High Dose Semaglutide for Weight Loss and Cardiometabolic Risk Reduction in Overweight/Obesity

Jul 21, 2021 | Noelle Pavlovic, MSN; Justin Echouffo Tcheugui, MD; Chiadi E Ndumele, MD, PhD

Expert Analysis

Quick Takes

- The prevalence of obesity and its associated cardiometabolic complications have increased to historic levels in the US, with a disproportionate burden among individuals in minority racial/ethnic groups and those with low socioeconomic status. However, effective therapeutic options for obesity management are limited.
- In this study, once weekly 2.4 mg semaglutide injection versus placebo in conjunction with lifestyle modification therapy among non-diabetic individuals with obesity (or BMI ≥27 kg/m^2 with comorbidities) caused significant improvements in body weight (15% reduction vs. 2.4% in the placebo arm, over 68 weeks), cardiometabolic risk factors, self-reported physical functioning, and body composition, with low rates of major adverse effects or safety concerns.
- Obesity pharmacotherapies, including GLP-1 receptor agonists, are expensive and often not covered by insurance in the US, raising concerns for disparities in access to these medications, especially in populations disproportionately affected by obesity. There is need for improved coverage of these increasingly effective obesity pharmacotherapies, to enhance our ability to manage excess weight in clinical environments.

Obesity is a chronic, life-limiting disease associated with several cardiometabolic disorders,[1,2] which drive significant morbidity and premature mortality.[3-6] Over the past three decades, there have been upward trends in the prevalence of obesity across the United States (US)[7] and by 2030, nearly 50% of US adults are estimated to be classified as obese.[8] In the US, obesity disproportionately affects individuals from minority race/ethnic groups, with the highest prevalence in non-Hispanic black adults,[7] causing important disparities in cardiometabolic disease. In recent years, there has been a plateau and possible reversal in the previously observed national downwards trends in cardiovascular disease (CVD) mortality,[9] which is hypothesized to be associated with the rise in obesity and diabetes prevalence.[8,9]

Achieving weight loss of ≥5% initial weight among individuals with overweight or obesity is associated with an improved cardiometabolic disease risk profile, with re

triglycerides, and glycemia, as well as prevention of type 2 diabetes mellitus onset.[10] Greater degrees of weight loss are associated with further cardiometabolic improvements, with a dose-response relationship. Lifestyle interventions, including behavioral modification, medical nutrition therapy and physical activity, are fundamental to obesity management and are the first line recommendation for the prevention and treatment of excess weight and cardiometabolic disease.[10] However, weight loss through lifestyle intervention is difficult to achieve and maintain, with weight regain remaining a common challenge.[11] Bariatric surgery has been shown to be an effective intervention for weight loss in those with severe obesity, leading to clinically significant weight loss and long term-improvements in many CVD risk factors and outcomes.[12-14] However, not all individuals qualify for bariatric surgery and it is expensive, invasive, and can be associated with complications.[15-17] Further, weight regain after bariatric surgery is also a common occurrence with studies showing only 40% of individuals maintaining at least 30% of their post-surgery weight loss.[18] Pharmacologic therapy is recommended as an adjunct to lifestyle modification for those with a BMI ≥30 kg/m^2, or a BMI ≥27 kg/m^2 with comorbidities. However, the use of pharmacologic therapy has been limited by moderate efficacy, significant side effects, and poor affordability. With the prevalence of obesity and related-cardiovascular complications on the rise, there is clear need for additional effective, non-surgical strategies for treating overweight and obesity.

The recent randomized placebo-controlled trial published in the New England Journal of Medicine by Wilding et al. (2021) shows promising results for the use of the new weight loss dose of the glucagon-like peptide-1 (GLP-1) analog, semaglutide, for sustained, safe, well-tolerated weight loss in adults with obesity (or BMI ≥27 kg/m^2 with comorbidities) and without diabetes.[19] This randomized control trial had a number of important findings:

First, it showed that in combination with lifestyle modification, a weekly semaglutide dose of 2.4 mg subcutaneously resulted in a substantial average weight loss of 14.9% of body weight, versus 2.4% with placebo, over a 68-week period. Notably, weight loss was progressive throughout most of the study, with the weight loss nadir occurring near or at the end of the follow-up period. The average reduction in body weight with semaglutide was 15.3 kg, with weight loss of ≥5% achieved by 86% in the semaglutide group versus 31% in the placebo group.

Second, in an examination of pre-specified secondary endpoints, participants in the semaglutide group also exhibited significant improvements in clinical and patient-reported outcomes including decreased waist circumference, decreased systolic blood pressure and improved self-reported physical functioning. Moreover, 84% of those with prediabetes in the semaglutide group achieved normoglycemia by the end of the study. In a subset undergoing DXA scans, semaglutide was associated with reduced fat mass, with an increase in the proportion of lean body mass relative to total body mass.

