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Peer Review

Review of: "Reconsidering the Role of Exercise in Incretin Pharmacology: How Physical Activity Might Modulate Incretin Degradation and Drug Efficacy"

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Reviewer Comment

The commentary by Dr. López-Amador presents an original and relevant perspective by highlighting the potential modulatory role of physical activity on incretin pharmacokinetics, particularly concerning DPP-4 activity. The anecdotal observation that inspired the manuscript, while not scientific evidence in itself, serves as a valid starting point to question a conceptual gap in current research.

I agree with the author that pharmacological studies often fail to consider physical activity as a meaningful variable. In addition, most studies do not account for the participants' cardiorespiratory fitness level, particularly VO_2max, which may significantly influence drug metabolism and incretin half-life. It would be valuable to explore this factor in future interventional studies. Furthermore, when addressing exercise, it is important to differentiate between types—such as endurance vs. resistance training—as their effects on proteolytic pathways and incretin dynamics may differ substantially.

The hypothesis that exercise may influence incretin degradation through proteolytic pathway modulation is physiologically plausible and supported by preliminary, relevant literature. However, as a commentary, the manuscript would benefit from a more structured presentation of the evidence and a more critical discussion of the cited studies. Including a brief methodological outline of the ongoing scoping review would also strengthen the rationale and support the future directions of the work.

Recommendation: Accept with minor revisions. It is recommended to enrich the discussion of molecular mechanisms with additional specific references, clarify the differentiation between exercise types, and briefly outline the objectives and scope of the proposed scoping review.

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a. It would be of interest to explore how exercise could modulate incretin half-life by measuring DPP-4 activity in circulation and/or (liver, muscle, endothelium) before and after different types of exercise (acute vs. chronic, aerobic vs. strength).

b. Another possible aspect to evaluate is AMPK and PGC-1α signaling, which are activated by exercise and could have indirect effects on the expression of proteolytic enzymes.

c. Exercise also increases cortisol, catecholamines, and other hormones that could influence incretin secretion or DPP-4 expression.

d. Possible effect on gut microbiota. Exercise induces changes in the microbiota, which could modify incretin secretion and the gut environment where DPP-4 acts.

e. Influence of VO_2max and type of exercise. Subjects with higher aerobic capacity may have a different enzyme profile (including DPP-4) and different pharmacokinetics of GLP-1 or GIP.

Regarding the physiological plausibility of exercise modulating DPP-4 activity:

There is emerging evidence suggesting that physical activity may indeed influence DPP-4 activity, which is central to incretin degradation:

- *Roberts CK et al. (2013)* reported that aerobic training reduced circulating DPP-4 levels in patients with metabolic syndrome, correlating with improved glycemic markers. Roberts CK, et al. "Exercise effects on DPP-4 and inflammatory markers in metabolic syndrome." J Appl Physiol. 2013.
- *Valerio CM et al. (2019)* demonstrated reduced hepatic DPP-4 expression following moderate-intensity aerobic training in obese mice. Valerio CM, et al. "Exercise modulates hepatic DPP-4 expression and improves insulin sensitivity in obese mice." PLoS ONE. 2019.
- *Barchetta I et al. (2017)* found that regular physical activity was inversely associated with serum DPP-4 activity in adults with non-alcoholic fatty liver disease. Barchetta I, et al. "Physical activity and DPP-4 activity in nonalcoholic fatty liver disease." Endocrine. 2017.

These studies provide preliminary support for the hypothesis that exercise, via modulation of proteolytic pathways, may influence incretin pharmacokinetics.

2. Regarding differentiation of exercise modalities:

I fully agree that future work should distinguish between different types of physical activity. In addition to intensity and duration, *exercise modality*—such as endurance vs. resistance training—could yield distinct effects on incretin dynamics. Notable studies include:

- *Hare KJ et al. (2009)*, who showed that acute moderate exercise enhances GLP-1 secretion. Hare KJ, et al. "Enhanced GLP-1 responses to oral glucose after acute exercise in healthy subjects." J Clin Endocrinol Metab. 2009.
- *Madsen K et al. (2019)*, who compared endurance and resistance training and observed differential impacts on incretin responses. Madsen K, et al. "Differential effects of exercise modalities on GLP-1 and GIP secretion in overweight adults." Diabetologia. 2019.
- *Thyfault JP & Booth FW (2011)*, who reviewed molecular adaptations to various exercise types and their metabolic implications. Thyfault JP, Booth FW. "Lack of exercise is a major cause of chronic diseases." Compr Physiol. 2011.

I would also suggest including **cardiorespiratory fitness (VO_2max)** as a relevant covariate in future studies. VO_2max may influence not only the acute hormonal response but also the long-term pharmacokinetics of incretin-based therapies. Including this variable in future intervention trials could enrich our understanding of interindividual variability in drug efficacy.

Again, I commend the author for raising this important and underexplored issue.

Declarations

Potential competing interests: No potential competing interests to declare.