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J.D. Bashutski[1]*, R.M. Eber[1], J.S. Kinney[1], E. Benavides[1], S. Maitra[2], T.M. Braun[2], W.V. Giannobile[1,3], and L.K. McCauley[1,4]

[1]Department of Periodontics and Oral Medicine, Michigan Center for Oral Health Research, School of Dentistry, University of Michigan, 1011 N. University Ave., Room 3349, Ann Arbor, MI 48109, USA; [2]Department of Biostatistics, School of Public Health, University of Michigan, Ann Arbor, MI, USA; [3]Biomedical Engineering, College of Engineering, University of Michigan, Ann Arbor, MI, USA; and [4]Department of Pathology, Medical School, University of Michigan, Ann Arbor, MI; *corresponding author, jillbash@umich.edu

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The Impact of Vitamin D Status on Periodontal Surgery Outcomes

ABSTRACT

Vitamin D regulates calcium and immune function. While vitamin D deficiency has been associated with periodontitis, little information exists regarding its effect on wound healing and periodontal surgery outcomes. This longitudinal clinical trial assessed outcomes of periodontal surgery and teriparatide administration in vitamin-D-sufficient and -insufficient individuals. Forty individuals with severe chronic periodontitis received periodontal surgery, daily calcium and vitamin D supplements, and self-administered teriparatide or placebo for 6 wks to correspond with osseous healing time. Serum 25(OH)D was evaluated at baseline, 6 wks, and 6 mos post-surgery. Clinical and radiographic outcomes were evaluated over 1 yr. Placebo patients with baseline vitamin D deficiency [serum 25(OH)D, 16-19 ng/mL] had significantly less clinical attachment loss (CAL) gain (-0.43 mm *vs*. 0.92 mm, $p < 0.01$) and probing depth (PPD) reduction (0.43 mm *vs*. 1.83 mm, $p < 0.01$) than vitamin-D-sufficient individuals. Vitamin D levels had no significant impact on CAL and PPD improvements in teriparatide patients at 1 yr, but infrabony defect resolution was greater in teriparatide-treated vitamin-D-sufficient *vs*. -deficient individuals (2.05 mm *vs*. 0.87 mm, $p = 0.03$). Vitamin D deficiency at the time of periodontal surgery negatively affects treatment outcomes for up to 1 yr. Analysis of these data suggests that vitamin D status may be critical for post-surgical healing. (ClinicalTrials.gov number, CT00277706)

KEY WORDS: vitamin D, teriparatide, parathyroid hormone, periodontitis, periodontal surgery outcomes, osseous healing.

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INTRODUCTION

The main function of vitamin D is to support calcium homeostasis, but it also plays an important role in immunity, the cardiovascular system, diabetes, cancer, and chronic illness (Adams and Hewison, 2010). The primary sources of vitamin D are dietary intake and sunlight exposure in the form of vitamin D2 and D3, which are metabolized to 25-hydroxyvitamin D [25(OH)D] in the liver. Further metabolism in the kidneys produces the active form of vitamin D, 1,25-dihydroxyvitamin D (Holick, 2007).

Periodontitis is characterized by alveolar bone loss induced by the host immune response to bacterial insult. Because vitamin D plays a crucial role in bone maintenance and immunity, there is biologic rationale to suspect that a vitamin D deficiency could negatively affect the periodontium. A diagnosis of vitamin D deficiency is made through serum analysis of 25(OH)D levels. The normal range of serum 25(OH) D levels is 20-74 ng/mL. No absolute threshold for deficiency status is universally accepted, although most authorities agree that levels below 20-30 ng/mL constitute at least a mild deficiency, with severe vitamin D deficiency beginning at a level of 12 ng/mL (Malabanan *et al*., 1998; Bischoff-Ferrari *et al*., 2006; Holick, 2007). Vitamin D deficiency is highly prevalent, with an estimated 1 billion people affected worldwide (Holick, 2007); however, it is difficult to estimate the prevalence due to a lack of consensus about the definition, and recent information suggests that this may be overestimated (Ross *et al*., 2011). In addition, mean serum 25(OH)D levels appear to be declining over the past several decades, due to changes in BMI, dietary intake, and sun exposure (Looker *et al*., 2008).

