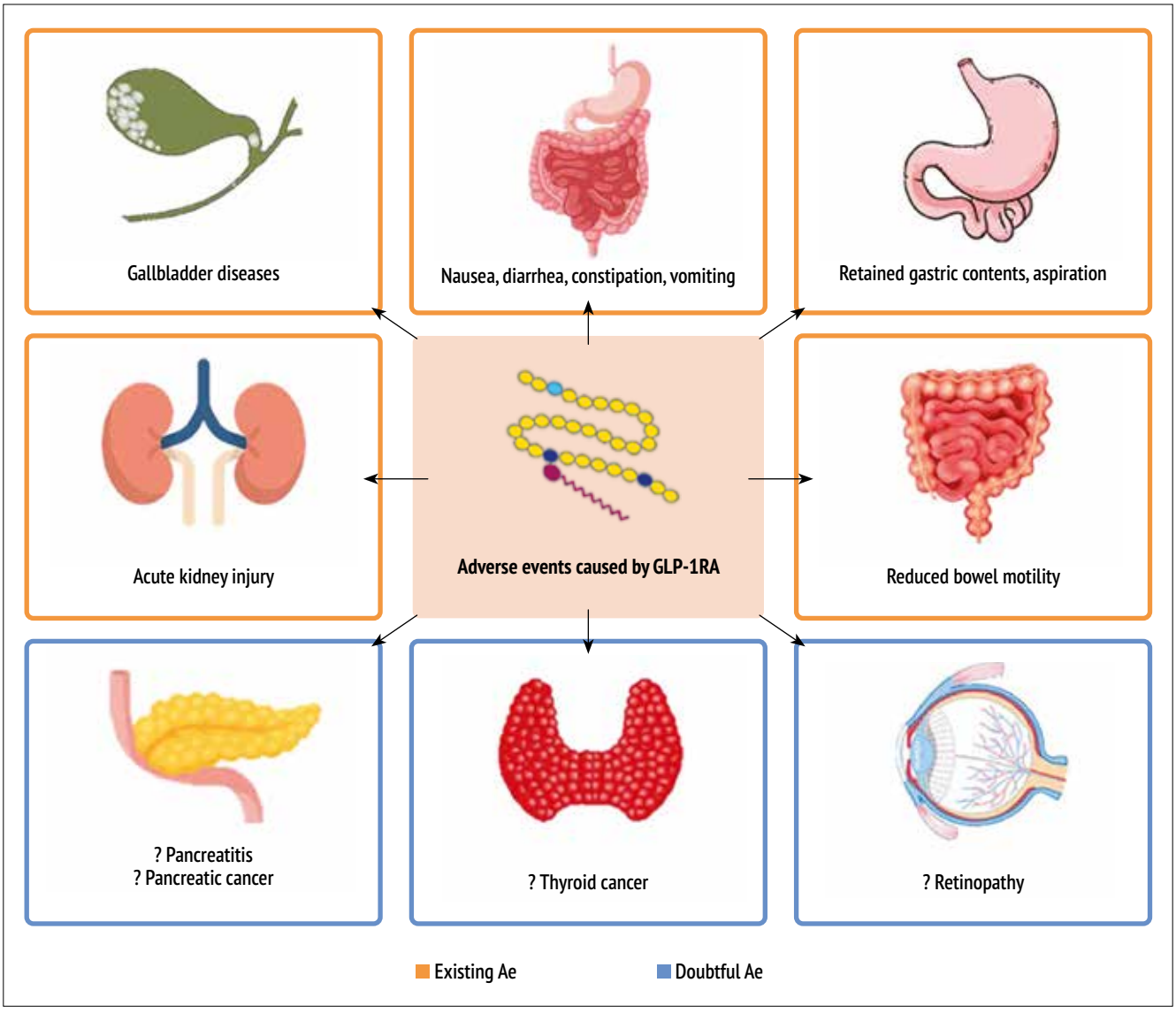
Risk Factors: Rapid titration, recent dose increase, and higher medication doses.

