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Journal of Diabetes and Clinical Research Commentary

Commentary on Once-Weekly Semaglutide in Adults with Overweight or Obesity

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Obesity is an undertreated global epidemic that increases morbidity and mortality by causing widespread harm to multiple organ systems. Severe obesity or obesity with associated comorbidities warrants a comprehensive treatment approach including lifestyle modifications plus either bariatric surgery or prescription medications. Before the STEP 1 trial [1], FDA-approved anti-obesity medications (AOMs) included 5 major drugs in 2021: phentermine, phentermine/topiramate, bupropion/naltrexone, orlistat, and liraglutide 3.0 mg. These AOMs have an average efficacy of 3-9% weight loss based on clinical trials and can achieve clinically meaningful weight loss with adjunctive lifestyle modifications [2,3]. As the average American's BMI continues to increase with worsening severe obesity incidence and related complications such as diabetes, cardiovascular disease, and nonalcoholic fatty liver disease, clinicians are routinely faced with an unmet need for potent therapeutic tools. Over the past decade, development of the novel FDA-approved GLP-1R agonist class of medications has revolutionized how we treat type 2 diabetes and obesity or 'diabesity' pathological dual diagnoses, where anorexigenic effects are coupled with benefits of HgbA1c lowering.

The multiple benefits of GLP-1R agonists including weight loss, improved cardiovascular risk, blood pressure control, reduced inflammation, and reversal of nonalcoholic steatohepatitis (NASH), along with the low-risk side effect profile, have caused great enthusiasm for treatment of patients with type 2 diabetes. Unfortunately, cost and coverage have been significant barriers in reaping the benefits of GLP-1 agonists for patients with obesity who do not carry a diagnosis of type 2 diabetes but are at high risk of developing obesity-related complications. While GLP1-R agonist liraglutide is an FDA-approved AOM, it is short acting requiring daily injections and offers moderate weight loss efficacy between 4-6% of total body weight in clinical trials [4-7]. For patients with class 3 obesity or class 2 obesity and type 2 diabetes, bariatric surgery is still the mainstay of treatment due to greater success in achieving target weight loss and sustained improvement in insulin sensitivity [8].

In the STEP 1 trial, long-acting once weekly semaglutide 2.4 mg plus lifestyle modifications demonstrated a highly efficacious 12.4% reduction in total body weight relative to placebo and lifestyle modifications after 68 weeks in patients with obesity without type 2 diabetes. Following the trial, semaglutide 2.4 mg was FDA-approved in June 2021 for weight management in patients with a BMI ≥ 30 kg/m^2 or ≥ 27 kg/m^2 plus at least one weight-associated comorbidity (diagnosis of type 2 diabetes not required). This potent weight loss effect of semaglutide 2.4 mg narrows the treatment gap between pharmacological and surgical management of obesity and carries important implications for remission of obesity-related comorbidities, from which a growing number of Americans are suffering.

Our growing understanding of the pathophysiology of obesity in recent years suggests the etiology of this chronic disease is multifactorial, influenced by a complex interplay between genes and the obesogenic environment of today's world. The obesogenic environment is characterized by

availability and cultural tendency toward processed foods, inactivity, weight promoting medications, endocrine disrupters, stress, poor sleep, and circadian rhythm disruption. Therefore, greatest success is obtained with combination lifestyle modification plus interventions to alter the genetically and environmentally influenced weight "set-point": either bariatric surgery or AOMs. In severe obesity, if the preferred route is medical management rather than surgery, often combination AOMs are required to obtain and maintain a healthy weight, similar to refractory hypertension that may require more than one anti-hypertensive to treat the underlying disease pathology [9]. Given the multi-factorial pathogenesis of obesity, it is no surprise that targeting different molecular mechanisms with multiple pharmacologic agents in combination achieves synergistic weight loss effects. Future clinical trials evaluating weight loss success with semaglutide 2.4 mg in combination with other available AOMs may help establish an effective, evidence-based treatment algorithm for clinicians in obesity management. A synergistic weight loss effect of combination semaglutide 2.4 mg plus other AOMs may change the paradigm of obesity treatment, knocking on the door of weight loss previously accomplished only with bariatric surgery.