Calcium, phosphorus, and parathyroid hormone levels all influence the rate of conversion of 25(OH)D to its active form (DeLuca, 2004). Parathyroid hormone (PTH) is an endogenous hormone with both catabolic and anabolic properties in bone, depending on the concentration and dosing regimen (Khosla *et al*., 2008; Kousteni and Bilezikian, 2008). Several studies have confirmed that serum levels of PTH are inversely proportional to those of 25(OH)D, and that there is seasonal variation in these levels (Thomas *et al*., 1998; Cranney *et al*., 2007). Recently, it was determined that a minimum 25(OH)D serum concentration of 28 ng/mL was required to stabilize PTH levels and maintain normal calcium availability (Okazaki *et al*., 2011). Consequently, low vitamin D levels may result in high, catabolic PTH levels that could negatively affect bone health.

Analysis of cross-sectional data from the third National Health and Nutrition Examination Survey (NHANES III) revealed that individuals with the highest 25(OH)D levels experienced 20% less bleeding on probing than those with the lowest levels, suggesting that vitamin D may reduce the risk of gingival inflammation by exerting anti-inflammatory effects (Dietrich *et al*., 2005). Analysis of data from this study also demonstrated an inverse relationship between clinical attachment loss (CAL) and 25(OH)D levels in persons aged 50 yrs or older (Dietrich *et al*., 2004). A 5-year prospective study found that calcium and vitamin D supplementation decreased the risk of tooth loss in elderly men and women (Krall *et al*., 2001). Similarly, periodontal maintenance patients taking calcium and vitamin D supplements had better periodontal health than those who did not (Miley *et al*., 2009; Garcia *et al*., 2011). A case-control study found that vitamin D insufficiency was associated with periodontal disease among pregnant women (Boggess *et al*., 2010). However, no study to date has evaluated long-term outcomes of surgical intervention based on a person's vitamin D status. The aim of this study was to evaluate the effect of presurgical vitamin D status on periodontal surgery outcomes with or without concomitant administration of anabolic doses of a commercially available form of PTH (teriparatide, PTH 1-34).

MATERIALS & METHODS

The University of Michigan Institutional Review Board approved the study, which was conducted from January 20, 2005 – June 25, 2009. Written informed consent was obtained from all participants prior to enrollment. A detailed study protocol along with separate outcomes data was published previously (Bashutski *et al*., 2010). Briefly, 40 individuals with severe periodontal disease received open flap debridement surgery in one sextant of the mouth and were followed for 1 yr post-surgery. The primary outcome variable was infrabony defect resolution, comparing those taking teriparatide with those receiving placebo medication. A *post hoc* analysis of the effect of vitamin D status on clinical and radiographic outcomes was then completed.

Study medications were randomized by the pharmacy, and each patient received either teriparatide (20 μg) or placebo that was self-administered daily *via* subcutaneous injection to the thigh or abdomen. Dosing of the study medication, along with daily 1000 mg calcium and 800 IU vitamin D oral supplements, was initiated 3 days prior to surgery and continued for 6 wks to correspond with osseous healing. To assess drug adherence, we collected all unused medication and monitored serum bone alkaline phosphatase levels throughout the drug administration phase.

Periodontal surgery consisted of an open flap debridement procedure in the study quadrant by 2 blinded operators (R.M.E. and J.D.B.). To maintain blinding, the operators did not evaluate the individuals on whom they performed surgery. Supra- and sub-gingival scaling, polishing, and oral hygiene instruction were provided every 3 mos post-surgically.