Gastrointestinal Motility Reduction

GLP-1 receptor agonists slow down small intestinal peristalsis and increase the gastrointestinal transit time in individuals with and without T2D [49]. The mechanisms underlying this effect are currently unknown but are likely mediated by parasympathetic influences and direct effects on the central nervous system. Even less is known about the impact of GLP-1 receptor agonists on colorectal function. In a patient with a neuroendocrine tumor secreting large amounts of GLP-1 and GLP-2, delayed transit through the gastrointestinal tract, including the colon, was observed [50]. As previously mentioned, the use of GLP-1 receptor agonists in patients more often associated with lower quality of bowel preparation for colonoscopy. The clinical significance of this phenomenon is sometimes linked to a higher risk of intestinal obstruction. However, existing data on the association between intestinal obstruction and GLP-1 receptor agonist use are contradictory. While some studies suggest an increased risk up to threefold, others report no association. A recent high-quality study, analyzing nationwide registries from Sweden, Denmark, and Norway, involving 121,254 patients who initiated GLP-1 therapy between 2013 and 2021, compared them with 185,027 patients who recently started SGLT-2 inhibitors. Unlike previous studies, the frequency of intestinal obstruction (including bowel obstruction, intussusception, volvulus, neurogenic bowel, megacolon, and other types) was not significantly different between SGLT-2 inhibitors and GLP-1 receptor agonists, and a trend toward fewer events was observed with GLP-1 therapy (OR 0.83 95% CI, 0.69–1.01) [51].

Clearly, further research is needed to clarify the effects of GLP-1 receptor agonists on the motility of the small and large intestines and their clinical implications.

● ***Figure 3.*** Adverse events associated with the use of GLP-1 receptor agonists1 (adapted from [5])
● ***Рисунок 3.*** Нежелательные явления, которые связывают с приемом арГПП-1 (адаптированно [5])



Gallbladder and Bile Duct Diseases

Use of GLP-1 receptor agonists is associated with a modest increase (not exceeding 3%) in gallbladder diseases, including cholelithiasis, cholecystitis, bile duct obstruction, sometimes requiring cholecystectomy. These adverse events are more common in obese patients than in those with diabetes.

Mechanism: GLP-1 receptor agonists weaken the gallbladder's response to cholecystokinin, reducing postprandial gallbladder emptying (although this phenomenon was already attenuated within 12 weeks of liraglutide therapy initiation in healthy volunteers). Animal studies and in vitro data have shown that GLP-1 receptor agonists are associated with increased activity and proliferation of cholangiocytes. Rapid weight loss (≥1.5 kg/week) may also alter bile salts, leading to supersaturation, biliary sludge, and gallstone formation [52, 53].

Risk factors: Use of GLP-1 receptor agonists in obese individuals for weight loss, higher doses (noted with semaglutide ⩾ 1.0 mg), treatment duration exceeding 26 weeks, rapid weight loss (>1.5 kg/week), significant weight reduction exceeding 25% of baseline.

Comment: For patients with a history of gallstones, initiation of semaglutide therapy should be accompanied by long-term ursodeoxycholic acid (UDCA) at 10–15 mg/kg throughout the active weight loss period (but not during maintenance). For those with weight loss exceeding 1.5 kg/week, authors recommend ultrasound after 3 months; if biliary sludge is detected, UDCA at 10–15 mg/kg should be prescribed during active weight reduction.

Pancreatitis and Pancreatic Cancer

Some studies on incretin-based therapies have reported cases of acute pancreatitis, including hemorrhagic and necrotizing pancreatitis, as well as exacerbations of chronic pancreatitis and development of pancreatic adenocarcinoma. However, well-structured adverse event audits, such as in SUSTAIN-6, showed that

● ***Table 2.*** Recommendations to manage gastrointestinal adverse events [48]
● ***Таблица 2.*** Рекомендации по коррекции гастроинтестинальных нежелательных явлений [48]

