Reviewers' comments:

Reviewer #1:

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Accept (High priority)

Specific Comments to Authors: No specific comments

Dear Reviewer, thank you for the positive comment.

Reviewer #2:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Add in detail about the pharmacodynamics and pharmacokinetic of this new drug Semaglutide. How it acts at different levels to reduce obesity , Improves cardiac output and helps in glycemic - regulation.

Thank you for the comment. Detailed information on pharmacodynamics and pharmacokinetics of semaglutide has been added at the end of DISCUSSION as a separate section.

Semaglutide has a 94% amino acid sequence homology to native GLP-1. However, structural modifications from endogenous GLP-1, i.e., alanine residue substitution at the 8th position with Aib, make it less susceptible to degradation by dipeptidyl peptidase 4 (DPP-4) while acylation of Lysine residue at the 26th position and attachment of a C18 fatty-diacid increase its binding affinity to albumin. The above changes result in a half-life of approximately one week, making it appropriate for once-weekly use in clinical practice. In the phase-3 SUSTAIN trials. semaglutide showed superiority to different comparators and during different stages of diabetes in reducing HbA1c and body weight. In a SUSTAIN-6 trial investigating cardiovascular outcomes, semaglutide led to a 26% reduction in risk of the primary 3-point MACE (a composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke) when compared to placebo. The pharmacokinetic properties of semaglutide are not significantly affected by impaired hepatic or renal function. Therefore no dose adjustments are required in that case. It achieves a steady state concentration in 4 to 5 weeks (both subcutaneous and oral form). Indeed, in the case of subcutaneous semaglutide, 1 to 3 days are needed to achieve the maximum concentration, and, in the case of oral semaglutide, one hour is needed following intake. Moreover, during clinical pharmacology studies, no relevant impact of semaglutide on concomitant orally administered medications was observed, making its use safe in a broad population (**Ikushima I**, Jensen L, Flint A, Nishida T, Zacho J, Irie S. A Randomized Trial Investigating the Pharmacokinetics, Pharmacodynamics, and Safety of Subcutaneous Semaglutide Once-Weekly in Healthy Male Japanese and Caucasian Subjects. Adv Ther. 2018 Apr;35(4):531-544. doi: 10.1007/s12325-018-0677-1. Epub 2018 Mar 13. PMID: 29536338; PMCID: PMC5910468 Semaglutide improves the efficiency of incretin function by activating GLP-1 receptors and enhancing GLP-1 to supraphysiological levels. It reduces fasting and postprandial glucose levels by promoting insulin secretion in a glucose-dependent manner and suppressing hepatic gluconeogenesis through blunted glucagon release. Moreover, it improves both proinsulin to insulin ratio, which suggests

improved β-cell function and insulin sensitivity through body weight and fat loss consequent to reduced energy intake and gastric motility (**Mahapatra MK**, Karuppasamy M, Sahoo BM. Semaglutide, a glucagon like peptide-1 receptor agonist with cardiovascular benefits for management of type 2 diabetes. Rev Endocr Metab Disord. 2022 Jun;23(3):521-539. doi: 10.1007/s11154-021-09699-1. Epub 2022 Jan 7. PMID: 34993760; PMCID: PMC8736331.).

A cardiovascular risk (3-P MACE) reduction effect compared to placebo was shown for injectable and oral semaglutide in SUSTAIN-6 and PIONEER-6 trials, respectively. Animal studies have shown antiatherosclerotic effects mediated by regulating multiple inflammatory pathways and antiapoptotic effects in cardiac cells (**Iorga RA**, Bacalbasa N, Carsote M, Bratu OG, Stanescu AMA, Bungau S, Pantis C, Diaconu CC. Metabolic and cardiovascular benefits of GLP-1 agonists, besides the hypoglycemic effect (Review) Exp Ther Med. 2020;20(3):2396–2400. doi: 10.3892/etm.2020.8714.). In addition, three ongoing trials, i.e., SOUL (NCT03914326), SELECT (Semaglutide Effects on Heart Disease and Stroke in Patients with Overweight or Obesity; NCT03574597), and STRIDE (NCT04560998), will give further insight into different cardiovascular effects of both oral and subcutaneous semaglutide in patients with and without T2DM, and overweight/obesit (**ClinicalTrials**. A Heart Disease Study of Semaglutide in Patients With Type 2 Diabetes (SOUL). 2019. https://clinicaltrials.gov/ct2/show/NCT03914326; **ClinicalTrials**. Semaglutide Effects on Heart Disease and Stroke in Patients With Overweight or Obesity (SELECT). 2018. https://clinicaltrials.gov/ct2/show/NCT03574597, **ClinicalTrials.** A Research Study to Compare a Medicine Called Semaglutide Against Placebo in People With Peripheral Arterial Disease and Type 2 Diabetes (STRIDE). 2020. https://www.clinicaltrials.gov/ct2/show/NCT04560998).

