The role of nutrition therapy in the era of new weight-lowering drugs

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Abstract

Novel weight-lowering drugs are transforming the treatment of obesity. These so-called incretin mimetics not only lead to substantial weight loss but may also improve severe comorbidities associated with obesity. At the same time, it is increasingly clear that while these medications support lifestyle changes, such as adopting a healthier diet, they cannot fully replace behavioral modifications. Therefore, a balance approach that combines lifestyle measures with adjuvant pharmacotherapy offers much better treatment options for individuals with obesity. The aim of this article is to provide an assessment of the clinical utility of these drugs based on clinical studies and their application in routine care.

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Background

Obesity medicine is currently experiencing significant transformations, mainly driven by novel weight-lowering drugs that represent a breakthrough in weight loss potential and safety compared to previous medical options. These new medications reduce appetite and enhance satiety via central nervous pathways, leading to decreased caloric intake and subsequent weight loss [1].

Two recently approved drugs, semaglutide (Wegovy®), a GLP1-receptor agonist, and tirzepatide (Mounjaro®), a dual GLP1-/GIP-receptor agonist, demonstrate significantly greater weight loss than earlier weight-lowering agents and are also more effective than multimodal lifestyle interventions for obesity [2]. The first GLP1-receptor agonist approved for weight loss, liraglutide, (Saxenda®) is less potent, which may explain why it is infrequently prescribed for weight reduction. While these new medications require a physician's prescription, but are not reimbursed by health insurance, placing a financial burden of more than 300€ per month on patients.

The pharmaceutical companies that produce these two medications are actively promoting them, and they receive extensive coverage in the media. Social media, in particular, has amplified the hype surrounding injectable weight loss medications. This heightened attention is not surprising considering the prevalence of obesity in Germany, where approximately 15 million adults are affected, alongside a growing interest in dieting and personal weight management.

However, many media reports are exaggerated and confusing, leading to uncertainty among health professionals regarding the appropriate use of these novel drugs. Ongoing discussions raise concerns about whether dietary counseling will remain necessary for weight control in the future. In this context, it is essential to provide an assessment of the clinical utility of these drugs based on evidence from clinical trials and initial experience in routine care since their introduction for obesity treatment.

How effective are these novel weight-lowering medications?

GLP1-receptor agonists were originally developed as antidiabetic agents and have been established for the treatment of type 2 diabetes (T2DM) for more than 15 years. They exhibit a strong glucose-lowering effect, reducing HbA1c by 1.0 to 2.0%, primarily by increasing insulin secretion and inhibiting glucagon release from the pancreas. Alongside these ef-

fects, a moderate decrease in body weight has been observed, particularly with semaglutide (Ozempic®). Semaglutide was further developed for weight loss at higher doses during clinical trials and was ultimately approved for obesity treatment under the new trade name Wegovy®. The same approach was initially applied to liraglutide, although it is less effective for weight loss (Victoza® for T2DM, Saxenda® for weight loss only).

Since then, numerous clinical trials have been conducted to evaluate the weight-lowering effects of semaglutide and tirzepatide [1]. A meta-analysis of clinical trials in participants with obesity revealed that administering 2.4 mg of semaglutide once per week resulted in a weight loss 11.4% greater than that seen with placebo treatment [3]. Another meta-analysis that included patients with T2DM showed that 10 mg and 15 mg doses of tirzepatide once per week led to a 12.4% greater weight reduction compared to placebo [4]. In individuals with obesity alone, weight loss is by about one third greater than in those with T2DM. In the absence of T2DM, weight loss with 15 mg tirzepatide ranged from11.6 to 21.4% [5]. A large retrospective cohort study of 41,222 adults with obesity under usual care found that after 12 months, weight loss was 6.9% greater with 15 mg tirzepatide compared to 2.4 mg semaglutide [6].

Duration of weight loss efficacy with incretin mimetics

Current data on semaglutide treatment over several years are available from the SELECT trial, which initially involved 17,694 participants with overweight or obesity and cardiovascular disease. The trial found a mean weight reduction of 10%, with continued treatment at the same 2.4 mg weekly dose stabilizing this weight loss for at least 4 years [7]. However, discontinuation of the medication was associated with rapid weight regain, indicating that long-term use may be necessary, as these drugs directly act on central hunger and appetite regulation and delay gastric emptying. It remains unknown whether a dose reduction could help maintain weight loss, highlighting the urgent need for long-term clinical studies to address this question.

Adverse effects of incretin mimetics

Within the first weeks of treatment, mild to moderate gastrointestinal side effects are common. Over time, these adverse effects generally lessen and resolve in most cases. Around 30–45% of participants report nausea, 20–30% experience diarrhea and 10–25% vomiting or obstipation. To date, comparative studies on whether significant differences in the profile or frequency of adverse events exist between the two medications are lacking. Other side effects include gastroparesis and gastrointestinal motility disorders although cases of pancreatitis are rare. Such side effects are more frequently observed in "real world" studies compared to phase 3 trials with stringently selected patient populations [8]. There are also reports on other rare and potentially severe side effects under conditions of broad application [9]. Notably, around 5–10% of participants in clinical trials discontinued treatment due to drug-specific adverse events [10]. Overall, however, these new drugs are well tolerated and have a favorable side effect profile.

