

Semaglutide in Diabetic Periodontitis-Induced Osteoblast Ferroptosis: Pharmacological and Methodological Insights [Letter]

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Dear editor

Zhang et al¹ should be commended for addressing an important and underexplored question: whether semaglutide, a long-acting glucagon-like peptide-1 receptor (GLP-1R) agonist, can protect osteoblasts against diabetic periodontitis-induced bone loss by inhibiting ferroptosis. Their study suggests that semaglutide can effectively mitigate osteoblast ferroptosis induced by high glucose plus palmitic acid (HGHP), and improve osteogenic function via the Wnt5a/Ror2/p38 MAPK pathway. This finding is clinically relevant, but several points warrant further discussion.

The dosing strategy is important for interpreting the pharmacological and translational relevance of semaglutide's effects. In the cellular experiments, this study used 10 μ M semaglutide to alleviate HGHP-induced osteogenic dysfunction. However, previous *in vitro* characterization showed that semaglutide activates GLP-1R with picomolar functional potency, with a reported EC₅₀ of 6.2 pM, while its receptor-binding affinity was reported at 0.38 ± 0.06 nM.² Population pharmacokinetic analyses indicate that total steady-state plasma concentrations achieved with approved once-weekly subcutaneous dosing are generally within the nanomolar range.³ Therefore, 10 μ M represents a concentration several orders of magnitude higher than required for GLP-1R activation, and vastly exceeds typical clinical systemic exposure. Additionally, the 0.5 mg/kg/time *in vivo* regimen used in this study appears to substantially exceed the mouse-equivalent dose estimated from the highest approved clinical injectable dosing, approximately 0.15 mg/kg/time.^{4,5} Supraphysiological concentrations may engage receptor-independent or off-target cytoprotective pathways. Consequently, a broader dose-response analysis, particularly across a wider range of physiologically relevant concentrations, is warranted to further confirm the therapeutic potential of semaglutide in diabetic periodontitis.

Besides, the role of cyclic adenosine monophosphate (cAMP) signaling deserves further clarification in the mechanistic interpretation of semaglutide's effects. Canonical GLP-1R signaling predominantly promotes intracellular cAMP accumulation and activates downstream protein kinase A (PKA) or Epac cascades.⁶ cAMP/PKA signaling has been implicated in directly suppressing NF- κ B activity and dampening pro-inflammatory transcriptional programs,⁷ which are highly relevant to diabetic periodontitis.⁸ Furthermore, PKA-mediated phosphorylation of HePTP can release p38 from phosphatase-mediated inhibition and thereby modulate MAPK activity.⁹ cAMP/PKA signaling may have the capability to regulate p38 MAPK independently of Wnt5a. Therefore, assessing cAMP signaling would help determine whether semaglutide's effects are mainly mediated through the Wnt5a/Ror2/p38 MAPK pathway or partly through other cAMP-related mechanisms.

Additionally, a critical technical point concerns the solvent used for the drug. In this study, semaglutide is dissolved in DMSO for subsequent experiments. DMSO is a polar solvent known to subtly alter cell membrane fluidity, disrupt lipid packing, and shift baseline oxidative stress responses, even at very low concentrations.^{10,11} More importantly, ferroptosis is fundamentally driven by lipid peroxidation.¹² Therefore, further clarification of identical solvent exposure across all experimental groups would be necessary to support the observed anti-ferroptosis effects arising from semaglutide rather than DMSO.

Overall, this study provides a valuable foundation for investigating the therapeutic effects of semaglutide in preventing diabetic patients' alveolar bone loss. Future studies might look into more appropriate pharmacological strategies and deeper upstream pathway exploration to elucidate the clinical translational potential of semaglutide for diabetic periodontitis.

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Disclosure

The author declares no competing interests in this communication.

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