July 2025

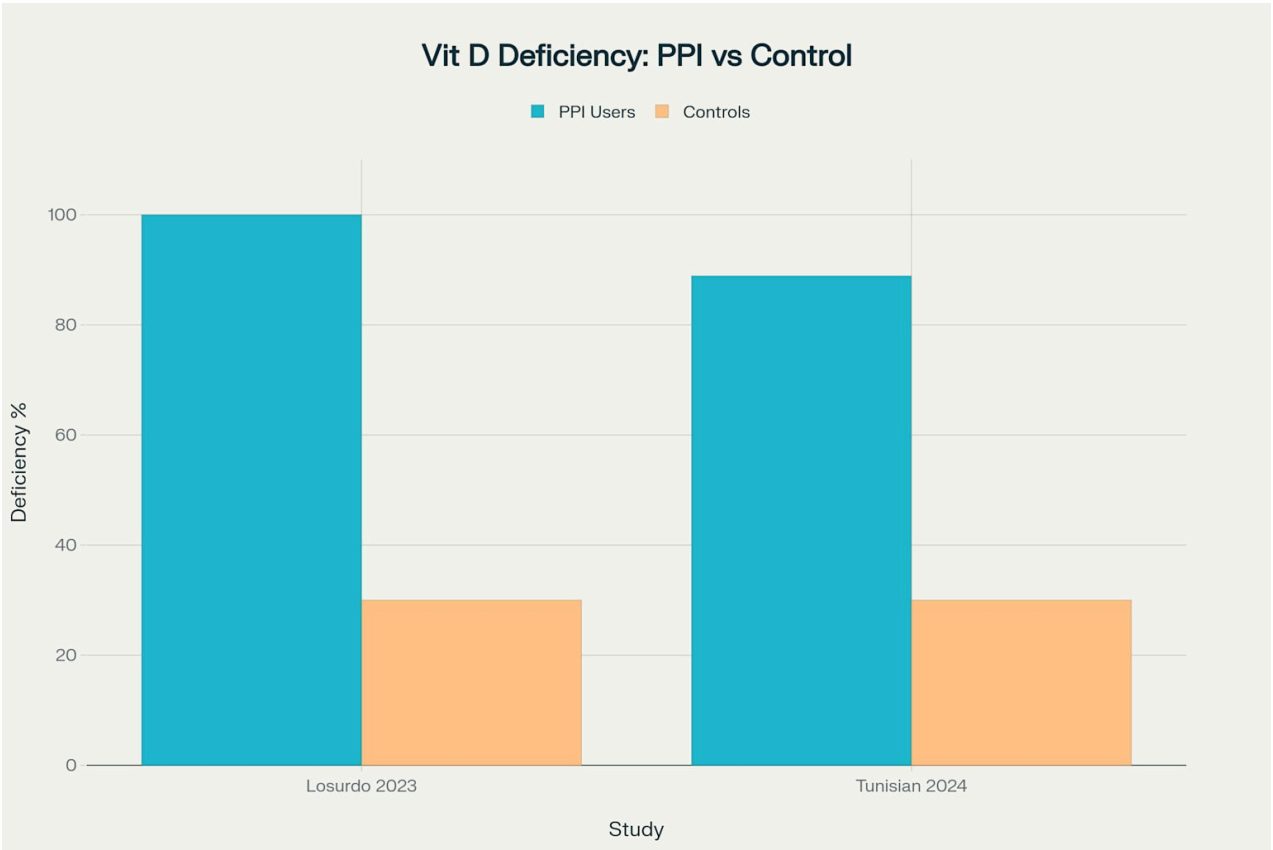
perplexity

Association Between PPIs and Vitamin D

Yes, there is a significant association between proton pump inhibitors (PPIs) and vitamin D deficiency, with multiple studies demonstrating that long-term PPI use is linked to substantially higher rates of vitamin D deficiency compared to non-users.

Key Evidence

The most compelling evidence comes from recent well-designed studies that show dramatic differences in vitamin D status between PPI users and controls. A 2023 Italian study found that **100% of long-term PPI users had vitamin D deficiency compared to only 30% of controls** ($p < 0.001$), with significantly lower blood vitamin D levels in PPI consumers (15.5 ± 6.8 vs 36.6 ± 21.2 ng/mL)[1]. Similarly, a 2024 Tunisian case-control study involving 180 subjects found that **88.9% of PPI users had vitamin D deficiency compared to 30% of controls** ($p < 0.001$)[2].