2. Does it causes sudden hypoglycaemia and leads to flaring of Diabetic - Retinopathy ?

Thank you for the comment. The additional information has been added.

The semaglutide mechanism of action is glucose-dependent and, therefore, associated per se with a shallow risk of hypoglycemia. Nevertheless, semaglutide cannot avoid the risk of hypoglycemia due to add-on sulfonylureas or insulin. Such drug association might initially cause acute glucose level drops and probably transiently worsening DR, as observed in the first four weeks of treatment (**Vilsbøll T,** Bain SC, Leiter LA, Lingvay I, Matthews D, Simó R, Helmark IC, Wijayasinghe N, Larsen M. Semaglutide, reduction in glycated haemoglobin and the risk of diabetic retinopathy. Diabetes Obes Metab. 2018 Apr;20(4):889-897. DII: 10.1111/dom.13172. Epub 2018 Jan 8. PMID: 29178519; PMCID: PMC5888154).

3. How many human trials / randomised controlled trials have been undertaken and with what sample -size and follow up to clearly assess it's role in causing DR ?

Thank you for your comment, it has been further explored within the Manuscript.

Both semaglutide formulations (subcutaneous and oral) have been investigated in two phase-3 clinical programs – i.e., the SUSTAIN and PIONEER program. Combining all individual studies within these two programs, over 21,500 patients participated in the studies with a treatment duration of at least 26 weeks, giving a plethora of safety evidence (**Smits MM**, Van Raalte DH. Safety of Semaglutide. Front Endocrinol (Lausanne). 2021 Jul 7;12:645563. doi: 10.3389/fendo.2021.645563.). Data insinuating a connection between semaglutide and DR

emerged during the phase-3 trials. However, the answer to whether that phenomenon depended on the drug itself or the magnitude of fast-occurring glucose lowering will come from the presently underway FOCUS trial on approximately 1,500 patients with T2DM, a bilateral 10 to 75 Early Treatment Diabetic Retinopathy Study (ETDRS) score and no need for ophthalmologic therapy. Such a study will analyze once-weekly subcutaneous semaglutide 1.0 mg compared with placebo for up to 5 years, with the primary endpoint of at least three-digit ETDRS score progression.

4. What drugs and therapy can be given along with Semaglutide to keep it's side -effects on the lower side ?

Thank you for the comment. We added summarized clinical advice based on currently available data.

Until FOCUS results become available, caution is mandatory in patients with DR.. It may be wise to perform fundoscopy prior to semaglutide therapy, and existing DR should be treated concomitantly. In addition, given the strong effects of semaglutide on glucose levels, down-titrating basal insulin therapy or stopping sulphonylurea will prevent rapid decreases in glucose concentrations, thereby reducing the risk of acute DR worsening.

5. Can anti - vegf be administered to avoid progression of DR ?

Thank you for the comment; it has been incorporated within the Manuscript.

Currently, guidelines on DR management do not differ for patients receiving other antidiabetic agents. Therefore, the same treatment, including anti-VEGF agents, should be applied.6. Future role of this class of drugs in Diabetes , CVD and Obesity.

Thank you for the comment. It is of great interest and quite broad, therefore exceeding the scope of this review. We added a short sentence in the Manuscript.

Both current and future research of GLP-1RA is quite exciting and targeting different metabolic conditions and health aspects associated with both T2DM and obesity, such as cognitive health and dementia, PCO, and NAFLD.