Serum samples were collected to determine 25(OH)D levels at baseline, 6 wks, and 6 mos post-surgery and analyzed independently at the Mayo Clinic. Clinical parameters were evaluated at baseline, 6 wks, and 3, 6, 9, and 12 mos by three blinded examiners (J.D.B., R.M.E., and J.S.K.) and included probing depth (PD), clinical attachment level (CAL), and bleeding on probing (BOP). Standardized periapical and bitewing radiographs of the treatment area were taken at baseline, 3, 6, 9, and 12 mos (Duckworth *et al*., 1983; Reddy and Jeffcoat, 1993) and analyzed with digital software (Emago™, Oral Diagnostic Systems, Amsterdam, Netherlands). Independent analyses of linear defect resolution, assessed radiographically, were completed by two calibrated and blinded examiners (J.D.B. and E.B.). Linear defect resolution was measured from the deepest point of the initial defect to the first point at which complete bone fill occurred.

The study participants were stratified by treatment group (teriparatide *vs*. placebo) and by whether they were vitamin-D-deficient at baseline, defined as a serum vitamin D less than 20 ng/mL. For each of the four groups (vitamin-D-deficient/placebo, vitamin-D-sufficient/placebo, vitamin-D-deficient/teriparatide, vitamin-D-sufficient/teriparatide), changes in CAL, PD, and linear bone gain were evaluated for the surgical sites at each time-point.

A paired *t* test was used for within-patient comparisons, and a two-sample *t* test was used for between-patient group comparisons. Statistical significance was defined as a p-value less than 0.05. We also used generalized estimating equations to compare treatment groups at all time-points simultaneously, but these gave results similar to those reported when two-sample *t* tests were used at each time-point.

RESULTS

Baseline demographics of the study population are presented in Table 1 with no significant differences between groups. The compliance rate of the 40 enrolled individuals was high, with only 2 missed follow-up appointments—one 9-month (vitamin-D-sufficient teriparatide patient) and one 12-month (vitamin-D-sufficient teriparatide patient) (Appendix Fig.). At baseline, 11 participants were vitamin-D-deficient (28%); of these, four received teriparatide as part of the study. At 6 wks, five vitamin-D-deficient placebo patients converted to sufficiency; of those, four returned to a deficient status at 6 mos. All of the vitamin-D-deficient teriparatide patients achieved sufficiency at 6 wks, and only one became deficient again at 6 mos. Table 2 shows the mean serum 25(OH) vitamin D levels over time for each group.

For individuals who received placebo, periodontal surgery resulted in improved CAL gain and PD reduction at the surgical site if they had sufficient vitamin D levels prior to surgery (Figs. A, C). Those who were initially vitamin-D-deficient lost clinical attachment post-surgically. Significant differences in clinical outcomes between vitamin-D-deficient and -sufficient participants were noted at all follow-up time-points in the study, beginning 6 wks post-operatively. At 12 mos, vitamin-D-sufficient individuals had greater CAL gain (0.92 mm *vs*. −0.43 mm, $p < 0.01$) and PD reduction (1.83 mm *vs*. 0.43 mm, $p < 0.01$) compared with -deficient individuals. Radiographic linear infrabony defect resolution was minimal, and there were no significant differences between groups at any time-point (Fig. E). Bleeding

Table 1. Demographics of the Study Population

	Placebo		Teriparatide	
Characteristic Vitamin D Status	Deficient (N = 7)	Sufficient (N = 13)	Deficient (N = 4)	Sufficient (N = 16)
Median age in yrs (range)	43 (31-64)	57 (38-65)	48 (43-61)	47 (30-61)
Gender				
Male	2	4	3	6
Female	5	9	1	10
Race/ethnicity				
Caucasian	4	11	2	13
African-American	2	2	0	2
Asian	1	0	0	1
Hispanic	0	0	1	0
Arabic	0	0	1	0
Smoking status				
Current	4	2	3	6
Former	2	5	0	5
Never	1	6	1	5

Table 2. Serum 25(OH) Vitamin D Changes over Time Based on Status (Deficient or Sufficient) at Baseline

Mean Serum Vitamin D Level (ng/mL) ± Standard Error	Placebo			Teriparatide		
	Deficient	Sufficient		Deficient	Sufficient	
Time-point	(N = 7)	(N = 13)	p-value	(N = 4)	(N = 16)	p-value
0	17.29 ± 0.42	33.92 ± 2.76	< 0.001	17.75 ± 0.63	31.69 ± 1.53	< 0.001
6 wks	26.43 ± 4.44	40.54 ± 5.65	0.050	38.25 ± 8.23	31.19 ± 2.41	0.410
6 mos	20 ± 2.54	31.08 ± 2.37	0.001	26.25 ± 5.94	29.69 ± 1.81	0.580

upon probing (BOP) was reduced by 36% in deficient participants and 42% in sufficient participants at 12 mos, with no significant differences between groups.