Previously, the most efficacious FDA-approved drug for obesity was combination drug phentermine/topiramate, which reduces total body weight by 8.6% compared to placebo [2]. Bariatric surgery including gastric bypass and sleeve gastrectomy has been shown to reduce total body weight loss by 21-28% after 5-7 years of follow up [10,11]. Among these, the randomized-controlled STAMPEDE trial found bariatric surgery to be superior in effectively lowering HbA1c and remitting type 2 diabetes compared to intensive medical therapy [8]. The results from the STAMPEDE trial are heavily relied upon today in clinical decision making for patients with diabesity. However, extrapolation of this study today is limited because the intensive medical therapy arm did not include modern-day anti-diabetes drugs like GLP-1R agonists. The STAMPEDE researchers followed the American Diabetes Association algorithm from 2008 for treatment guidance in the medical therapy arm, which included metformin, sulfonylureas, glitazones, α-glucosidase inhibitors, sitagliptin, and insulin [12,13]. While bariatric surgery remains a powerful and necessary tool for weight loss and metabolic disease remission, we are beginning to see a narrowing of the efficacy gap between what can be achieved with medical therapy versus bariatric surgery in the era of semaglutide 2.4 mg. Results from the STEP 1 trial show semaglutide 2.4 mg to be a highly effective, safe, and well-tolerated medical weight loss option that far surpasses its predecessors. Updated randomized-controlled trials are needed to compare weight loss, HbA1c, morbidity, and mortality in patients with diabesity who undergo bariatric surgery versus long term treatment with novel AOMs including GLP-1R agonist semaglutide 2.4 mg.

For any given weight loss intervention, whether it be medication, metabolic surgery, or dietary changes, biological responses are usually variable in a predictable distribution. This gradation of responses to interventions is likely multi-factorial and influenced by genetic variability which in turn affects sensitivity to treatment. Despite the inherent genetic diversity of the study population, an impressive 69.1% of STEP 1 trial participants on semaglutide 2.4 mg were able to achieve ≥10% of their total body weight, which represents a clinically meaningful weight loss threshold in obesity-related disease prevention and eradication. In a large prospective study, patients with NASH who achieved ≥ 10% weight loss through lifestyle changes experienced histological improvement and resolution in 100% and 90% of cases, respectively [14]. Development of type 2 diabetes can be reduced by 80% in high-risk patients who lose ≥ 10% weight loss [15]. In a post-hoc analysis of the Look AHEAD trial, patients with type 2 diabetes and overweight or obesity who lost ≥ 10% of total body weight had a 20% lower risk of cardiovascular death compared to the control group [16]. Semaglutide 2.4 mg produces more weight loss than any other currently available prescription AOM, and a high percentage of patients can lose ≥ 10% of total body weight. Semaglutide 2.4 mg will not only help patients achieve the vast benefits of weight reduction including improved energy, activity level and mobility, body image, mental health, and reduced pain and disability. It is intriguing to posit that long-term use of semaglutide 2.4 mg will significantly improve or remit obesity-related comorbidities including type 2 diabetes, cardiovascular disease, and non-alcoholic fatty liver disease. Left untreated, complications of these obesity-related diseases, for example emergent cardiovascular revascularization, end stage renal disease requiring hemodialysis, and cirrhosis requiring liver transplant are responsible for a significant amount of hospital admissions and healthcare costs in today's obesogenic world. Further studies are needed to assess degree of improvement and resolution of obesity-related complications with chronic semaglutide 2.4 mg treatment.

Subsequent clinical trials STEP 2, 3, and 4 have explored weight loss endpoints, varying diabesity status, adjunct therapy, and treatment cessation versus continuation [17-19]. In the STEP 2 trial, semaglutide 2.4 mg achieved a superior and clinically meaningful weight loss effect compared to semaglutide 1.0 mg or placebo in patients with type 2 diabetes [17]. STEP 3 demonstrated semaglutide 2.4 mg plus intensive behavioral therapy (IBT) accelerated initial weight loss, but long-term effect at 68 weeks was comparable to that of the STEP 1 trial, without IBT [19]. STEP 4 showed 20 weeks of semaglutide 2.4 mg followed by treatment withdrawal for 48 weeks caused initial weight loss, then weight regain, compared to continued weight loss in participants who remained on treatment for the full 68 weeks [18]. The rebound weight regain in the first group

demonstrates the body's maladaptive attempt to defend its prior fat mass, giving evidence to the chronicity of obesity and the need for long-term treatment to maintain a healthy weight. The weight loss success of semaglutide 2.4 mg in the STEP 1 trial, followed by subsequent STEPs 2-4, offer hope for an increasingly prevalent chronic disease that has been historically challenging to treat.

To meet the urgent need for obesity management and disease reversal, scientific and pharmacological advancement must coincide with improved access to treatment. HIV was once a death sentence but now treatment is easily accessible, regardless of socioeconomic or insurance status. The valuable lesson is that scientific innovation coupled with successful awareness and education, government support, and reduced cost barriers can diminish social determinants of health and provide access to treatment for a deadly disease. Obesity remains a growing epidemic that shortens the lifespan of millions of underserved Americans and escalates health care costs. There is a critical need for improved support, education, and cost barrier reduction for lifesaving AOMs including semaglutide 2.4 mg, particularly for populations on government insurance plans. In the era of semaglutide 2.4 mg and other forthcoming novel AOMs and further research, reducing the devastating impact of obesity and its complications is on the horizon.

Disclosures

EMG and KDN have no disclosures. GS has served as advisor for Novo Nordisk and Eli Lilly and is on the Speakers Bureau for Novo Nordisk. GS is also a consultant for Rhythm Pharmaceuticals. No funding was provided for the manuscript.

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