PICO Search Assignment Worksheet **Name: Jay Kolasinac**

Brief description of patient problem/setting (summarize the case very briefly)

51 year old obese, male, with PMH of metabolic syndrome and HLD presents to the office today for his routine check up. He recently heard about the drug semaglutide and its possible effects on weight loss in patients who suffer from obesity. He wants to know how effective this drug is and if it could help him or not.

Search Question: In obese adult patients, how effective is semaglutide in reducing weight loss?

Question Type: What kind of question is this? (boxes now checkable in Word)

☐Prevalence ☐Screening ☐Diagnosis
☐Prognosis ☒Treatment ☐Harms

Assuming that the highest level of evidence to answer your question will be meta-analysis or systematic review, what other types of study might you include if these are not available (or if there is a much more current study of another type)?

Please explain your choices.

Randomized control trials will be studies I will be searching for because my question is all about treatment and the efficacy of the intervention [semaglutide]. Prospective cohort studies could also be included because these studies track patients over a period of time to see how they respond although their quality of evidence is not as high as the RCTs.

PICO search terms:

P	**I**	**C**	**O**
Obese	Semaglutide	Placebo	Reduced weight loss
Overweight		None	Reduced body fat
Adults			Reduced appetite

Search tools and strategy used:

Database	**Terms**	**Filter**	**# of Articles**
PubMed	Semaglutide obesity weight loss	Medline, last 5 years	488
ScienceDirect	Semaglutide obesity weight loss	Last 5 years, research articles	134
MEDLINE Complete	Semaglutide obesity weight loss	last 10 years	20

I narrowed down my search results to articles that were published within 5 years and that were Medline. Many articles were focused on the different trials that were going on for the past few years researching semaglutide and its effects on weight loss. I needed the actual published version rather than a trial overview so that was what I was looking for.

Results found:

Article 1

Citation:

Wilding JPH, Batterham RL, Calanna S, Davies M, Van Gaal LF, Lingvay I, McGowan BM, Rosenstock J, Tran MTD, Wadden TA, Wharton S, Yokote K, Zeuthen N, Kushner RF; STEP 1 Study Group. Once-Weekly Semaglutide in Adults with Overweight or Obesity. N Engl J Med. 2021 Mar 18;384(11):989. doi: 10.1056/NEJMoa2032183. Epub 2021 Feb 10. PMID: 33567185.

https://pubmed.ncbi.nlm.nih.gov/33567185/

Article Type:

Randomized Control Trial

Abstract:

Background: Obesity is a global health challenge with few pharmacologic options. Whether adults with obesity can achieve weight loss with once-weekly semaglutide at a dose of 2.4 mg as an adjunct to lifestyle intervention has not been confirmed.
Methods: In this double-blind trial, we enrolled 1961 adults with a body-mass index (the weight in kilograms divided by the square of the height in meters) of 30 or greater (≥27 in persons with ≥1 weight-related coexisting condition), who did not have diabetes, and randomly assigned them, in a 2:1 ratio, to 68 weeks of treatment with once-weekly subcutaneous semaglutide (at a dose of 2.4 mg) or placebo, plus lifestyle intervention. The coprimary end points were the percentage change in body weight and weight reduction of at least 5%. The primary estimand (a precise description of the treatment effect reflecting the objective of the clinical trial) assessed effects regardless of treatment discontinuation or rescue interventions.
Results: The mean change in body weight from baseline to week 68 was -14.9% in the semaglutide group as compared with -2.4% with placebo, for an estimated treatment difference of -12.4 percentage points (95% confidence interval [CI], -13.4 to -11.5; P<0.001). More participants in the semaglutide group than in the placebo group achieved weight reductions of 5% or more (1047 participants [86.4%] vs. 182 [31.5%]), 10% or more (838 [69.1%] vs. 69 [12.0%]), and 15% or more (612 [50.5%] vs. 28 [4.9%]) at week 68 (P<0.001 for all three comparisons of odds). The change in body weight from baseline to week 68 was -15.3 kg in the semaglutide group as compared with -2.6 kg in the placebo group (estimated treatment difference, -12.7 kg; 95% CI, -13.7 to -11.7). Participants who received semaglutide had a greater improvement with respect to cardiometabolic risk factors and a greater increase in

participant-reported physical functioning from baseline than those who received placebo. Nausea and diarrhea were the most common adverse events with semaglutide; they were typically transient and mild-to-moderate in severity and subsided with time. More participants in the semaglutide group than in the placebo group discontinued treatment owing to gastrointestinal events (59 [4.5%] vs. 5 [0.8%]).
Conclusions: In participants with overweight or obesity, 2.4 mg of semaglutide once weekly plus lifestyle intervention was associated with sustained, clinically relevant reduction in body weight. (Funded by Novo Nordisk; STEP 1 ClinicalTrials.gov number, NCT03548935).