For individuals who received teriparatide, open flap debridement surgery resulted in improved clinical and radiographic outcomes at 12 mos (Figs. B, D, F; Bashutski *et al*., 2010). Vitamin-D-sufficient participants had significantly greater CAL gain at 6 mos ($p < 0.01$; Fig. B), and significantly greater PD reduction from the 3-month time-point to the 9-month time-point ($p < 0.01$; Fig. D). However, at 1 yr, the outcomes for vitamin-D-deficient and -sufficient participants were similar for CAL gain (1.54 mm *vs*. 1.75 mm, NS) and PD reduction (2.57 mm *vs*. 1.88 mm, NS). In contrast, those who were vitamin-D-sufficient at baseline experienced more radiographic infrabony defect resolution compared with those who were deficient at baseline (Fig. F, 2.05 mm *vs*. 0.87 mm, $p = 0.03$). Teriparatide patients who were vitamin-D-deficient at baseline had a 12% increase in BOP at 12 mos, compared with a 39% decrease in vitamin-D-sufficient teriparatide patients ($p < 0.01$).

DISCUSSION

Vitamin D is necessary for bone formation and proper immune function, which are also important to the success of periodontal therapy. The prevalence of vitamin D deficiency in this study was high and comparable with that of the general population (Chapuy *et al*., 1997; Guardia *et al*., 2008), with 28% of enrolled participants presenting with mild deficiency [16-19 ng/mL serum 25(OH)D level]. 25OHD values lower than 16 ng/mL have been shown to have a drastic effect on PTH levels (Carnevale *et al*., 2010). Participants with moderate to severe deficiency were excluded from the study, and constituted 9.7% of all individuals screened.

Previously, only a few studies had assessed the role of vitamin D on periodontal disease status. A recent survey of periodontal maintenance patients found that only 7% had vitamin D intake levels that met published guidelines (Dixon *et al*., 2009). In cross-sectional studies, low vitamin D levels have been associated with increased gingival inflammation, tooth loss, clinical attachment loss, and maternal periodontal disease

