Title

Is the GLP-1 receptor agonist, semaglutide, a good option for weight loss in persons with HIV?

Journal

AIDS, 38(4)

ISSN

0269-9370

Authors

Lee, Daniel

Capeau, Jacqueline

Publication Date

2024-03-15

DOI

10.1097/qad.0000000000003816

Is the GLP-1 receptor agonist, semaglutide, a good option for weight loss in persons with HIV?

Daniel Lee[a] and Jacqueline Capeau[b]

See related paper on page 531

AIDS 2024, **38**:603–605

Obesity has reached epidemic levels in the United States and most of the westernized world and its prevalence is increasing in most countries. Obesity contributes to most of the cardiovascular disease risk factors, including increased glycemia and risk of type 2 diabetes, blood pressure and risk of hypertension, dyslipidemia, and fatty liver [1]. These cardiometabolic comorbidities are generally associated with trunk fat repartition (android obesity) leading to increased ectopic visceral, epicardial and liver fat deposition.

In persons with HIV (PWH), the prevalence of obesity is rising as well [2,3]. In addition, altered fat repartition has long been observed: facial lipoatrophy resulting from treatment with thymidine analogs, truncal fat accumulation with protease inhibitors, global fat gain with integrase inhibitors (INSTI) and tenofovir alafenamide, while efavirenz and tenofovir disoproxil fumarate limit weight gain [4,5]. Moreover, PWH often present with a higher prevalence of cardiometabolic comorbidities than paired controls [6] in relation to android obesity, some antiretroviral agents, HIV fat reservoirs, immune dysfunction, gut dysbiosis, but also sedentary lifestyle and poor dietary choices [4].

Obesity treatment is a difficult challenge. Exercise and diet restriction generally allow for a moderate weight loss, often transient. Use of novel antiobesogenic drugs, such as glucagon-like peptide-1 (GLP-1) receptor agonists (GLP-1RAs), in diabetic and nondiabetic subjects is a very promising and powerful tool. GLP-1, an incretin hormone released by the intestine L-cells in response to oral nutrient intake [7], stimulates insulin secretion, slows gastric emptying and reduces food intake. GLP-1RA, have shown their efficacy in reducing glycemia in diabetics and in reducing weight. After the STEP1 [8] and STEP2 [9] studies, once-weekly subcutaneous semaglutide 1.0 mg was approved by the US Food and Drug Administration (FDA) in 2017 and the European Medicines Agency (EMA) in 2018 for the treatment of type 2 diabetes. Semaglutide exerts higher weight-losing effects than the other GLP-1RAs. Following the STEP3 Trial [10] in nondiabetic obese subjects that revealed the marked effect of 2.4 mg once-weekly subcutaneous semaglutide on weight loss, it was approved for weight loss in June 2021 in the US in adults with obesity or overweight with at least one weight-related comorbidity, in the UK (September 2023) and by the EMA (November 2021) [7]. Semaglutide decreases both subcutaneous, visceral, and limb fat and also epicardial and liver fat, arguing for an improved metabolic profile [11–13]. Regarding cardiovascular disease, the SELECT study [14] revealed that semaglutide 2.4 mg/week reduced the occurrence of major adverse cardiovascular events (MACE) by 20%.

Clinicians routinely prescribe semaglutide to treat diabetes in PWH. It is well tolerated and just as effective as in the general population. Its most common adverse effects are gastrointestinal: nausea, diarrhea, vomiting, constipation, generally mild-to-moderate in severity and transient in nature.

[a]University of California, San Diego Health, Owen Clinic, Division of Infectious Diseases & Global Public Health, San Diego, California, USA, and [b]Inserm UMR_S938, Centre de Recherche Saint-Antoine, Institut Hospitalo-Universitaire de Cardio-Métabolisme et Nutrition (ICAN), Sorbonne Université, Paris, France.

Correspondence to Daniel Lee, MD, Clinical Professor of Medicine, UCSD Health System: University of California San Diego Health System, San Diego, CA 92103, USA.

E-mail: dalee@health.ucsd.edu

Received: 1 December 2023; accepted: 9 December 2023.

DOI:10.1097/QAD.0000000000003816

The first real-world evidence study of the effectiveness of semaglutide for weight loss in PWH, published by Haidar *et al.* [15] in this issue of *AIDS*, included data from 222 PWH from the CNICS cohort who initiated semaglutide between 2018 and 2022. At 1 year, treatment with semaglutide (oral or subcutaneous formulations) resulted in an average of 6.5 kg weight loss, 5.7% body weight loss, and a 1.1% reduction in HbA1c. These results were comparable to similar studies in the non-HIV population. The authors concluded that semaglutide may play a key role in the obesity and diabetes epidemics in PWH.