Key points:

- Double blind randomized control trial included 1,961 participants
- Followed subjects over a 68 week period
- Subjects were either given the semaglutide injection once-weekly or a placebo
- At 68 weeks, there was a 14.9% reduction in weight loss compared to the 2.4% reduction of weight loss in the placebo group
- Those who are overweight, along with lifestyle modifications, use of semaglutide can be associated with reduction in body weight

Why I chose this article:

- I liked that the article was a RCT
- It specifically focused on my PICO question.
- Published in 2021
- Large sample size of close to 2000 participants

Article 2

Citation:

Friedrichsen, M, Breitschaft, A, Tadayon, S, Wizert, A, Skovgaard, D. The effect of semaglutide 2.4 mg once weekly on energy intake, appetite, control of eating, and gastric emptying in adults with obesity. *Diabetes Obes Metab*. 2021; 23: 754– 762. https://doi.org/10.1111/dom.14280

https://dom-pubs.onlinelibrary.wiley.com/doi/full/10.1111/dom.14280

Article Type:

Randomized Control Trials

Abstract:

Aim
To investigate the effects of once-weekly subcutaneous (s.c.) semaglutide 2.4 mg on gastric emptying, appetite, and energy intake in adults with obesity.
Materials and Methods
A double-blind, parallel-group trial was conducted in 72 adults with obesity, randomized to once-weekly s.c. semaglutide (dose-escalated to 2.4 mg) or placebo for

20 weeks. Gastric emptying was assessed using paracetamol absorption following a standardized breakfast. Participant-reported appetite ratings and Control of Eating Questionnaire (CoEQ) responses were assessed, and energy intake was measured during ad libitum lunch.

Results

The area under the concentration–time curve (AUC) for paracetamol 0 to 5 hours after a standardized meal ($AUC_{0–5h,para}$; primary endpoint) was increased by 8% ($P = 0.005$) with semaglutide 2.4 mg versus placebo at week 20 (non-significant when corrected for week 20 body weight; $P = 0.12$). No effect was seen on $AUC_{0–1h,para}$, maximum observed paracetamol concentration, or time to maximum observed paracetamol concentration. Ad libitum energy intake was 35% lower with semaglutide versus placebo (1736 versus 2676 kJ; estimated treatment difference −940 kJ; P <0.0001). Semaglutide reduced hunger and prospective food consumption, and increased fullness and satiety when compared with placebo (all P <0.02). The CoEQ indicated better control of eating and fewer/weaker food cravings with semaglutide versus placebo (P <0.05). Body weight was reduced by 9.9% with semaglutide and 0.4% with placebo. Safety was consistent with the known profile of semaglutide.

Conclusions

In adults with obesity, once-weekly s.c. semaglutide 2.4 mg suppressed appetite, improved control of eating, and reduced food cravings, ad libitum energy intake and body weight versus placebo. There was no evidence of delayed gastric emptying at week 20, assessed indirectly via paracetamol absorption.

Key points:

- Double blind randomized control trial
- 72 patients included in the RCT
- Either patients received a once-weekly 2.4mg injection or a placebo for 20 weeks
- Bodyweight was reduced by 9.9% with semaglutide vs 0.4% with placebo.
- In adults with obesity, once-weekly s.c. semaglutide 2.4 mg suppressed appetite, improved control of eating, and reduced food cravings, ad libitum energy intake and body weight versus placebo. There was no evidence of delayed gastric emptying at week 20, assessed indirectly via paracetamol absorption

Why I chose this article:

- It was a randomized control trial
- It took place within the last 5 years
- It focused directly on my PICO question
- It measured certain statistics that other articles did not such as appetite suppression, food cravings etc