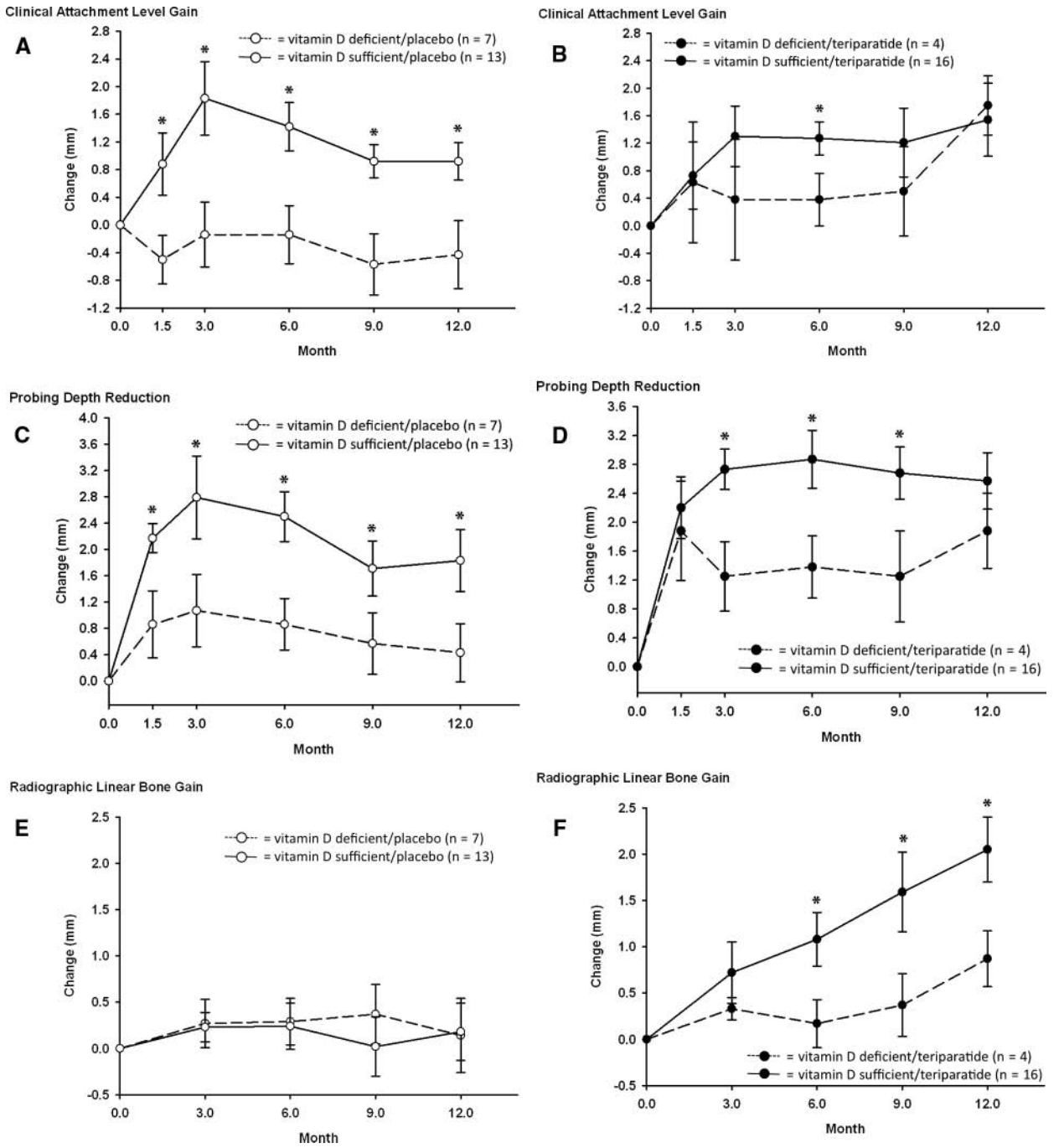

Figure. Clinical and radiographic outcomes of vitamin-D-sufficient and -deficient participants supplemented with placebo or teriparatide for 6 wks. Mean (± SE) changes from baseline for clinical attachment level gain **(A, B),** probing depth reduction **(C, D),** and linear defect resolution as measured radiographically with bitewing radiographs **(E, F)**. In participants taking placebo, clinical attachment level gain was significantly greater in vitamin-D-sufficient individuals at all time-points, with vitamin-D-deficient persons experiencing a loss of attachment compared with baseline (A, $p < 0.01$). Probing depth reductions were significantly greater in vitamin-D-sufficient participants compared with vitamin-D-deficient participants at all time-points (C, $p < 0.01$). Neither group experienced significant radiographic defect resolution compared with baseline, or between groups (E, p = NS). For those supplemented with teriparatide, both vitamin-D-sufficient and -deficient groups experienced significant improvement in all parameters at 12 mos compared with baseline (B,D,F, $p < 0.01$). Clinical attachment level gain and probing depth reduction were not significantly different between vitamin D groups at the 12-month time-point, although vitamin-D-deficient participants had significantly less improvement in clinical attachment gain at 6 mos (B, $p < 0.01$) and significantly less improvement in probing depth reduction at 3, 6, and 9 mos (D, $p < 0.01$). Teriparatide recipients who were vitamin-D-sufficient experienced significantly greater radiographic linear defect resolution than -deficient participants beginning at 6 mos (F, p = 0.03).

during pregnancy (Krall *et al*., 2001; Dietrich *et al*., 2004, 2005; Miley *et al*., 2009; Boggess *et al*., 2010). However, ours was the first study to report on the effect of vitamin D status on periodontal surgery. Vitamin D sufficiency in placebo patients at the time of surgery resulted in an average of 1.35 mm greater CAL gain and 1.4 mm greater PD reduction compared with deficient patients at 12 mos. Cross-sectional studies evaluating non-treatment situations found mean differences of 0.21-0.39 mm in CAL between vitamin-D-sufficient and -deficient patients (Dietrich *et al*., 2004; Miley *et al*., 2009).