Adverse Events	Preventive Measures	Recommendations for Correction
Nausea, occurs in 15–50% of patients, more frequently during the first 4–8 weeks when gastric emptying is significantly delayed. Symptoms are mild to moderate and resolve in about 8 days after onset.	Separate food intake from fluid consumption: there should be at least a 30-minute interval between eating and drinking fluids. Avoid strong odors. Recommend foods that can help alleviate nausea symptoms, such as unsalted crackers, apples, mint tea, or ginger root tea. Reduce the portion size of meals but increase the frequency of eating. To maintain proper fluid balance in the body, drink more often in small sips of clear, fresh beverages that do not contain carbohydrates.	Use domperidone 10–20 mg (but not metoclopramide) up to 4 weeks, three times daily (30–40 minutes before meals), or itopride 50 mg three times daily (30–40 minutes before meals), extending the current dose of semaglutide for 2–4 weeks. If complaints persist, reduce the semaglutide dose to the previous level.
Vomiting, occurs in 5–21% of patients, symptoms are usually mild to moderate and resolve within 8 days.		Maintain adequate hydration and correct electrolyte disturbances. Domperidone 10–20 mg (but not metoclopramide) before main meals or itopride 50 mg three times daily (30–40 minutes before meals).
Diarrhea, occurs in 5–25%, mostly during the first 4 weeks of treatment, symptoms resolve within 3 days. Sometimes semaglutide may worsen diarrhea in patients taking metformin.	Drink more water, for example, with lemon and ½ teaspoon of baking soda. Avoid isotonic sports drinks. Avoid dairy products, coffee, alcohol, sweet drinks or juices, and very cold or very hot foods. Avoid (or temporarily reduce intake of) high-fiber foods such as cereals, nuts, seeds, rice, barley, whole grain bread or baked goods, vegetables such as artichokes, asparagus, beans, cabbage, cauliflower, garlic and garlic salt, lentils, mushrooms, onions, peeled fruits like apples, apricots, raspberries, cherries, mangoes, nectarines, pears, and plums. Consume low-fat and low-fiber foods: canned and/or soft fruits such as applesauce or ripe bananas, turkey and cheese sandwiches, broths-based soups (chicken and rice), vegetables without seeds and skins such as boiled carrots or green beans.	Rehydration with the use of electrolytes. Take loperamide according to the scheme (4 mg initially, then 2 mg after each episode of diarrhea – not exceeding 16 mg per day). If the history indicates that diarrhea is related to metformin, its dose should be reduced or discontinued if the clinical situation allows. If the history indicates that diarrhea is related to the use of a proton pump inhibitor, its dose should be reduced or the medication should be discontinued if the clinical situation permits.
Constipation, occurs in 4–22% of patients, more often in obese patients without T2D, mainly within the first 16 weeks, lasting up to ~47 days.	Drink a large amount of water (or other carbohydrate-free fluids). Increase fiber intake: consume more whole grain products, and choose foods containing 4 grams or more of dietary fiber per serving. If appetite decreases, consider fiber supplements. Incorporate more beans, fresh fruits, and vegetables with skins into the diet. Increase physical activity.	Administration of laxatives/dietary fibers – one sachet of plantain seed shell three times daily as a course, and/or macrogol 4000 mg as symptomatic treatment, and/or lactulose preparations (20–30 mL/day) divided into 2–3 doses.

the incidence of acute pancreatitis with semaglutide was comparable to placebo. The lack of difference in pancreatitis and pancreatic cancer risk between semaglutide and placebo has been confirmed in all major recent studies [56, 57].

Mechanisms: The exact mechanisms are unknown. It is hypothesized that stimulation of GLP-1 receptors on pancreatic β-cells and exocrine duct cells may cause excessive cell proliferation, leading to ductal obstruction, hyperplasia, increased pancreatic mass, and subsequent inflammation—acute or chronic [5].

Risk factors: Hypertriglyceridemia ⩾ 5.6 mmol/L, gallstones, alcohol abuse, morbid obesity.