Article 3

Citation:

O'Neil, P. M., Birkenfeld, A. L., McGowan, B., Mosenzon, O., Pedersen, S. D., Wharton, S., … Wilding, J. P. H. (2018). *Efficacy and safety of semaglutide compared with liraglutide and placebo for weight loss in patients with obesity: a randomised, double-blind, placebo and active controlled, dose-ranging, phase 2 trial. The Lancet.* doi:10.1016/s0140-6736(18)31773-2

https://pubmed.ncbi.nlm.nih.gov/30122305/

Article Type:

Randomized control trial

Abstract:

Background: Obesity is a major public health issue, and new pharmaceuticals for weight management are needed. Therefore, we evaluated the efficacy and safety of the glucagon-like peptide-1 (GLP-1) analogue semaglutide in comparison with liraglutide and a placebo in promoting weight loss.

Methods: We did a randomised, double-blind, placebo and active controlled, multicentre, dose-ranging, phase 2 trial. The study was done in eight countries involving 71 clinical sites. Eligible participants were adults (≥18 years) without diabetes and with a body-mass index (BMI) of 30 kg/m^2 or more. We randomly assigned participants (6:1) to each active treatment group (ie, semaglutide [0·05 mg, 0·1 mg, 0·2 mg, 0·3 mg, or 0·4 mg; initiated at 0·05 mg per day and incrementally escalated every 4 weeks] or liraglutide [3·0 mg; initiated at 0·6 mg per day and escalated by 0·6 mg per week]) or matching placebo group (equal injection volume and escalation schedule to active treatment group) using a block size of 56. All treatment doses were delivered once-daily via subcutaneous injections. Participants and investigators were masked to the assigned study treatment but not the target dose. The primary endpoint was percentage weight loss at week 52. The primary analysis was done using intention-to-treat ANCOVA estimation with missing data derived from the placebo pool. This study is registered with ClinicalTrials.gov, number NCT02453711.

Findings: Between Oct 1, 2015, and Feb 11, 2016, 957 individuals were randomly assigned (102-103 participants per active treatment group and 136 in the pooled placebo group). Mean baseline characteristics included age 47 years, bodyweight 111·5 kg, and BMI 39·3 kg/m^2. Bodyweight data were available for 891 (93%) of 957 participants at week 52. Estimated mean weight loss was -2·3% for the placebo group versus -6·0% (0·05 mg), -8·6% (0·1 mg), -11·6% (0·2 mg), -11·2% (0·3 mg), and -13·8% (0·4 mg) for the semaglutide groups. All semaglutide groups versus placebo were significant (unadjusted p≤0·0010), and remained significant after adjustment for multiple testing (p≤0·0055). Mean bodyweight reductions for 0·2 mg or more of semaglutide versus liraglutide were all significant (-13·8% to -11·2% vs -7·8%). Estimated weight loss of 10% or more occurred in 10% of participants receiving placebo compared with 37-65% receiving 0·1 mg or more of semaglutide (p<0·0001 vs placebo). All semaglutide doses were generally well tolerated, with no new safety

concerns. The most common adverse events were dose-related gastrointestinal symptoms, primarily nausea, as seen previously with GLP-1 receptor agonists. **Interpretation:** In combination with dietary and physical activity counselling, semaglutide was well tolerated over 52 weeks and showed clinically relevant weight loss compared with placebo at all doses.

Key points:

- Double blinded randomized control trial
- Published within the last 5 years
- Compared efficacy and safety of semaglutide vs liraglutide vs placebo
- Study involved in eight countries involving 71 clinical sites
- Patients involved were 18+ with no diabetes and BMI of 30+ totaling 957 participants
- Tracked patients over 52 weeks
- In combination with other lifestyle changes, semaglutide was well tolerated and showed clinically relevant weight loss over the 52 weeks

Why I chose this article:

- This was a randomized control tiral
- Published in within last 5 years
- Focused directly on PICO question
- The study compared the efficacy of semaglutide vs other GLP-1 agonist and placebo

Article 4

Citation:

Blundell, J., Finlayson, G., Axelsen, M., Flint, A., Gibbons, C., Kvist, T., & Hjerpsted, J. B. (2017). *Effects of once-weekly semaglutide on appetite, energy intake, control of eating, food preference and body weight in subjects with obesity. Diabetes, Obesity and Metabolism, 19(9), 1242–1251.* doi:10.1111/dom.12932

https://dom-pubs.onlinelibrary.wiley.com/doi/full/10.1111/dom.12932

Article type:

Randomized control trial

Abstract:

Aim

The aim of this trial was to investigate the mechanism of action for body weight loss with semaglutide.