Third, although the main side effects of semaglutide (gastrointestinal disorders) were higher than with glucose-lowering doses of semaglutide, side effects were transient, typically mild-to-moderate in severity, and mostly resolved without the need for treatment discontinuation (4.5% discontinuation for gastrointestinal symptoms in the semaglutide group). The incidence of serious adverse events was low, reflecting the dose titration over the 16-week run-in period, and indicating the safety of high dose semaglutide for potential long-term use. This is key, as the majority of anti-obesity medications currently approved for use in the US are only indicated for short-term use because of significant side-effects and safety considerations.[20]

Finally, semaglutide dosing in this study was weekly, as opposed to the daily dosing in the other dedicated GLP-1 receptor agonist weight loss trial (using the weight loss dose of daily liraglutide injections, marketed as Saxedna®),[21] which reduces medication burden on individuals and may favor treatment adherence.

This study does have limitations with regards to generalizability, with the study sample being predominantly white and female. Future studies should have more demographic inclusivity, including more non-white and non-female participants, particularly as obesity disproportionately affects individuals from minority race/ethnicity groups[7] and those with low socioeconomic status.[22] Additionally, while the secondary endpoints examining cardiometabolic risk factors appear promising, there is need to understand the effects of semaglutide on cardiovascular morbidity and mortality among individuals with obesity but without diabetes, a question which is currently being assessed in a large 17,500 participant clinical trial (the SELECT trial). The marked weight loss with

trials), are cause for some optimism. Additionally, recently announced plans to evaluate the effects of high doses of oral semaglutide on weight loss are important, as oral formulations may be acceptable to a broader range of patients than the injectable dose used in this study.

From a health policy standpoint, despite the major clinical and public health impact of obesity, there is currently poor insurance coverage for obesity pharmacotherapies in the US. A recent study showed that only 11% of health insurance marketplace plans had some coverage for obesity medications, with some coverage available in only nine states, and Medicare completely excludes drug therapies for the treatment of obesity.[25] Patients are therefore often forced to pay for obesity pharmacotherapies out of pocket, significantly curtailing access to these medications for those with limited financial resources. As promising pharmacotherapies for obesity emerge, it will be crucially important to provide widespread insurance coverage for obesity pharmacotherapies across diverse populations, including for vulnerable populations with government health insurance such as Medicare and Medicaid. This is critical to population efforts to address obesity and to promote health equity. Such broad access to obesity medications will be of even greater importance if semaglutide and other emerging obesity pharmacotherapies are associated with long term maintenance of weight loss and improved cardiovascular outcomes in ongoing clinical trials.

In summary, this important study shows that once weekly 2.4 mg dosing of semaglutide provides safe, well-tolerated and substantial weight loss in individuals with overweight or obesity, as well as an improvement in cardiometabolic risk factors and physical function measures. Notably, the 2.4 mg weekly injection of semaglutide has recently been approved by the US Food and Drug Administration (FDA) as of June 2021 (brand name Wegovy) for the chronic management of weight in adults with obesity or overweight and at least one weight-related comorbidity,[26] providing a powerful new tool in the arsenal of obesity therapies. However, enhanced coverage of obesity pharmacotherapies is needed to make sure that such effective agents can actually reach individuals in the community who might benefit from them. Additionally, ongoing, and future GLP-1 analog studies that include longer follow-up, more diverse study populations, evaluations of the weight loss effects of oral semaglutide formulations, and assessments of cardiovascular outcomes data are needed.