Comment: Acute pancreatitis is a life-threatening surgical diagnosis; upon confirmation, semaglutide should be discontinued and not resumed. However, exacerbations of chronic pancreatitis should be managed with standard conservative approaches, and continuation of semaglutide therapy can be considered if the potential advantages exceed possible harms.

Dehydration

Studies with volunteers have shown a tendency for reduced fluid intake during treatment with dulaglutide, liraglutide, and tirzepatide, with semaglutide having the highest potential to affect water balance [58].

Mechanisms: Animal experiments indicate that endogenous GLP-1 receptor systems in the central nervous system participate in controlling not only food intake but also fluid consumption. Activation of these receptors by agonists may predispose to decreased sensitivity to dehydration [59].

Risk factors: Gastrointestinal disturbances such as nausea, vomiting, and diarrhea, which predispose patients to dehydration.

Acute Kidney Injury (AKI)

AKI has been reported in large studies, primarily in patients who experienced gastrointestinal symptoms (nausea, vomiting, diarrhea, and/or dehydration) at the initiation of GLP-1 receptor agonist therapy.

Subsequent analyses of several clinical trials in patients with T2D found no significant difference in the incidence of AKI between semaglutide and comparator or placebo groups. Conversely, in the SUSTAIN 1–7 studies, semaglutide was associated with an initial reduction in estimated glomerular filtration rate (eGFR), followed by a notable decrease in the albumin-to-creatinine ratio after stabilization [60]. The nephroprotective properties of GLP-1 receptor agonists have been further confirmed in the FLOW and SELECT studies involving patients with T2D and/or obesity [22].

Mechanisms: The effect is dose-independent; pre-renal AKI may occur due to dehydration and hypovolemia caused by gastrointestinal adverse events such as nausea, vomiting, or diarrhea.

Risk Factors: Reduced fluid intake (e.g., during episodes of severe vomiting or diarrhea), concomitant use of medications that impair renal function during dehydration episodes (e.g., RAAS blockers), and pre-existing chronic kidney disease.

Diabetic Retinopathy

Progression of diabetic retinopathy (DR) during semaglutide therapy was observed in the SUSTAIN-6 study, which showed increased rates of vitreous hemorrhages, onset of diabetes-related blindness, and the requirement for intravitreal injections of anti-angiogenic agents or laser photocoagulation. An analysis of the SUSTAIN trial program reported that this effect was mainly seen in patients with pre-existing DR at baseline and was primarily related to the magnitude and rapidity of glycemic and HbA1c reduction during the first 16 weeks of therapy [61]. Currently, this effect has been described for semaglutide, exenatide, and dulaglutide.

Mechanisms: The mechanisms are thought to involve transient changes in osmotic pressure in the lens due to rapid glucose reduction in ocular fluids [62], although the exact cause remains unclear. The osmotic theory suggests a role in cataract progression and diabetic macular edema (DME) development rather than DR progression, sometimes leading to neovascularization after abrupt normalization of glycemia [63]. A more plausible explanation involves activation of vascular endothelial growth factor (VEGF) due to hypoxia-induced rapid glycemic lowering. In vitro studies on human and bovine retinal cells demonstrated that hypoxia and hypoglycemia significantly increased VEGF production, whereas hypoxia combined with hyperglycemia suppressed VEGF expression [64].

Risk Factors: Presence of DR at baseline (especially clinically significant forms), rapid HbA1c reduction (>1.5%) within 16 weeks of therapy initiation [61].

A recent large multicenter study involving 37.1 million patients with T2D across 14 databases found that semaglutide use was associated with a modest 32% increased risk of non-arteritic anterior ischemic optic neuropathy (NAION) (OR 1.32; 95% CI, 1.14–1.54; p < 0.001) [65]. The mechanism linking GLP-1 receptor agonists and NAION remains unclear, as these agents are generally neuroprotective and associated with reduced ischemic risk. It is hypothesized that GLP-1 receptor agonists may influence intraocular hemodynamics via the autonomic nervous system and lower systemic blood pressure, potentially affecting optic nerve perfusion and increasing NAION risk 65. Importantly, the risk of NAION with semaglutide was comparable to other glucose-lowering agents such as empagliflozin (OR 1.44; 95% CI, 0.78–2.68; p = 0.12), sitagliptin (OR 1.30; 95% CI, 0.56–3.01; p = 0.27), and glipizide (OR 1.23; 95% CI, 0.66–2.28; p = 0.25), which reduces concern about this adverse event and underscores the need for further research.