Vitamin D deficiency rates in PPI users versus controls from two major studies

Prevalence and Clinical Significance

The association appears to be particularly strong with **long-term PPI use (>1 year)**. Studies consistently show that chronic PPI users have vitamin D deficiency rates of **70-100%**, compared to **25-30%** in control populations[1] [2]. This represents a **3-4 fold increase** in vitamin D deficiency risk among long-term PPI users.

However, the evidence is not entirely consistent. A 2023 survey-based study from Pakistan found no significant association between PPI use and vitamin D deficiency ($p > 0.05$)[3], though this study had methodological limitations including variable PPI duration and reliance on self-reported data.

Proposed Mechanisms

The association between PPIs and vitamin D deficiency likely involves **multiple interconnected mechanisms**:

Magnesium-Mediated Pathway: The primary mechanism appears to involve PPI-induced hypomagnesemia, which subsequently affects vitamin D metabolism. Magnesium serves as a cofactor in several critical steps of vitamin D metabolism, including vitamin D binding to vitamin D binding protein, 25(OH)D synthesis, and 1,25(OH)2D synthesis[4] [5]. PPI-induced hypomagnesemia can lead to **deactivation of important cellular functions including vitamin D metabolism**[5].

Calcium Absorption Interference: PPIs may affect calcium absorption through gastric acid suppression, which can indirectly impact vitamin D homeostasis. The acidic gastric environment is important for calcium ionization and absorption, and **profound acid suppression may theoretically interfere with calcium solubilization**[6]. However, studies on calcium absorption have shown mixed results, with some showing no significant impact on fractional calcium absorption[7].

Hyperparathyroidism: Long-term PPI use can lead to secondary hyperparathyroidism through hypergastrinemia and calcium malabsorption, which may further disrupt vitamin D and calcium homeostasis[6] [2].

Clinical Implications

The association has important clinical implications for bone health. Studies show that **PPI-induced vitamin D deficiency is associated with decreased bone mineral density and increased fracture risk**[2]. Risk factors for more severe bone effects include age >50 years, menopause, limited sun exposure, higher PPI doses, and daily administration[2].

Monitoring Recommendations

Despite the clear association, monitoring practices remain inconsistent. A 2013 study found that **only 49.6% of chronic PPI users had vitamin D levels checked**, with monitoring more frequent in patients ≥60 years old and those on PPIs for ≥24 months[8]. Current guidelines emphasize the need for **periodic review of PPI necessity** and consideration of vitamin D supplementation when appropriate[9].

Duration and Reversibility

The association appears to be **time-dependent**, with stronger effects seen after prolonged use. Short-term PPI therapy (7-30 days) does not appear to significantly affect vitamin D levels[7], while effects become more pronounced with use exceeding 12 months[1]. The reversibility of vitamin D deficiency after PPI discontinuation has not been extensively studied.

Conclusion

The evidence supports a **clinically significant association between long-term PPI use and vitamin D deficiency**, with deficiency rates of 70-100% in chronic PPI users compared to 25-30% in controls. The mechanism likely involves magnesium depletion affecting vitamin D metabolism rather than direct effects on vitamin D absorption. Clinicians should consider monitoring vitamin D levels in patients requiring long-term PPI therapy and ensure adequate supplementation when indicated, while regularly reassessing the clinical necessity for continued PPI use.

⁂

1. https://pmc.ncbi.nlm.nih.gov/articles/PMC10146626/
2. https://journals.lww.com/ajg/fulltext/2013/10001/monitoring_of_vitamin_d_in_chronic_ppi_users_is.141.aspx
3. https://pmc.ncbi.nlm.nih.gov/articles/PMC4110863/
4. https://www.pharmacytimes.com/view/proton-pump-inhibitors-how-to-deprescribe-these-nutrient-robbers-
5. https://e-acnm.org/journal/view.php?doi=10.15747%2FACNM.2022.14.1.20
6. https://effectivehealthcare.ahrq.gov/get-involved/nominated-topics/what-are-the-risks-of-taking-ppis
7. https://www.mdpi.com/1422-0067/21/1/323
8. https://www.mdpi.com/2077-0383/12/8/2910/review_report
9. https://inpharmd.com/inquiries/ed60f0ab18a98b993e2f4cf5fc1be63ddd97ae1d08b4f3daecdaeb0bd3bce936