Two studies presented at ID Week 2023 evaluated the effects of semaglutide and other GLP-1RAs in PWH. First, McComsey *et al.*[16] performed a single-site randomized, double-blind, placebo-controlled study of semaglutide in PWH with lipohypertrophy and similarly found that semaglutide use over 32 weeks was effective at decreasing weight by 8.3% and total fat by 15%. A decline of 13% and 17% was seen in visceral adipose tissue (VAT) and trunk fat, respectively, and a decline of 13% was seen in both subcutaneous adipose tissue (SAT) and limb fat. This study raised some surprising concerns in that semaglutide did not decrease liver or pericardial fat depots. In addition, lean mass loss of 5.4% was seen. Second, Nguyen, *et al.*[17] presented a single-site retrospective cohort data evaluating 225 PWH who initiated a GLP-1RA between February 2021 and February 2023. The majority of study participants received semaglutide, but other GLP-1RAs included liraglutide, dulaglutide, and tirzepatide. 57% had a diagnosis of diabetes. Overall, the mean weight change was −5.4 kg in the entire cohort with a BMI change of $-1.8\,kg/m^2$ and a HbA1c change of −0.6%. The mean decline in weight and BMI in those without diabetes was greater at −7.3 kg and $-2.3\,kg/m^2$, respectively.

A small retrospective chart review presented by Lloyd *et al.* [18] at IAS 2023 evaluated the impact of GLP-1RAs on body weight in noninfected diabetics (DM, $n = 30$) and in PWH with diabetes (PWHD, $n = 15$). They observed a weight loss of only −1.73 kg in DM in contrast to a weight loss of −10.4 kg in PWHD. This group concluded that the greater weight loss observed in PWH may be related to differences in the mechanistic pathways leading to weight gain.

The multitude of current studies evaluating semaglutide and other GLP-1RAs in PWH for weight loss clearly demonstrate the effectiveness of these agents [15–18] and parallel similar studies in people without HIV. However, these studies raise some unique concerns regarding the use of semaglutide in PWH. Reduction in lean mass, also reported in the general population with the GLP-1RAs, is a concern in PWH [19]. Some PWH present with sarcopenic obesity and increased sarcopenia (related to possibly accelerated aging and chronic inflammation despite controlled HIV infection), which leads to a higher risk of frailty [20]. Loss of lean mass requires clinicians to prescribe exercise training to preserve skeletal muscle mass and physical function. Another concern is the potential development or worsening of lipoatrophy in PWH, resulting from semaglutide and GLP-1RA usage. Furthermore, semaglutide likely needs to be continued on a long-term basis, which can increase the risks of long-term toxicity and cost.

The presentation of weight gain and fat distribution in PWH is variable and dependent on multiple factors, including prior exposure to legacy antiretroviral therapies [4]. An important clinical distinction to make is whether the excess weight is composed of more VAT than SAT (lipohypertrophy phenotype) or more SAT than VAT (obesity phenotype). For those PWH with an obesity phenotype, the use of GLP-1RAs is appropriate. However, for those PWH with more VAT and other ectopic fat depots (epicardial and liver fat), consideration of tesamorelin treatment may be more appropriate. Tesamorelin has been shown to reduce VAT [21], while also reducing liver fat [22] and preserving lean muscle [23], but it is not available in all countries. McComsey *et al.* [16] did demonstrate that semaglutide can reduce VAT, but it did not decrease fat in ectopic depots as has been seen in other studies in the non-HIV population [14,24]. Further studies are likely needed to confirm this finding in PWH. However, since ectopic fat is linked to cardiometabolic risk, it is mandatory to analyze the effect of semaglutide on MACE in PWH.

Thus, in the current obesogenic environment, the use of semaglutide is effective in inducing weight loss in PWH, even in those receiving an INSTI [15], which is a reassuring point. Adverse effects different from those observed in the general population have not been reported. Therefore, semaglutide is a promising drug to decrease weight in PWH. However, some concerns regarding its use in this population need to be addressed.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

References

1. Lavie CJ, Bhatt DL, Neeland IJ, Heymsfield SB. **Editorial commentary: weight loss for cardiovascular disease prevention — is semaglutide the answer?** *Trends Cardiovasc Med* 2023; **33**: 167–169.
2. Erlandson KM, Zhang L, Lake JE, Schrack J, Althoff K, Sharma A, *et al.* **Changes in weight and weight distribution across the lifespan among HIV-infected and -uninfected men and women.** *Medicine (Baltimore)* 2016; **95**:e5399.