1. Abdullah A, Peeters A, de Courten M, Stoelwinder J. The magnitude of association between overweight and obesity and the risk of diabetes: a meta-analysis of prospective cohort studies. *Diabetes Res Clin Pract* 2010;89:309-19.
2. Longo M, Zatterale F, Naderi J, et al. Adipose tissue dysfunction as determinant of obesity-associated metabolic complications. *Int J Mol Sci* 2019;20:2358.
3. Di Angelantonio E, Bhupathiraju SN, Wormser D, et al. Body-mass index and all-cause mortality: individual-participant-data meta-analysis of 239 prospective studies in four continents. *Lancet* 2016;388:776-86.
4. MacMahon S, Baigent C, Duffy S, et al. Body-mass index and cause-specific mortality in 900 000 adults: collaborative analyses of 57 prospective studies. *Lancet* 2009;373:1083-96.
5. Kolotkin RL, Andersen JR. A systematic review of reviews: exploring the relationship between obesity, weight loss and health-related quality of life. *Clin Obes* 2017;7:273-89.
6. Uzogara SG. Obesity epidemic, medical and quality of life consequences: a review. *Int J Public Health Res* 2017;5:1-12.
7. Hales CM, Carroll MD, Fryar CD, Ogden CL. Prevalence of Obesity Among Adults and Youth: United States, 2015–2016 *(CDC website).* 2017. Available at: ***https://www.cdc.gov/nchs/data/databriefs/db288.pdf***. Accessed 06/20/2021.
8. Ward ZJ, Bleich SN, Cradock AL, et al. Projected U.S. state-level prevalence of adult obesity and severe obesity. *N Engl J Med* 2019;381:2440-50.
9. Virani S, Alonzo A, Aparicio HJ, et al. Heart Disease and Stroke Statistics - 2021 Update: a report from the American Heart Association. *Circulation* 2021;143:e254-e743.
10. Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol* 2019;74:e177-e232.
11. Hall KD, Kahan S. Maintenance of lost weight and long-term management of obesity. *Med Clin North Am* 2018;102:183-97.
12. Wilding JPH, Jacob S. Cardiovascular outcome trials in obesity: a review. *Obes Rev* 2021;22:e13112.
13. English WJ, Spann MD, Aher CV, Williams DB. Cardiovascular risk reduction following metabolic and bariatric surgery. *Ann Transl Med* 2020;8:S12-S12.
14. Wolfe BM, Kvach E, Eckel RH. Treatment of obesity: weight loss and bariatric surgery. *Circ Res* 2016;118:1844-55.

15. Kassir R, Debs T, Blanc P, et al. Complications of bariatric surgery: presentation and emergency management. *Int J Surg* 2016;27:77-81.
16. Kizy S, Jahansouz C, Wirth K, Ikramuddin S, Leslie D. Bariatric surgery: a perspective for primary care. *Diabetes Spectr* 2017;30:265-76.
17. Lim R, Beekley A, Johnson DC, Davis KA. Early and late complications of bariatric operation. *Trauma Surg Acute Care Open* 2018;3:1-7.
18. Velapati SR, Shah M, Kuchkuntla AR, et al. Weight regain after bariatric surgery: prevalence, etiology, and treatment. *Curr Nutr Rep* 2018;7:329-34.
19. Wilding JPH, Batterham RL, Calanna S, et al. Once-weekly semaglutide in adults with overweight or obesity. *N Engl J Med* 2021:384:989.
20. Bessesen DH, Van Gaal LF. Progress and challenges in anti-obesity pharmacotherapy. *Lancet Diabetes Endocrinol* 2018;6:237-48.
21. Le Roux CW, Astrup AV, Fujioka K, et al. 3 years of liraglutide versus placebo for type 2 diabetes risk reduction and weight management in individuals with prediabetes: a randomised, double-blind trial. *Lancet* 2017;389:1399-1409.
22. Newton S, Braithwaite D, Akinyemiju TF. Socio-economic status over the life course and obesity: systematic review and meta-analysis. *PLoS One* 2017;12:e0177151.
23. Marso SP, Bain SC, Consoli A, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2016;375:1834-44.
24. Husain M, Birkenfeld AL, Donsmark M, et al. Oral semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2019;381:841-51.
25. Gomez G, Stanford FC. US health policy and prescription drug coverage of FDA-approved medications for the treatment of obesity. *Int J Obes (Lond)* 2018;42:495-500.
26. Schaffer R, Heymsfield SB, Garvey TW. FDA approves once-weekly semaglutide for weight loss (*Healio website*). 2021. Available at: ***https://www.healio.com/news/endocrinology/20210604/fda-approves-onceweekly-semaglutide-for-weight-loss***. Accessed 6/24/2021.

Clinical Topics: **Cardiovascular Care Team, Diabetes and Cardiometabolic Disease, Dyslipidemia, Hypertriglyceridemia, Lipid Metabolism, Nonstatins**

Keywords: *Cholesterol, LDL, Glucagon-Like Peptide 1, Ethnic Groups, Weight Loss, Diabetes Mellitus, Type 2, Obesity, Obesity, Morbid, Prediabetic State, Cardiovascular Diseases, Waist C…*

Prevalence, African Americans, Triglycerides, Mortality, Premature, Mortality, Absorptiometry, Photon, Glucose, Vulnerable Populations, Body Mass Index, Risk Factors, Risk Factors, Follow-Up Studies, Medicare, Life Style, Bariatric Surgery, Weight Gain, Insurance Coverage, Nutrition Therapy, Gastrointestinal Diseases, Health Policy, Costs and Cost Analysis, Metabolic Syndrome