


Calcifediol Is Not Superior to Cholecalciferol in Improving Vitamin D Status in Postmenopausal Women

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To the Editor:

We have read with interest the article published in the *Journal of Bone and Mineral Research* (the *JBMR*) by Pérez Castrillón and colleagues,⁽¹⁾ comparing the efficacy and safety of calcifediol versus cholecalciferol in improving vitamin D status in postmenopausal women.

We would point out a series of inaccuracies that question the validity and certainty of their conclusions. Due to limitations we cannot cite them all, but we describe the most relevant:

- The women studied are postmenopausal with hypovitaminosis or vitamin D deficiency (25(OH) vitamin D levels less than 20 ng/mL). Therefore, the results cannot be extrapolated to all postmenopausal women, as the title suggests.
- The cholecalciferol doses prescribed are not those recommended for subjects with vitamin D deficiency. The authors justify the monthly dose of cholecalciferol (25,000 IU) recommended by Kanis and colleagues⁽²⁾ and Pludowski and colleagues.⁽³⁾ However, in Kanis and colleagues⁽²⁾ guidelines, the doses are for treating osteoporosis, not for vitamin D deficiency, so not applicable here. Furthermore, the Pludowski and colleagues⁽³⁾ guidelines indicate that “for patients with a laboratory confirmed vitamin D deficiency, ie, 25(OH)D concentration lower than 20 ng/mL (50 nmol/L), a vitamin D treatment should be implemented. (...) The dosage should

be as follows (...): for adults and the elderly 7000–10,000 IU/ day (175–250 mg/day) or 50,000 IU/week (1250 mg/week).” Clearly, the cholecalciferol dose was not adequate, but markedly lower than those recommended in this latest, reported guideline. Therefore, the cholecalciferol treatment group was underdosed.

Other guidelines recommend that, regarding vitamin D deficiency, defined by levels of 25(OH) vitamin D below 20 ng/mL, higher doses than those indicated here should be prescribed. The Endocrine Society recommends cholecalciferol doses administered at 50,000 IU weekly for 8 weeks (alternatively 6000 IU daily), followed by 1500–2000 daily maintenance IU⁽⁴⁾; the National Osteoporosis Society recommends 2000 IU daily,⁽⁵⁾ between 45,000 and 60,000 IU monthly of cholecalciferol. More recently, the American Association of Clinical Endocrinologists (AACE) recommended 5000 IU daily for 8 to 12 weeks⁽⁶⁾; ie, 150,000 IU monthly.

Thus, 25,000 IU of cholecalciferol administration once a month used by Pérez Castrillón and colleagues⁽¹⁾ is insufficient and explains why they deem cholecalciferol “inferior” to calcifediol.

- The article reflects partial results at 4 months in a study designed for 1 year. This should have been reflected in the title. According to the reported dates, the last patient would have completed his annual visit on June 25, 2020 (visit at

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4 months: October 25, 2019). The article with the results at 4 months was sent to the journal in February 2021. What happened in those remaining 8 months? Why have those data not been shown?

It is important to know the percentage of patients who, in this 4–12-month window, develop 25(OH) vitamin D levels above the optimal desirable range of 30–50 ng/mL.⁽⁷⁾ It would be interesting to know the speed with which the levels of 25(OH) vitamin D fall again after discontinuing calcifediol at 4 months (group A.2). The authors have not included a similar group of cholecalciferol that would permit comparisons. Also, not all clinically relevant results were taken into account, because although it is important to correct low vitamin D levels, the ultimate benefit is to prevent hypovitaminosis complications. The time in which vitamin D levels remain stable after treatment is not specified; it only focuses on correcting levels and the speed with which correction occurs. A quick correction would not be useful if after 4 months complications begin to appear. The expected benefits do not currently outweigh the risks and costs, because the long-term adverse effects of calcifediol are not known and cholecalciferol treatment has so far been effective, safe, and cheap.^(8,9)

In our opinion, this study of Pérez Castrillón and colleagues⁽¹⁾ holds some issues of concern that could invalidate the results shown and could mislead readers to a false understanding.

Author Contributions

Manuel Sosa-Henríquez: Conceptualization; investigation; methodology; supervision; validation; visualization; writing – original draft; writing – review and editing. **M.a Jesús Gómez de Tejada-Romero:** Conceptualization; methodology; supervision; validation; visualization; writing – original draft. **M.a Jesús Cancelo-Hidalgo:** Conceptualization; methodology; supervision; validation; visualization. **Guillermo Martínez Díaz-Guerra:** Conceptualization; supervision; validation; visualization. **Íñigo Etxebarria Foronda:** Conceptualization; investigation;

supervision; validation; visualization. **Francisco José Tarazona-Santabalbina:** Conceptualization; supervision; validation; visualization. **Óscar Torregrosa-Suau:** Conceptualization; methodology; supervision; validation; visualization. **Carmen Valdés-Llorca:** Conceptualization; investigation; resources; supervision; validation; visualization.

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