3. Bailin SS, Gabriel CL, Wanjalla CN, Koethe JR. **Obesity and weight gain in persons with HIV.** *Curr HIV/AIDS Rep* 2020; **17**:138–150.
4. Koethe JR, Lagathu C, Lake JE, Domingo P, Calmy A, Falutz J, *et al*. **HIV and antiretroviral therapy-related fat alterations.** *Nat Rev Dis Primers* 2020; **6**:48.
5. Capeau J, Lagathu C, Béréziat V. **Recent data on the role of antiretroviral therapy in weight gain and obesity in persons living with HIV.** *Curr Opin HIV AIDS* 2024; **19**:14–20.
6. Zino L, Tack CJ, Richel O, Burger DM. **GLP-1 agonists for people living with HIV and obesity, is there a potential?** *HIV Med* 2023; **24**:1029–10347.
7. Chao AM, Tronieri JS, Amaro A, Wadden TA. **Semaglutide for the treatment of obesity.** *Trends Cardiovasc Med* 2023; **33**: 159–166.
8. Wilding JPH, Batterham RL, Calanna S, Davies M, Van Gaal LF, Lingvay I, *et al*. **Once-weekly semaglutide in adults with overweight or obesity.** *N Engl J Med* 2021; **384**:989–1002.
9. Davies M, Færch L, Jeppesen OK, Pakseresht A, Pedersen SD, Perreault L, *et al*. **Semaglutide 2 4 mg once a week in adults with overweight or obesity, and type 2 diabetes (STEP 2): a randomised, double-blind, double-dummy, placebo-controlled, phase 3 trial.** *Lancet* 2021; **397**:971–984.
10. Wadden TA, Bailey TS, Billings LK, Davies M, Frias JP, Koroleva A, *et al*. **Effect of subcutaneous semaglutide vs placebo as an adjunct to intensive behavioral therapy on body weight in adults with overweight or obesity: the STEP 3 Randomized Clinical Trial.** *JAMA* 2021; **325**:1403–1413.
11. Kadowaki T, Isendahl J, Khalid U, Lee SY, Nishida T, Ogawa W, *et al*. **Semaglutide once a week in adults with overweight or obesity, with or without type 2 diabetes in an east Asian population (STEP 6): a randomised, double-blind, double-dummy, placebo-controlled, phase 3a trial.** *Lancet Diabetes Endocrinol* 2022; **10**:193–206.
12. Iacobellis G, Villasante Fricke AC. **Effects of semaglutide versus dulaglutide on epicardial fat thickness in subjects with type 2 diabetes and obesity.** *J Endocr Soc* 2020; **4**:bvz042.
13. Mantovani A, Byrne CD, Targher G. **Efficacy of peroxisome proliferator-activated receptor agonists, glucagon-like peptide-1 receptor agonists, or sodium-glucose cotransporter-2 inhibitors for treatment of nonalcoholic fatty liver disease: a systematic review.** *Lancet Gastroenterol Hepatol* 2022; **7**:367–378.
14. Lincoff AM, Brown-Frandsen K, Colhoun HM, Deanfield J, Emerson SS, Esbjerg S, *et al*. **Semaglutide and cardiovascular outcomes in obesity without diabetes.** *N Engl J Med* 2023; **389**:2221–2232.
15. Haidar L, Crane HM, Nance RM, Webel A, Ruderman SA, Whitney BM, *et al*. **Weight loss associated with semaglutide treatment among people with HIV.** *AIDS* 2024; **38**:531–535.
16. McComsey GA, Sattar A, Wu Q, Gilani KA, Labbato D, Foster T, Eckard A. **Effects of semaglutide on adipose tissue in HIV-associated lipohypertrophy.** *ID Week, Boston, abstract 1894;* 2023.
17. Nguyen QP, Wooten D, Duren K, Moreno M, Promer K, Rajagopal A, *et al*. **GLP-1 receptor agonists promote weight loss among people with HIV.** *ID Week, Boston, abstract 1892;* 2023.
18. Lloyd AN, Brizzi MB, Lyons MM, Rotert LM, Fichtenbaum CJ. **Impact of GLP-1 receptor agonists on body weight in patients with type 2 diabetes and HIV. 12th International AIDS Society Conference on HIV Science (IAS 2023).** *Brisbane, Australia, abstract EPB0195;* 2023.
19. Sargeant JA, Henson J, King JA, Yates T, Khunti K, Davies MJ. **A review of the effects of glucagon-like peptide-1 receptor agonists and sodium-glucose cotransporter 2 inhibitors on lean body mass in humans.** *Endocrinol Metab (Seoul)* 2019; **34**:247–262.
20. Hawkins KL, Zhang L, Ng DK, Althoff KN, Palella FJ Jr, Kingsley LA, *et al*. **Abdominal obesity, sarcopenia, and osteoporosis are associated with frailty in men living with and without HIV.** *AIDS* 2018; **32**:1257–1266.
21. Falutz J, Potvin D, Mamputu JC, Assaad H, Zoltowska M, Michaud SE, *et al*. **Effects of tesamorelin, a growth hormone-releasing factor, in HIV-infected patients with abdominal fat accumulation: a randomized placebo-controlled trial with a safety extension.** *J Acquir Immune Defic Syndr* 2010; **53**:311–322.
22. Stanley TL, Feldpausch MN, Oh J, Branch KL, Lee H, Torriani M, Grinspoon SK. **Effect of tesamorelin on visceral fat and liver fat in HIV-infected patients with abdominal fat accumulation: a randomized clinical trial.** *JAMA* 2014; **312**:380–389.
23. Adrian S, Scherzinger A, Sanyal A, Lake JE, Falutz J, Dubé MP, *et al*. **The growth hormone releasing hormone analogue, tesamorelin, decreases muscle fat and increases muscle area in adults with HIV.** *J Frailty Aging* 2019; **8**:154–159.
24. Newsome PN, Buchholtz K, Cusi K, Linder M, Okanoue T, Ratziu V, *et al*. **A placebo-controlled trial of subcutaneous semaglutide in nonalcoholic steatohepatitis.** *N Engl J Med* 2021; **384**:1113–1124.