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Peer Review

Review of: "Calcium-Magnesium Balance —Clinical Implications for Global Human Health"

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In this study, the authors provided a comprehensive review of Calcium-Magnesium Balance in human health. The following are the comments for the authors to consider.

1. In the abstract, there is a redundant sentence: “However, the benefits of a balanced ratio extend well beyond that due to improved vitamin D efficacy.”

2. On page 3, in the following sentence, “An imbalanced Ca^{2+}: Mg^{2+} ratio has been directly linked to the onset and progression of cardiovascular risk [11] and mortality [12][13], cancer, autoimmune disorders, infections, dementia [14][15], and obesity [16][17],” reference 11 is a cross-sectional study. Since the temporal sequence is not clear in cross-sectional studies, it is better to add a prospective cohort study with a clear causal relationship. PMID: 23430595 is a prospective cohort study and is also the first prospective study that found the association between Ca:Mg intake ratios and cardiovascular disease risk.

3. Remove “Yang T, C, Wei Q, Cheng Y, Xiao Y” on page 7.

4. On page 8, the authors mentioned that “According to a 2018 study, any attempt to correct a high Ca^{2+}: Mg^{2+} ratio by increasing Mg intake may exacerbate the imbalance when circulatory 25(OH) D exceeds 30 ng/mL [83]. When 25(OH) D levels are below 30 ng/mL, the demands of Mg-dependent 25(OH) D synthesis surpass those of Mg-dependent PTH synthesis. Hypomagnesemia reduces the release and synthesis of hormones, especially PTH [84]. As Mg intake is increased, serum 25(OH) D levels also increase, up to about 25(OH) D levels of 30 ng/mL, together with upregulation of Mg-dependent PTH synthesis.”

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The 2018 randomized trial found that reducing the Ca:Mg ratios to around 2.3 increased circulating levels of 25(OH)D to around 35 ng/mL among those with 25(OH) D levels below 30 ng/mL, whereas for those with 25(OH) D levels close to 50 ng/mL, reducing Ca:Mg ratios reduced 25(OH) D levels (see Table 1 in the 2018 publication). Thus, it should be up to about 25(OH)D levels of 35 ng/mL instead of 30 ng/mL.

5. On page 11, the authors mentioned, "A ratio of 1.7-2.6 (weight-to-weight in mg/day) has been recommended based on increased all-cause mortality in those outside this range [102]. One study from China involving 75,000 females and 62,000 males determined a median ratio of 1.7, lower than that found by NHANES, where the ratio exceeds 3 [103]."

Reference 103 determined 1.7 as the lower limit for the range between 1.7 and 2.6. It is better for the authors to provide the reference (PMID: 22475836) that found 2.6 as the upper bound for the range. In a later study (PMID: 31543516) conducted in PLCO, the upper bound for the Ca:Mg intake ratios was found to be around 2.5. The authors can mention the finding of 2.5 as it supports the authors' discussion later on the page that "These Chinese serum mmol/L levels, with 70% of Mg unbound and 50% of calcium unbound, translate to a Ca^{2+}: Mg^{2+} ratio between 1.7 and 2.5, closely replicating the recommended 1.7-2.6 weight-to-weight intake."

6. As mentioned in comment 2, reference 11 is a cross-sectional study, and the temporal sequence is not clear. In "Table 3. Examples of disorders linked to an imbalanced Ca: Mg," for cardiovascular disease, the statement "Elevated dietary Ca: Mg intake increases the risk for CVD [11]" is not correct, as reference 11 is a cross-sectional study. Also, the authors can add the results from PMID: 23430595, a prospective cohort in which the causal relationship is clear.

7. On page 16, the authors mentioned that "A low calcium-to-magnesium (Ca: Mg) ratio has also been linked to increased sickle cell disease sickling." Please provide a reference.

8. In the footnote of Figure 2, the authors mentioned that "One study suggests that the upper limit of optimal Ca: Mg be reduced to 2.5[128]." Please see comment 5; the reference (PMID: 31543516) also indicates a Ca:Mg ratio of 2.5 as the upper bound for the optimal Ca:Mg ratio range.

9. On page 18, the authors mentioned that "As previously discussed, a 2018 study [83] reported that when baseline 25(OH) D exceeded 30 ng/mL, Mg supplementation (e.g., 200 mg/day) surprisingly reduced 25(OH) D synthesis[83]."

Please see comment 4: the 2018 randomized trial found that reducing Ca:Mg ratios to around 2.3 increased the levels of 25(OH)D to around 35 ng/mL among those with 25(OH) D levels below 30 ng/mL, whereas for those with 25(OH) D levels close to 50 ng/mL, reducing Ca:Mg ratios reduced 25(OH) D levels (see Table 1 in the publication).

10. On page 18, the authors mentioned that "A study on FFQs in individuals not taking supplements found that a Ca: Mg ratio between 2.2 and 3.2 offered the greatest protection against osteoporosis[95]".

As mentioned in comments 4 and 9, the 2018 randomized trial found that reducing the Ca:Mg ratios to around 2.3 optimized the levels of 25(OH)D, which is also consistent with the ratio ranges from 2.2 to 3.2.

A Ca:Mg ratio of 2.3 is also consistent with the authors' estimation of 2.33. The authors mentioned on page 19 that "If one adjusts the 2:1 Ca: Mg weight to weight recommendation of Durlach for differential molar weights (40:24) and dissociation constants (50% v 70%), then this weight to weight ratio should be 2.33.".

11. In general, the authors need to 1) confirm that the references match the contents in the review; and 2) explicitly differentiate the hypotheses the authors proposed from those the authors paraphrased from the references.

Declarations

Potential competing interests: No potential competing interests to declare.