Commentary: Considering the current evidence, the authors recommend that patients with T2D undergo ophthalmologic examination, including slit-lamp biomicroscopy or ophthalmoscopy with pupil dilation, before initiating semaglutide therapy. If pre- or proliferative retinopathy or diabetic macular edema (DME) is detected, semaglutide should be withheld until ophthalmologic treatment and stabilization of visual function are achieved. For patients with these conditions, therapy should only be started after HbA1c levels are controlled below 8%.

Thyroid Cancer

Prolonged use of GLP-1 receptor agonists in animal studies causes hyperplasia of pancreatic C-cells and medullary thyroid carcinoma in rats and mice due to direct activation of GLP-1 receptors, which are expressed in the C-cells of rodents' thyroid glands. In primates and humans, normal C-cells have significantly lower GLP-1 receptor expression, and the number of C-cells in humans is markedly less than in rodents. Clinical monitoring of tens of thousands of calcitonin measurements in studies has found no functional link between calcitonin levels and GLP-1 receptor expression in individuals with T2D or obesity [5].

The actual incidence of thyroid cancer in patients with T2D treated with various GLP-1 receptor agonists remains controversial: some studies report no increased risk [66], while others suggest an increased incidence of differentiated thyroid cancer and medullary thyroid carcinoma within 1–3 years of therapy initiation [67]. The main limitation of these studies is the lack of baseline ultrasound examinations, which introduces a risk of detection bias.

This may explain why a recent meta-analysis reported a 28% increased overall risk of thyroid disease with GLP-1 receptor agonists compared to placebo or other interventions, but no significant correlation with thyroid cancer was found [68]. This finding is plausible considering that obesity itself is a significant oncological risk factor [69], and weight reduction strategies should contribute to lowering cancer risk, which is supported by existing evidence [70].

Additionally, data from electronic health records in the US comparing the impact of other medications

on thyroid cancer risk in T2D patients showed that, after adjusting for HbA1c and BMI at diagnosis, the 5-year incidence was 0.24% in insulin users, 0.26% in liraglutide users, 0.18% in dulaglutide users, and only 0.10% in semaglutide users—significantly lower than in insulin-treated patients [71].

Despite limited human data, GLP-1 receptor agonists are contraindicated in patients with medullary thyroid carcinoma or multiple endocrine neoplasia type 2 (MEN 2) in personal or family history.

Commentary: Based on current evidence, the authors do not recommend routine calcitonin screening before starting semaglutide, focusing instead on personal or family history of medullary thyroid carcinoma or MEN 2.

CONCLUSION

More than 20 years after the approval of the first short-acting GLP-1 mimetic, exenatide derived from animal sources, the range of options of clinicians has been significantly expanded with newer, more effective long-acting GLP-1 receptor agonists. This has sparked interest in the practical aspects of their widespread use, especially given their proven long-term efficacy and safety profile. The extensive database of studies on semaglutide provides confidence in its successful clinical application in individuals with T2D and/or obesity, with the important perspective of reducing major adverse cardiovascular events (MACE) in patients with T2D or obesity and cardiovascular disease. Much less information is available regarding the long-term safety and additional benefits of semaglutide in people with obesity without cardiovascular disease, patients with severe comorbidities, children and adolescents, and, conversely, in those over 75 years of age. Although clinical experience with GLP-1 receptor agonists in these populations is limited, the need for such therapy is quite significant.

Many of the approaches discussed in this article require further validation through additional research. However, current clinical practice already demands solutions that can optimize semaglutide therapy in various clinical situations for patients with T2D and obesity.

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