Materials and methods

This randomised, double-blind, placebo-controlled, two-period crossover trial investigated the effects of 12 weeks of treatment with once-weekly subcutaneous semaglutide, dose-escalated to 1.0 mg, in 30 subjects with obesity. *Ad libitum* energy

intake, ratings of appetite, thirst, nausea and well-being, control of eating, food preference, resting metabolic rate, body weight and body composition were assessed.

Results

After a standardised breakfast, semaglutide, compared with placebo, led to a lower *ad libitum* energy intake during lunch (−1255 kJ; $P < .0001$) and during the subsequent evening meal ($P = .0401$) and snacks ($P = .0034$), resulting in a 24% reduction in total energy intake across all *ad libitum* meals throughout the day (−3036 kJ; $P < .0001$). Fasting overall appetite suppression scores were improved with semaglutide vs placebo, while nausea ratings were similar. Semaglutide was associated with less hunger and food cravings, better control of eating and a lower preference for high-fat foods. Resting metabolic rate, adjusted for lean body mass, did not differ between treatments. Semaglutide led to a reduction from baseline in mean body weight of 5.0 kg, predominantly from body fat mass.

Conclusion

After 12 weeks of treatment, *ad libitum* energy intake was substantially lower with semaglutide vs placebo with a corresponding loss of body weight observed with semaglutide. In addition to reduced energy intake, likely mechanisms for semaglutide-induced weight loss included less appetite and food cravings, better control of eating and lower relative preference for fatty, energy-dense foods.

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Key points:

- Double-blinded randomized control trial
- 12 week study where patients either received semaglutide or placebo injection once weekly
- 30 subjects in involved in the study
- After a standardised breakfast, semaglutide, compared with placebo, led to a lower *ad libitum* energy intake during lunch (−1255 kJ; $P < .0001$) and during the subsequent evening meal ($P = .0401$) and snacks ($P = .0034$), resulting in a 24% reduction in total energy intake across all *ad libitum* meals throughout the day (−3036 kJ; $P < .0001$).
- Semaglutide was associated with less hunger and food cravings, better control of eating and a lower preference for high-fat foods
- Average of 5.0kg from body fat mass was lost over the 12 week period

Why I chose this article:

- It was a randomized control trial
- Published in within the last 5 years
- Focused directly on my PICO question and compared the efficacy vs a placebo group
- It tracked ad libitum energy intake, ratings of appetite, thirst, control of eating, and more

What is the clinical "bottom line" derived from these articles in answer to your question?

The GLP-1 agonist, semaglutide, is a known diabetes type II injectable medication. Wilding JPH et al., conducted a randomized control trial that included over 1900 obese participants receiving weekly semaglutide injections who did **not** have diabetes, but also participated in lifestyle management, and saw significant weight loss results over 68 weeks. The other randomized control trials above also focused on semaglutide weekly injections, although differing sample sizes, were able to replicate the same results in their patients seeing significant/clinically relevant weight reductions even in fewer than 68 weeks. As of right now, the FDA has not approved the use of semaglutide as a weight loss medication, however, with the high qualities of evidence being published, I can see many clinicians strongly considering prescribing this medication off-label for their obese patients. I do want to mention that all of the patients who participated in the trial did also implement lifestyle changes while receiving the weekly injections. Clinicians should make it clear that this is not a miracle drug where you can binge eat and enjoy all the fatty/unhealthy foods you please, but it is rather an adjunct tool that can help patients counteract the adverse effects that can arise from being obese. If this is FDA-approved, I think this can be a game changer for the United States because roughly 1 out of 3 adults are obese in the US. Maintaining a healthy weight and exercising consistently can prevent all sorts of problems down the line and can thus improve the longevity of the people here in the US. We have long ways to go before we see any kind drastic changes happening, but FDA approval can be the start to something beneficial in the future.