

Metabolism

Reconsidering the role of active vitamin D in preventing sarcopenia: Letter to the editor --Manuscript Draft--

Manuscript Number:	METABOLISM-D-25-01272
Article Type:	Letter to the Editor
Corresponding Author:	Li Wang The First Affiliated Hospital of Liaoning University of Traditional Chinese Medicine CHINA
First Author:	Xin-Xin Luo
Order of Authors:	Xin-Xin Luo
	Juntong Liu
	Li Wang

Cover Letter

Corresponding Author: Li Wang

Affiliation: Affiliated Hospital of Liaoning University of Traditional Chinese Medicine

Address: Shenyang City, Liaoning Province, China

Email: 1784113869@qq.com

Date: April 23, 2025

To the Editor,

We are pleased to submit our Letter to the Editor titled "Reconsidering the role of active vitamin D in preventing sarcopenia" for consideration in your esteemed journal. This letter comments on the insightful study by Kawahara et al. (2025) published in *Metabolism*, which investigated the anti-sarcopenic effects of active vitamin D (eldecalcitol) in human skeletal muscle.

Key Points of Our Letter

Critical Analysis: We highlight the need for larger, more diverse cohorts to validate the generalizability of the findings, especially in populations with advanced diabetes or non-prediabetic individuals.

Methodological Suggestions: We propose exploring additional biomarkers (e.g., autophagy-related proteins or mRNA analysis) to better understand the molecular mechanisms of sarcopenia.

Safety Concerns: We emphasize the importance of long-term safety evaluations of eldecalcitol, particularly regarding hypercalcemia risks at higher doses.

Why This Letter Matters

Our commentary aims to stimulate further research on vitamin D's role in sarcopenia prevention, addressing gaps in sample diversity, biomarker sensitivity, and long-term safety—an essential step toward clinical translation.

Author Declarations

Conflict of Interest: All authors declare no competing interests.

Funding: No external funding was received for this work.

Ethical Approval: Not applicable.

We kindly request your consideration for publication and welcome feedback from reviewers. Thank you for your time and effort.

Sincerely,

Li Wang, on behalf of the authors

Xinxin Luo, Juntong Liu

Liaoning University of Traditional Chinese Medicine

**Reconsidering the role of active vitamin D in preventing sarcopenia: Letter to
the editor**

Author name1*:Xinxin Luo

Author name2*: Juntong Liu

*These authors contributed equally to this work

¹Author affiliations: Liaoning University of Traditional Chinese Medicine

²Author affiliations: Liaoning University of Traditional Chinese Medicine

Correspondence: Li Wang

Address: Affiliated Hospital of Liaoning University of Traditional Chinese Medicine, Shenyang City,

Liaoning Province

Email: 1784113869@qq.com

Dear Editor,

We read with great interest the article by Kawahara et al., titled "Anti-sarcopenic effects of active vitamin D through modulation of anabolic and catabolic signaling pathways in human skeletal muscle: A randomized controlled trial." This study provides valuable insights into the potential therapeutic role of active vitamin D, specifically eldecalcitol, in modulating muscle metabolism[1]. The study's implications for sarcopenia prevention, particularly in individuals with prediabetes, are promising. However, we believe there are several important points that warrant further discussion and investigation.

1 Firstly, the study's small sample size (32 participants) raises concerns regarding
2
3 the generalizability of the results. A larger, more diverse cohort would strengthen the
4
5 findings and make them more applicable to a wider population, including individuals
6
7 with more advanced stages of diabetes or those without prediabetes[2]. Furthermore,
8
9 the study primarily focuses on muscle degradation markers such as MuRF1, atrogin-1,
10
11 and cathepsin L. Although no significant changes were observed, this calls into
12
13 question the sensitivity and suitability of these markers. Future research could
14
15 consider employing additional autophagy-related proteins or alternative methods,
16
17 such as mRNA analysis, which may provide deeper insights into the molecular
18
19 mechanisms underpinning sarcopenia .
20
21
22
23
24
25
26
27
28

29 Additionally, while the study examines the effects of a daily dose of 0.75 µg of
30
31 eldecacitol over one year, the long-term safety of this dosage, particularly at higher
32
33 levels, remains uncertain[3]. Given the potential for vitamin D to influence calcium
34
35 metabolism, it is crucial to evaluate the long-term safety profile, especially
36
37 concerning the risk of hypercalcemia, which was noted in the eldecacitol group .
38
39
40
41
42
43 Future studies should assess a broader range of doses and monitor calcium levels over
44
45 extended periods to ensure the safety of long-term supplementation.
46
47
48
49

50 Finally, the study's findings regarding the lack of significant changes in certain
51
52 markers warrant further investigation. It would be valuable for future research to
53
54 explore other signaling pathways or regulatory mechanisms that may be involved in
55
56 muscle atrophy and to consider the effects of vitamin D on muscle function in various
57
58
59
60
61
62
63
64
65

clinical settings[4]. This will help establish a clearer understanding of its potential role in sarcopenia prevention.

In conclusion, while Kawahara et al.'s study makes a significant contribution to our understanding of the potential of active vitamin D in sarcopenia prevention, further research is needed. Larger sample sizes, the exploration of additional biomarkers, and comprehensive evaluations of the long-term safety of vitamin D supplementation are essential to solidify these promising findings.

Declaration of competing interest

The authors declare no conflict of interest.

References

- [1] Kawahara T, Inazu T, Mizuno S, Tominaga N, Toda M, Toyama N, et al. Anti-sarcopenic effects of active vitamin D through modulation of anabolic and catabolic signaling pathways in human skeletal muscle: A randomized controlled trial. *Metabolism*. 2025 Mar 28;168:156240.
- [2] Pittas AG, Kawahara T, Jorde R, Dawson-Hughes B, Vickery EM, Angellotti E, et al. Vitamin D and Risk for Type 2 Diabetes in People With Prediabetes : A Systematic Review and Meta-analysis of Individual Participant Data From 3 Randomized Clinical Trials. *Ann Intern Med*. 2023 Mar;176(3):355 – 63.
- [3] Jiang Y, Gao R, Ying Q, Li X, Dai Y, Song A, et al. Eldecalcitol ameliorates diabetic osteoporosis and glucolipid metabolic disorder by promoting Treg cell differentiation through SOCE. *Cell Mol Life Sci*. 2024 Oct 5;81(1):423.
- [4] Hosoyama T, Kawai - Takaishi M, Iida H, Yamamoto Y, Nakamichi Y, Watanabe T, et al. Lack of vitamin D signalling in mesenchymal progenitors causes fatty infiltration in muscle. *J Cachexia Sarcopenia Muscle*. 2024 Mar 27;15(3):907 – 18.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

Declaration of interests

☐The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☒The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Xin-Xin Luo reports was provided by Affiliated Hospital of Liaoning. Li reports a relationship with that includes:. Has patent pending to. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.