Interestingly, vitamin D supplementation at the time of surgery failed to prevent the negative clinical outcomes associated with baseline deficiency. Patients were supplemented with vitamin D for only a six-week period, and it takes up to 3 mos for serum 25(OH)D levels to stabilize after vitamin D intake is increased (Vieth *et al*., 2001). Six-week vitamin D supplementation alone did not exert long-term effects, since serum 25(OH)D levels returned to baseline levels in placebo patients by 6 mos. However, vitamin D levels remained elevated in teriparatide patients, which may account for the lack of significant differences in clinical outcomes in the teriparatide groups. The transient increase in serum levels of 25(OH)D that coincided with the six-week healing phase may also have had important anti-inflammatory effects. This phenomenon may explain the early improvements in CAL gain and PD decreases in the vitamin-D-deficient teriparatide patients. However, this increase did not reach the threshold level of 28 ng/mL required to stabilize PTH levels and maintain normal calcium availability for all patients and may explain the greater improvement in bone defects in the vitamin-D-sufficient teriparatide patients.

In participants taking teriparatide, vitamin D status was not a modifier of the clinical findings at the one-year time-point. However, there was a trend toward better outcomes in participants who were vitamin-D-sufficient. Among teriparatide patients, vitamin-D-deficient individuals had significantly less improvement in CAL gain at 6 mos ($p < 0.01$) and significantly less improvement in PD reduction at 3, 6, and 9 mos ($p < 0.01$). Thus, the lack of significance at 1 yr may be due to the small sample size in this subset. Alternatively, analysis of these data could suggest that teriparatide overrides the negative effects of vitamin D deficiency. In a previous study, vitamin D and calcium supplementation was shown to have a positive effect on outcomes of fracture healing in osteoporotic women during the first 6 wks of healing, although the effects were no longer significant at the 12-week time-point (Doetsch *et al*., 2004).

Open flap debridement surgery does not result in appreciable bone gain (Dybvik *et al*., 2007; Shirakata *et al*., 2008), explaining the lack of significance of vitamin D status on radiographic outcomes in the placebo group. In contrast, for participants taking teriparatide and for whom we previously reported a significant benefit in radiographic linear bone gain (Bashutski *et al*., 2010), baseline vitamin D deficiency resulted in less infrabony defect resolution compared with that in participants with sufficient levels. Results from animal studies suggest that vitamin D may play a predominant role in mandibular anabolic bone formation (Liu *et al*., 2009), and may exert positive effects on fracture healing (Fu *et al*., 2009). Vitamin D deficiency has also been associated with compromised osseous healing in the oral cavity in bisphosphonate-associated osteonecrosis of the jaw pre-clinical studies, supporting a role for vitamin D in bone healing in the oral cavity (Hokugo *et al*., 2010; Yamashita *et al*., 2010).

Analysis of these data suggests that if an individual is vitamin-D-deficient, minimal benefits can be obtained from periodontal surgery. Furthermore, vitamin D supplementation at the time of surgery is unable to prevent this effect. Since vitamin D deficiency is highly prevalent, it may be advisable to ensure adequate vitamin D levels well in advance of periodontal surgery, to attain the best possible results. Radiographic outcomes were better in vitamin-D-sufficient patients taking teriparatide, suggesting that an anabolic agent, such as teriparatide, benefits from vitamin D sufficiency to promote oral bone formation. However, due to the small sample size of this pilot study and, particularly, the vitamin-D-deficient groups, larger-scale trials are needed to confirm these initial results.

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