Other beneficial effects of incretin mimetics

In addition to lowering plasma glucose and body weight, recent studies highlight beneficial effects on cardiovascular diseases as well as the progression of renal diseases. These effects were mainly observed in patients with T2DM [11]. In people with obesity and pre-existing cardiovascular disease, but without T2DM, treatment with semaglutide over an average of 3.3 years resulted in a significant 20% reduction in the composite cardiovascular endpoint (myocardial infarction, stroke, cardiovascular death)(SELECT trial, [10]). Recent clinical studies also demonstrated that semaglutide significantly improves heart failure with preserved or moderately restricted left ventricular ejection fraction [12]. Similar advantageous effects were reported for tirzepatide, although the cardiovascular endpoint trial with this drug is still ongoing. These findings strongly suggest that incretin mimetics may offer additional benefits beyond weight loss. However, it is remains unclear whether these effects are a consequence of weight loss or occur independently of body weight. Regardless of this ongoing debate, these recent reports are promising for individuals with obesity and related comorbidities.

As obesity is an established risk factor for multiple cancer types, a recent analysis indicates that treatment with incretin mimetics in individuals with obesity and T2DM was associated with a reduced risk of developing obesity-associated cancers compared to those treated with insulin or metformin [13]. It is interesting to note that incretin mimetics may also have positive effects on addictive behaviors (such as smoking, alcohol abuse, or drug abuse) and may be linked to a lower risk of dementia [14]. Thus, these novel medications could be particularly beneficial for individuals

who want to quit smoking but are concerned about potential weight gain. However, definitive conclusions on these topics are not yet possible, as results from ongoing trials are still pending.

A recent US report examined the effect of incretin mimetics on health variables in 215,970 individuals with obesity. After a mean treatment duration of 3.7 years, the risk for 42 health conditions was moderately reduced, whereas the risk for 19 health conditions increased [15]. In conclusion, the authors noted that the long-term risks of cancer associated with the limited treatment duration remains unknown.

Are changes in the treatment of obesity effective?

According to the revised German guidelines for obesity management, multimodal therapy is the first step in treatment [16]. The goal is to modify current lifestyle habits to achieve weight reduction followed by weight stabilization. This approach can lead to a mean weight loss of around 5% over 12 months, although individual response may vary significantly.

After the active treatment phase, partial weight regain frequently occurs. However, using a very low calorie diet, such as an 800 kcal per day formula diet, can result in a more substantial initial weight loss of 10–20%, although this approach carries a higher risk of weight regain [16].

According to the approval regulations for novel weight-loss medications from the European health authorities and the recommendations from the revised obesity guidelines, adjunct pharmacotherapy may be considered if a multimodal program proves insufficient for achieving individual weight loss goals.

> **There is general consensus that pharmacotherapy should serve as an adjunct treatment rather than the primary option for weight reduction. Pharmacotherapy may be justified as a primary option only if an individual convincingly demonstrates that previous attempts to lose weight were not successful.**

Every treatment team should be aware that around 10% of patients may not respond to treatment with incretin mimetics. Due to potential adverse effects, close medical monitoring is essential after initiating pharmacotherapy. To mitigate the risk of initial side effects, pharmacological treatment should start with a low dose and, if adequately tolerated, can be gradually escalated monthly, depending on weight loss and tolerability. For this purpose, prefilled pen injectors are available and can be prescribed.

Role of nutrition and exercise therapy

Concerns that the new medications may render nutritional counseling unnecessary are completely unjustified. Treatment with semaglutide or tirzepatide typically results in a decrease of caloric intake of around 800 kcal per day. Although there is some evidence of reduced consumption of fat- and sugar-rich "convenience foods", it is crucial to maintain high nutritional quality. Rapid weight loss can lead to a loss of muscle mass which requires attention and adequate protein intake. This should be complemented by regular physical activity, particularly strength training, to help preserve muscle mass.

With reduced caloric intake, there is also a risk of inadequate micronutrient supply, which may necessitate specific supplementation. A new phenomenon has also emerged where some individuals lose interest in eating while on pharmacotherapy, leading to inadequate caloric intake and potential malnutrition. In such cases, not only may a reduction in medication dosage be necessary, but also competent nutrition support is essential.

The quality of the diet, independent of body weight, is highly relevant as a protective or risk factor for a variety of diseases. Therefore, nutritional therapy is indispensable for maintaining a balanced diet in accordance with current guidelines, such as those from the German Nutrition Society (DGE). This goal can be successfully facilitated by concomitant pharmacotherapy.

Similarly, adopting a physically active lifestyle can be facilitated by pharmacologically-supported weight loss, as it may motivate individuals to engage in physical activities more readily. Despite the current lack of extensive study data, both nutritional and physical activity therapies remain essential components alongside pharmacotherapy [17].

Current challenges for pharmacotherapy of obesity

At present, the high costs of pharmacotherapy pose a significant barrier for the use of these medications in Germany. Although many patients are willing to cover the expenses over a few months, long-term treatment is unfeasible for most given these financial conditions. Experience from the US, where these medications have been available for a longer period and are used more frequently, indicates that around 50% of individuals who begin

treatment with weight-loss drugs discontinue it within the first 12 months [18]. Reasons for discontinuation vary and may include side effects, limited efficacy and financial constraints [19]. The latter concern has sparked a lively discussion about social disparities in access to these medications [20].

From an expert perspective, and in light of a growing body of scientific evidence supporting their significant health benefits, it is important to view these weight-loss agents not merely as "lifestyle medications" that are not covered by health insurance, but as effective, well-studied treatments for obesity and its related complications. Under the regulations of the German healthcare system, these medications should be reimbursed by health insurance. Despite the financial challenges faced by the public healthcare system, there is hope for a pragmatic solution that would enable reimbursement for treatment with these novel drugs, particularly for individuals with severe obesity (BMI ≥ 35 kg/m²) and existing cardiometabolic diseases.

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